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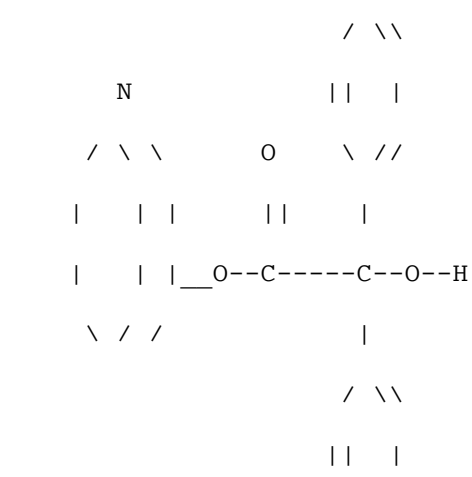
Letter to Prime Minister 25 March 2003

Backgrounder: The chemical warfare agent 3-quinuclidinyl benzilate (QNB, BZ) **BZ Gas**

BZ

(3-quinuclidinyl benzillate)



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Background: The chemical warfare agent 3-quinuclidinyl benzilate (QNB, BZ) is an anticholinergic agent that affects both the peripheral and central nervous systems (CNS). It is one of the most potent anticholinergic psychomimetics known, with only small doses necessary to produce incapacitation. It is classified as a hallucinogenic chemical warfare agent. QNB usually is disseminated as an aerosol, and the primary route of absorption is through the respiratory system. Absorption also can occur through the skin or gastrointestinal tract. It is odorless. QNB's pharmacologic activity is similar to other anticholinergic drugs (eg, atropine) but with a much longer duration of action.

Pathophysiology: QNB acts by competitively inhibiting muscarinic receptors. Muscarinic receptors primarily are associated with the parasympathetic nervous system, which innervates numerous organ systems, including the eye, heart, respiratory system, skin, gastrointestinal tract, and bladder. Sweat glands, innervated by the sympathetic nervous system, also are modulated by muscarinic receptors. The ICt50 (concentration in air of QNB necessary to incapacitate 50% of exposed and unprotected individuals through inhalation during a set time) has been reported to be 100 mg·min/m3. Effects of QNB by any route of exposure are slow in onset and long in duration. The onset of action is approximately 1 hour, with peak effects occurring 8 hours postexposure. Symptoms gradually subside over 2-4 days. Most of the QNB that enters the body is excreted by the kidneys, making urine the choice for detection.

Frequency:
In the US: Use of QNB against the US has never been reported. Currently, the US government is funding numerous programs to prepare the nation for potential chemical terrorist attacks against citizens and the military.
Internationally: Use of QNB has been suggested in a number of international conflicts. In January 1992, soldiers in Mozambique experienced an explosion above their troop formation. Subsequent symptoms resembled those expected from QNB. In July 1995, approximately 15,000 people attempted to walk from the enclave of Srebrenica to the free territory in Bosnia. Many experienced hallucinations during their march that were suspected to be secondary to QNB.
Mortality/Morbidity: The LCt50 of QNB is reportedly 200,000 mg·min/m3. This means, for example, that 50% of an unprotected group would die following inhalation of air that contained 200,000 mg of QNB per cubic meter for 1 minute. By comparison, the highly toxic compound hydrogen cyanide has an LCt50 of 5000 mg·min/m3. The LD50 (lethal dose to 50% of an exposed population) for BZ is estimated to be similar to that of atropine, which is approximately 100 mg. Other factors also are important, such as the exposed patient's preexisting health status and the time from exposure to medical care.

BZ (also known as QNB) is a dangerous hallucinogenic also produced by the United States in the 1950's and 1960's, but quickly discontinued and destroyed due to its unreliability.

Antidote
I know Dr. James Moore who used to be a prof at the U of DE and made compounds for the CIA. He tells some amazing tales.

Case in point: He made BZ for the CIA and got some on his hands. He felt very disoriented. "I felt like the whole world turned sideways on me." This effect lasted for days and so he asked the big boys at the CIA how to get back. They told him to take some THA (tetrahydroacridine) that is now used as an experimental Alzheimers treatment. He claims it straightened him right out.

The gas causes temporary slowing of physical and mental activity, disorientation, and hallucinations. The effects last for up to 6 hours. According to the U.S. Army's Center for Health Promotion and Preventive Medicine, which publishes current factsheets on many known chemical warfare agents, "BZ" is the Army's designation of the psychedelic chemical 3-quinuclidinyl benzilate, also know as in military circles as "agent buzz" or by the Army chemical code designation EA2277. While BZ was produced at the Pine Bluff Arsenal in Arkansas between 1962 and 1965, it was discontinued from the chemical arsenal in the late 1960's because "its effects on enemy front-line troops would be varied and unpredictable"(WWW1). To indicate the magnitude of BZ's role in the Army's chemical arsenal at that time, military records reveal that in 1962 alone two million dollars were allocated to the construction of a facility designed exclusively for weaponizing coventional bombs with BZ. Between 1962 and 1964, over one hundred thousand pounds of the chemical were produced solely for that purpose (Harris and Paxman 1982). With the incapacitating dose (ICt50) of BZ at 110 mg-min/m3, which translates to an effective respiratory dose of about 2 milligrams, the sheer quantity of BZ production reveals the considerable potential of its intended use. Still, in comparison to other chemical agents stockpiled in the US arsenal such as nerve and blister agents, the quantities of BZ were relatively small (SIPRI 1973).

The Army factsheet indicates that the primary method of dispensing BZ was in aerosol form, which would facilitate entry into the body via the respiratory system (WWW1). However, the possibility of BZ as a contact hazard is documented by the record of a chemical defense employee's resultant incapacitation after exposure through a punctured rubber glove (SIPRI 1973). Additionally, BZ's ability to penetrate the skin could be magnified 25 times or more by solvating in dimelthylsulfoxide, or DMSO (SIPRI 1973 cit. Stroughton 1964). Quinuclidinyl benzilate is a glycolate

ester (SIPRI 1973) and a potent competitive inhibitor of acetylcholine at postganglionic muscarinic synaptic sites, although in high doses it can also affect nicontic sites as well (Voth 1994). Pharmocologically, it acts on central and peripheral nervous system like atropine, but with a much longer duration, blocking the action of acetylcholine in the brain as well as in the peripheral nervous system (WWW2) and directly at base organs. Both atropine and BZ are tertiary amines, posses a similar structure (SIPRI 1973) and have the ability to cross the blood brain barrier. The basic signs of acute exposure outlined in the Army factsheet are increased heart and respiratory rates, pupil dilation (involving contraction of the dilator muscles), paralysis of eye muscles used for near focusing, dryness of skin and mouth, elevated body temperature, impaired coordination, flushing of skin, hallucinations, stupor, forgetfulness, confusion. Within 15 minutes and up to 4 hours after exposure, the principal effects are dizziness, dry mouth, and elevated heart rate. These are followed by restlessness, involuntary muscle movements, rear vision difficulty, and total incapacitation. The final symptoms occur 6-10 hours later and are listed as "psychotropic in nature." Full recovery is expected after 4 days (WWW1 and Glanze 1986).

The symptoms of BZ exposure listed above are consistent with those linked with atropine poisoning: dry mouth, difficulty swallowing and talking, blurred vision, increased heart rate, dry/flush skin, rash on face, neck, and upper chest, increased ventilation, and increased temperature due to atropine's secondary inhibition of sweating. The nicotinic effects of atropine overdose include orthostatic hypotension, attributable to an overall decrease in vascular tone, and skeletal muscle weakness, which has also been indicated in soldiers exposed to BZ in controlled tests (WWW2). High doses of atropine, and especially of other anticholinergics such as scopolamine, can lead to restlessness, confusion, delirium, and even seizures, coma, and respiratory failure due to medullary ventilary center paralysis (Voth 1994). The sites of primary anti-muscarinic activity are the heart, salivary glands, and smooth muscle of the gastrointestinal and genitourinary tract (Negele 1997). Atropine increases the heart rate by slowing down some parts of the nervous system while simultaneously speeding up other parts (WWW3). Clinical uses of atropine as well as other anticholinergics include pre-operative sedation and antisialagogue (i.e. saliva inhibiting) effects, treatment of reflex-mediated bradycardia, and the reversal of non-depolarizing neuromuscular blocking drugs when administered with acetylcholinesterase (Negele 1997).

Although BZ is similar in structure and effect to atropine, subtle structural differences can contribute to remarkable changes in pharmocologic effects. For example, scopolamine and atropine differ only by a single oxygen atom attached as cyclic ether (SIPRI 1973), but scopolamine is most often selected for its sedative effect over atropine because it is 100 times more potent than atropine in depressing the reticular activating system (Negele 1997), a network of nerve fibers extending throughout the thalamus, hypothalamus, brainstem and cerebral cortex

which control the functions of attention, concentration, alertness, and introspection (Glanze 1986). Thus while BZ is structurally similar to atropine and scopolamine, and is often compared to the two in terms of its physiological and psychological effects, the possibility exists that pronounced pharmacological differences exist between BZ and other anticholingerics which could limit the value of the comparisons. The chief antidote for BZ is physostigmine, an anticholinergic inhibitor which reversibly binds to and inactivates anticholinesterase (Harvey and Champe 1992), usually administered via intravenous administration at 15-60 ug/kg (Voth 1994).

Major James S. Ketchum, who participated in research experiments at the US Army Chemical and Research and Development Laboratories at the Edgewood Arsenal in Maryland, published a 1963 technical memorandum (WWW2 cit. Ketchum 1963) which detailed BZ's effects on 362 human subjects (Marshall 1979). The report provides elaborate physiological descriptions obtained from secretive test performed on soldiers at the Dungaway Proving Ground in Utah in late 1964 under codename "Project Dork", and in Hawaii in 1966 and 1967. (Harris and Paxman 1982). Ketchum's reports is sufficiently detailed to reveal in some instances the military's intended use of the incapacitant, as illustrated by phrases such as "individuals in the vicinity of those who are affected or exposed may be recognized or be mistakenly identified."

Ketchum describes the first stage of BZ incapacitation, which lasts up to 4 hours, as characterized by feelings of discomfort and apprehension, manifested through extreme restlessness, muscle spasms in the extremities, and "bird-like flapping of the arms". The second stage lasting from 4 to 12 hours is marked by a sedated, stuporous inactivity. Individuals may sleep or appear to sleep and respond only to forceful stimulation, and alternatively may grope or crawl spontaneously after periods of lying still. The most extreme effects occur 12 hours after exposure: hallucinations take over individual perception and real events and objects are either ignored or grossly misinterpreted. Complex paranormal hallucinations continue 24 to 48 hours after exposure which can be merely amusing or intensely frightening. Attempts to converse with people not actually present can occur, and vertical objects can be misinterpreted for people. Ketchum concludes that there is "little difference how intelligent, adventurous, self-confident or competitive the individual might be; the agent apparently disables the strong and weak impartially without prejudice" (WWW2 cit. Ketchum 1963).

Most records of military experiments involving BZ are still classified and prolonged attempts to obtain them through the Freedom of Information Act have been unsuccessful (WWW2).A group called American Citizens for Honesty in Government, part of the Church of Scientology, tried to locate

former soldiers who were exposed to BZ during Army experiments by placing full-page advertisements in newspapers during the summer of 1979. They found 30 former volunteers who claimed residual after effects including memory gaps, difficulty concentrating, and occasional flashback hallucinations (Marshall 1979).

The Army's involvement with BZ can be traced back to the Chemical Corps's increasing interest in the 1950's in exploring chemical warfare agents which were not lethal, but merely "incapacitating." According to a 1968 Army technical manual, an incapacitating agent is:
"any compound which can interfere with the performance of military duties. In actual usage, however, the term has come to refer primarily to those agents which- (1) Are highly potent and logistically feasible. (2) Produce their effects mainly by altering or disrupting the higher regulatory activity of the central nervous system. (3) Have duration of actions of hours or days, rather than momentary or fleeting action. (4) Do not seriously endanger life except at doses exceeding many fold the effective dose, and produce no permanent injury." (TM 8-285 1968)

With a therapeutic index of approximately 1000 (SIPRI 1973), BZ fit the profile as an ideal chemical incapacitant.

As for the origins of BZ, the late 1950's and early 1960's were characterized by cooperation between civilian drug researchers and Army laboratories. During this time pharmaceutical companies were submitting drugs which had undesirable side effects to the Army's Chemical Corp with regularity:"The most important trend to emerge from the search for new agents over recent years is another example of the ironic twist so common in this field: the aim is to borrow knowledge from the pharmacologists in the hope of converting medically useful drugs into weapons of war. The establishments concerned have expressed interest in compounds which produce heat stroke, fainting, high blood pressure, muscular tremors and nausea- the very side- effects which drug houses spend so long on trying to eliminate. During 1962 about 400 possible drugs a month were supplied to the US Army Chemical Center for further testing (Clarke 1968)."

The patent for the process of making BZ was approved in 1962 and filed under an individual affiliated with the New York based Food Machinery and Chemical Corporation, an innocuously titled company which received multi-million dollar contracts from the Pentagon for designing and manufacturing large quantities of VX nerve gases, as well for conducting studies on growing biological warfare viruses in fertile eggs (Hersh 1968).

Cognizant of the fact that much of the Army's Chemical Corps's R&D budget was influenced by public opinion indirectly and Congressional approval more directly, the division began a public relations campaign in

1959 dubbed "Operation Blue Skies" with the goal of presenting the new chemical incapacitants as type of "humane warfare" which could win wars merely by temporarily stunning the enemy, avoiding the typical destruction of dwellings, infrastructure, and human life which characterized more conventional forms of warfare. In addition, the effort was to distance the incapacitants from the more infamous, deadly and disfiguring chemical agents such as nerve gases and blistering agents used in the first World War and elsewhere. Popular newspapers and magazines during the early 1960's published articles with titles such "War without Death" and "Silent Weapons Aired", which may have been encouraged with funding from Operation Blue Skies.

While army officers lobbied at closed Congressional hearings in praise of non-lethal chemical weaponry, academics at technical conferences were entertained with speeches extolling the virtues of psychochemicals as weapons. Dr. William S. Summerson, former research director at the Chemical Corps, proclaimed at the 1960 American Chemical Society meeting that military victories could be achieved "with a significant reduction in loss of life- particularly in comparison to the casualties associated with nuclear use" (Hersh 1968).

I**n light of the fact that Congress tripled** the Army's Chemical and Biological Warfare research budget from $38 million in 1959 to $129 million in 1964 (Spiers 1986), Operation Blue Skies was an evident success. A 1963 article in the Wall Street Journal conveyed the tone: "Exotic chemical sprays and powders, now under secrecy-wrapped development, hold promise of permitting relatively bloodless battles. They are designed to temporarily disable, but not permanently injure, masses of enemy troops and civilians. Some typically incapacitate a foe by casting him into a dreamworld of utter depression or witless euphoria." The Washington Star even directly unveiled the formerly secretive testing of BZ in a 1965 article: "New chemical weapons that win by creating confusion rather than death and destruction have proved so successful that they have been quietly added to the Army's arsenal. The latest and best, a gas called "BZ" by the Army, put a number of soldier guinea pigs out of action during field tests at a Utah Army base last November, and did it without harming a man. There are no specific plans for use of the 'benevolent incapacitators,' as one officer described them, even though they show clear tactical and humanitarian advantages over weapons that burn, blast, and tear their victims (Hersh 1968)."

A variety of military training manuals from that era indicate potential covert uses for BZ, such as "to affect the rationality of an important leadership group at some particularly crucial times." (Hersh 1968 cit. TM 3-215). Other manuals point out the potential unpredictability of BZ warning that, "incapacitating agents may cause passive personnel to become dangerously violent" (Hersh 1968). Ultimately, concern with the fact that maniacal behavior had been observed during BZ experiments, as well as

with other hallucinatory incapacitants such as LSD, caused senior Pentagon officers to de-emphasize research into psychochemicals citing the concern that "to confuse key leaders at crucial points in the nuclear age is an invitation to holocaust" (Hersh 1968). Nor could spraying BZ on front-line troops in possession of heavy artillery be considered tactical advantage. Robbing Clarke, author of We All Fall Down- the Prospects of Biological and Chemical Warfare, summed up the apprehension that eventually lead to BZ being excluded from the US Arsenal: "One of the major problems is that it is impossible to predict what effects the hallucinogenic drugs will produce. It is quite conceivable that they will increase belligerency and yet at the same time make a man less effective in his duties. The aim of using such a weapon could hardly be to produce a belligerent, maniacal and depressed machine gun operator or, worse, Army commander with nuclear power at his elbow. Further, there is considerable doubt as to how reversible large doses of such drugs might be; certainly if the doses were really high death could result and permanent psychological changes might be expected from slightly smaller doses (Clarke 1968)."

While there is no conclusive evidence that BZ was used during Vietnam War as the film "Jacob's Ladder" suggests, there is some indication that chemical warfare agents other than riot control gasses and leaf defoliants, such as "agent orange", were considered. A Wall Street Journal article from early 1966 reports that Joint Chiefs of Staff urged President Johnson to "expand" the use of non-lethal chemicals in South Vietnam (Hersh 1968 cit. WSJ 1966). A direct allegation that BZ was deployed in Vietnam was voiced by journalist Pierre Darcourt in France's prominent news magazine L'Express. Darcourt alleged that an offensive involving the 1st Airmobile Division in March 1966 during Operation "White Wing" (Hersh 1968 cit. Darcourt 1966) dropped hand grenades filled with BZ on a force 350-500 Vietcong guerrillas, leaving only 100 survivors. U.S. officials subsequently denied any involvement, and in support of that denial, the Army Chemical Reference Handbooks from January 1970 indicate that BZ was mounted only on 750 pound cluster bombs and field dispensers, not hand grenades (Hersh 1968). However, other references do indicate that BZ was available in small grenade-like 10 pound bombs (SIPRI 1973) which may have been described by Darcourt as grenades. It is also plausible however that covert munitions were stockpiled as well, including BZ in grenade form, as many covert operations took place during the Vietnam War with no official records or lasting documentation.

As for the effects of BZ present in the film "Jacob's Ladder", there is clearly a difference in the film's portrayal of the intended use of BZ versus that of existing chemical warfare literature. The film alleges that BZ was purposely administered to American soldiers to dramatically increase their aggressiveness (Rubin 1990), while the actual intended use of BZ was to temporarily incapacitate the enemy. As for the physiologically effects depicted in the film, it is highly unlikely that a powerful anticholinergic like BZ would induce vomiting, as it has a potent inhibitory effect on the smooth

muscles of gastrointestinal tract as well as salivary glands. Indeed, this effect is part of the anti-motion sickness prophylactic mechanism of scopolamine (Kalant and Roshlau 1990) In a Hollywood movie however, it would be difficult and uninteresting to show a person with decreased GI motility or urinary retention, while it would be far more dramatic to portray an actor vomiting in dry heaves. As for bleeding from the mouth, again, there is no recorded evidence that BZ causes capillary leakage in the mucosal vessels (WWW2 cit. Ketchum 1963), nor do other acetylcholinergic antagonists like atropine or scopolamine. Unlike what the film projected, BZ does not cause convulsions as parasympatholytic alone, although it has been documented to cause "extreme restlessness", apprehension, and spasmodic episodes which could be misinterpreted as convulsions. High doses of atropine have been linked to respiratory failure and convulsions, however (Merck 1992). The soldier clutching his head in pain implied an extreme headache, a symptom that BZ does not cause. Arguably, he could have been suffering from delirium or terrifying hallucinations, but these effects usually don't occur until many hours after the initial exposure. The smiling, stuporous soldier who appeared completely removed from the violence of his immediate environment did manifest the final stages of BZ incapacitation, but again this would take many hours to develop, and the onset would be much more gradual (WWW2 cit. Ketchum 1963).

The most telling scene in Jacob's Ladder occurs at the very end, and depending on interpretation, the scene could completely alter the realism of the film's depiction of BZ. Jacob is shown lying on a cot in an Army's MASH hospital tent. Surgeons leaning over him pronounce him dead, commenting on what a good fight he had put up. Until that point, the hallucinatory flashbacks that plagued Jacob's post war life were commingled with situationally similarly events that occurred immediately after his battle injury in Vietnam, suggesting that his entire post war life might have been merely a powerful hallucination. For example, in his New York apartment he suffers from an extremely high fever and has concerned neighbors leaning over him as he is cooled down in a bathtub with water dripping on his head. This scene is juxtaposed with a flashback in Vietnam in which rainfall is dripping down onto him from the trees and Army corpsmen lean over to dress his wounds and load him on a stretcher. The recurrence and overlap of similar situations depicted in both his post war life and flashbacks to Vietnam makes one wonder if he really left Vietnam at all. Since the final stages of BZ exposure results in a powerful hallucinogenic delirium which can last for several days, it is conceivable that a soldier critically wounded in battle and dying over a period of a day or two, like Jacob, could hallucinate an entire illusory postwar life. In addition, the omnipresence of biblical symbolism and obsession with death saturates the film and suggests a far more allegorical than literal interpretation. Could the scenes in New York, which comprise most of the movie, merely be an hallucinogenic projection of a man's last hours as he lay mortally wounded in combat? If so, then the film Jacob's Ladder is an excellent portrayal of BZ incapacitation from the subjective perspective of a person undergoing its potent hallucinogenic effects just before dying.

While BZ is no longer a part of the US military chemical arsenal, as late as 1986 bombs filled with BZ were stored at the Pine Bluff Arsenal and were still awaiting destruction (Chemical 1986). Surprisingly, BZ is readily available today from many chemical supply companies and can be easily ordered over the Internet (WWW4). An article in a 1979 issue of Science commented on the remarkable ease with which an ordinary citizen could obtain BZ, in this case from the drug company Hoffmann-La Roche (Marshall 1979). Because of its extremely high affinity for the muscarinic cholinergic receptors (Kalant and Roshlau 1990), much more so than atropine or scopolamine, it is often radio-labeled (especially with tritium) and used as neuropharmacological tag in muscarinic receptor binding assays (Liu et al. 1983). A keyword search for quinuclidinyl benzilate on MEDLINE or other scientific journal databases will reveal BZ as the industry standard high affinity ligand for the post-ganglionic muscarinic acetylcholine neurotransmitter receptor research (Iga et al. 1998; Kjome et al. 1998; Ellison et al. 1999; Abi-Gerges et al. 1997; Singh et al. 1994; Lenz et al 1994).

Since the Vietnam War, there have been records of the alleged use of BZ-like chemical arms in Kampuchea by the Vietnamese in late 1970's (Spiers 1986) and in Afghanistan during the Soviet invasion in the 1980's. More recently, an incident in Mozambique in 1992 involving an "atropine-like" agent was brought to the attention of the United Nations, and evidence that an incapacitating agent was used against Bosnians fleeing Srebnica during the war in Bosnia and Herzegovina was documented in 1995 (Seagrave 1981). More specific sources suggest that this may have been BZ or a similar compound. Survivors describe an attack by Bosnian Serbs under the command of General Ratko Mladi in which mortars left unusual lingering clouds of multicolored gases hovering over the refugees. Some of the marchers began to hallucinate and behave irrationally, a few allegedly killed friends or themselves. Further evidence supporting this incident include details from the Serbian Yugoslav People's Army (JNA) military manuals which reveal their possession of chemical incapacitants including BZ and procedures for their implementation. According to eye-witnesses, the attack in Srebnica closely resembled the protocol listed in the manual. Interviews with 35 survivors, UN Personnel and other witnesses, further suggested the use of BZ or a similar incapacitant. Although chemical traces test performed on the clothes and bodies of those who died yielded no physical evidence, the US intelligence community conducted its own investigation into the incident but refused to release its findings to the public, citing that the information could interfere with the Dayton Accords and the international efforts to achieve peace in the region. Most telling is the fact that the Federal Republic of Yugoslavia is the only state in Europe not to have signed the 1993 Chemical Weapons Convention (WWW5), a treaty banning the use of chemical warfare signed by over 120 nations. The Hague's international war crimes tribunal is still investigating the incident. (Phinney 1999).