ANNEX 2: TOXINS

1. Introduction

As a category, toxins have recently acquired greater prominence in the literature on biological warfare *(1, 2)*, though not because of any increase in their potential for weaponization, despite their being among the most toxic substances known today. It is, however, true that some toxins are becoming more accessible to quantity production than they once were.

"Toxin" is a word that has no commonly accepted meaning in the scientific literature. This may be of little account to the health authorities of Member States unless they become obliged to seek international assistance because of a toxin-warfare attack, whether actual or threatened. It may then be important to understand how toxins are treated in the Biological and Chemical Weapons Conventions since, to differing degrees, these two international treaties are potential sources of such assistance.

The 1972 Biological and Toxin Weapons Convention covers "toxins whatever their origin or method of production". It does not define toxins, but its *travaux préparatoires* show that the term is intended to mean toxic chemicals produced by living organisms. The actions of the United States are important in this connection. On 14 February 1970, during the negotiation of the Convention, the United States announced that it had decided to renounce offensive preparations for the use of toxins as a method of warfare. Shortly afterwards, it informed the treaty-negotiating body that toxins "are poisonous substances produced by biological organisms, including microbes, animals, and plants" *(3)*, and it has since reiterated and even expanded that definition in the legislation implementing the Convention in United States law. This states that:

> the term "toxin" means the toxic material of plants, animals, microorganisms, viruses, fungi, or infectious substances, or a recombinant molecule, whatever its origin or method of production, including – (A) any poisonous substance or biological product

> that may be engineered as a result of biotechnology produced by a living organism; or (B) any poisonous isomer or biological product, homolog, or derivative of such a substance *(4)*.

The essence of this definition evidently found favour with all the other States Parties to the Convention, for the Final Declaration of the Second Biological Weapons Convention Review Conference states that "toxins (both proteinaceous and non-proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered" by the treaty *(5)*.

Inasmuch as toxins are both toxic and chemical in nature, they also automatically fall within the scope of the 1993 Chemical Weapons Convention, which states that:

> "toxic chemical" means any chemical which through its chemical action on life processes can cause death, temporary incapacitation or permanent harm to humans or animals. This includes all such chemicals, regardless of their origin or of their method of production, and regardless of whether they are produced in facilities, in munitions or elsewhere.

So, although there is no consensus on the term among scientists, international law regards a wide range of substances as "toxins". At one end of the range are the bacterial toxins, such as botulinum toxin and staphylococcal enterotoxin, both of which have in the past been stockpiled for weapons purposes. They are high-molecular-weight proteins that can at present be produced on a significant scale only by the methods of industrial microbiology. In the middle of the range are the snake poisons, insect venoms, plant alkaloids and a host of other such substances, some of which are becoming accessible to chemical synthesis and others, e.g. curare, batrachotoxin and ricin, have been used as weapons. At the other end of the range are small molecules such as potassium fluoroacetate (found in the plant *Dicephalatum cymosum*), which are typically synthesized by chemical processes when they are needed even though they are also produced by certain living organisms, thereby falling within the legal definition of "toxin". Hydrogen cyanide is another such toxin. It occurs in some 400 varieties of plant, in certain animals, and is synthesized by at least one bacterium (*Bacillus pyocyaneus*).

In the sense of the Biological and Toxin Weapons Convention, "toxin" includes substances to which scientists would not normally apply the term. For example, there are chemicals that occur naturally in the human body that would have toxic effects if administered in large enough quantity. Where a scientist might see a bioregulator, say, the treaty would see a poisonous substance produced by a living organism, in other words a toxin – nor is this unreasonable. Wasp venom, for example, is clearly a toxin, yet its active principle is histamine, which is also a human bioregulator. Although histamine might not itself be made into an effective weapon, the same cannot necessarily be said for other bioregulators.

Indeed, now that large-scale production processes for biologically active peptides and similar substances are undergoing rapid commercial development, bioregulators and other toxins constitute a field rich in potential weapons as well as pharmaceuticals, and in particular weapons of intense disabling or incapacitating power. It is fortunate, therefore, that this advance in biotechnology should have coincided with the adoption of the Chemical Weapons Convention, since it places its States Parties under the express obligation to ensure that bioregulators and other toxins, like all other toxic chemicals, are used only for the purposes that the Convention does not prohibit.

Some of the toxins that have been weaponized in the past are described below. Others, such as hydrogen cyanide and its derivative cyanogen chloride, are covered in the annex on chemical agents (Annex 1), as is a toxin that is finding widespread use as a riot-control agent, namely oleoresin capsicum, also known as Agent OC.

The bioregulator that, in the 1960s, initiated consideration of these often complex chemicals as weapons was the endecapeptide known as Substance P *(6)*, a tachykinin. Several other bioregulatory peptides have recently attracted similar attention *(7–11)*, but are not discussed here.

2. Bacterial toxins

2.1 *Staphylococcus aureus* enterotoxins

Staphylococcal enterotoxins are a common cause of diarrhoeal food poisoning after ingestion of improperly handled food. They are proteins ranging in size from 23 to 29 kDa, and are thought to work by stimulating the massive release of a variety of cytokines that then mediate the different toxic effects. The toxins are known in at least five antigenically distinct forms, of which type B is the most studied. It is heat-stable and, in aqueous solution, can withstand boiling. It is active by inhalation, by which route it causes a clinical syndrome markedly different, and often more disabling, than that following ingestion. It has been studied as a warfare agent of the incapacitating type. The median disabling dose for human beings by inhalation has been estimated at 0.4 ng/kg body weight. The corresponding lethal dose is estimated as being 50 times larger *(12)*.

Sources

The toxins are excreted by the Gram-positive coccus *Staphylococcus aureus*, which occurs worldwide. The culturing of some strains can yield large amounts of type B enterotoxin.

Main clinical features

When *Staphylococcus aureus* contaminates food products and the resulting preformed toxin is ingested, symptoms – usually nausea, vomiting and diarrhoea – occur within 1–6 hours of eating the contaminated food.

After inhalation of staphylococcal enterotoxin B (SEB), intoxication is apparent within 3–12 hours with the sudden onset of fever, headache, chills, myalgias and a non-productive cough. More severe cases may develop dyspnoea and retrosternal chest pain. If toxin is swallowed, nausea, vomiting and diarrhoea will occur in many patients, and fluid losses may be substantial. The fever, with variable degrees of chills and prostration, may last up to 5 days, and the cough may persist for as long as 4 weeks.

Diagnosis and detection

The diagnosis of inhalation SEB intoxication is clinical and epidemiological. Patient samples are unlikely to test positive for the toxin

following aerosol exposure unless the exposure is large and samples are obtained rapidly. Enterotoxins may be detected in environmental samples using a variety of antibody-based tests.

Medical management

Supportive therapy has proved adequate in cases of accidental respiratory exposure to SEB aerosol. Hydration and oxygenation will require close attention. In severe cases, where pulmonary oedema develops, ventilation with positive and expiratory pressure and diuretics may be necessary. Most patients would be expected to do well after the initial acute phase of the illness, but will remain unfit for normal activities for 1–2 weeks *(13)*. Since the illness is an intoxication, no isolation or other quarantine measures are required.

Prophylaxis

No human vaccine is available, although several are in development, including some that, in animal studies, have been shown to protect against inhalation exposure to SEB. Passive protection has also been demonstrated.

Stability/neutralization

SEB can be detoxified by treatment with 0.5% hypochlorite for 10–15 minutes.

2.2 *Clostridium botulinum* neurotoxins

Clostridium botulinum neurotoxins are the cause of deadly food poisoning from canned foodstuffs that have been improperly prepared. They are proteins of around 150 kDa in size, and in culture are associated with other proteins to form complexes of some 300–900 kDa. There are seven antigenically distinct forms of botulinus neurotoxin, each consisting of two chains, the heavier of which binds to cholinergic synapses. The internalized lighter chain is a zinc protease and acts by cleaving proteins involved in the process of acetylcholine release. Particular substrate specificity varies between the different serotypes and may be correlated with observable differences in speed of onset of botulism and duration of paralysis. Botulinum toxins are the most acutely lethal of all toxic natural substances. As dry powder, they may be stable for long periods. They are active by inhalation as well as ingestion, the clinical picture being much the same by either route. They have long been studied as warfare

agents of the lethal type *(14)*, particularly, though not exclusively, types A and B. The median lethal dose of type A for humans by inhalation has recently been estimated at 2 ng per kg body weight. By ingestion, the dose is estimated to be some three times smaller *(12)*.

Sources

The toxins are excreted by the Gram-positive spore-forming bacillus *Clostridium botulinum*, which occurs in soil and aquatic sediments worldwide, and which grows and produces neurotoxin under anaerobic conditions.

Main clinical features

Botulism, in the natural form caused by ingestion of bad food, is a dramatic disease that is frequently fatal for animals and humans alike, causing 60% mortality in reported cases before 1950. It is well described in the medical literature *(15)*. Inhalation botulism, on the other hand, is rare, but efforts have recently been made to describe it systematically *(12, 13, 16)*.

Following inhalation exposure, symptoms may begin within 1–3 days; the smaller the dose, the longer the onset time. At the start, bulbar palsies may be prominent, with eye symptoms such as blurred vision due to mydriasis, diplopia, ptosis and photophobia, as well as other bulbar signs such as dysarthria, dysphonia and dysphagia. Skeletal-muscle paralysis follows, with symmetrical, descending and progressive weakness. This may culminate abruptly in respiratory failure.

Diagnosis and detection

Misdiagnosis of botulism is frequent *(16)*. It may be confused with stroke, for example, Guillain–Barré syndrome or myasthenia gravis. Several diagnostic tests should therefore be performed to rule out these other syndromes, since waiting for the definitive diagnosis of botulism can take days, and patients need to have treatment immediately. Diagnosis depends on identifying the presence of toxin in blood samples, using some form of antigen–antibody reaction. In the natural disease, the bacterium and/or preformed toxin may be identified in unconsumed food samples.

Medical management

The treatment of severe cases of botulism is essentially supportive, with mechanical ventilation. Administration of immune globulin (either

human or despeciated equine) to neutralize toxin not already bound to cholinergic synapses can help. The most serious complication, and the most common cause of death in botulism, is respiratory failure secondary to paralysis of the respiratory muscles. Intubation and ventilatory assistance will be needed, and tracheostomy may be required. There is no infection and thus no requirement for isolation or special hygiene measures.

Prophylaxis

Toxoid vaccines against types A–F have been produced and evaluated in animal and human studies. Type A toxoid has a product licence in the United Kingdom. The present toxoid vaccines require several doses over a period of weeks to produce protection. Primate studies have also demonstrated passive protection against inhalation or injection of toxin by equine or human immune globulin *(17)*. The level of protection depends entirely on the stoichiometric relationship between the amount of circulating antibody and the amount of toxin to which an individual may have been exposed.

Stability/neutralization

Botulinum toxins are rather easily inactivated. In food or drink, heating to an internal temperature of 85 °C for more than 5 minutes is sufficient. In the airborne state, the toxin is degraded by extremes of temperature or humidity. The rate of decay of aerosolized toxin has been estimated at 1–4% per minute, depending on the weather conditions *(16)*. Contaminated surfaces should be cleaned with 0.1% hypochlorite solution if they cannot be avoided for the few hours to days that natural degradation would require.

2.3 Aflatoxins and other fungal toxins

Before the 1960s, there was little systematic attention to fungal toxins as important causes of illness; the literature has developed mostly since the conclusion of the Biological and Toxin Weapons Convention. It is now well known that some fungi produce a single toxin, others may produce many, and different fungal genera may produce the same mycotoxin. Many genera, including *Acremonium*, *Alternaria*, *Aspergillus*, *Claviceps*, *Fusarium* and *Penicillium* produce mycotoxins. While the evidence indicates that ingestion of mouldy fodder is the primary route to animal mycotoxicoses, airborne fungal spores and infested/infected plant

particulates may also induce disease leading to death in both animals and humans *(18)*. The weapons potential of such airborne toxins has not been disregarded, although, in the 1992 returns of information under the BWC confidence-building measures in which the Russian Federation declared offensive biological research and development programmes during the period since 1946, it is stated that "in the opinion of the experts, mycotoxins have no military significance" *(19)*.

Nevertheless, two categories of mycotoxin have been considered as warfare agents, namely the aflatoxins and the trichothecenes, and will be considered briefly here. The United Nations Special Commission (UNSCOM) on Iraq mentioned weaponization of an aflatoxin in its synoptic report of January 1999, stating that the "question remains open regarding the aims and reasons of the choice of aflatoxin as an agent". However, it went on to report that one Iraqi document "refers to military requirements to produce liver cancer using aflatoxin and the efficacy against military and civilian targets" *(20)*. The trichothecenes were the subject of allegations of weapons use ("yellow rain") in Cambodia and the Lao People's Democratic Republic during 1975–1984 that have since been discredited *(21)*.

Aflatoxicosis in humans is associated with the consumption of aflatoxin from food contaminated with the mould *Aspergillus flavus*. A number of aflatoxins with a range of potency ($B_1 > G_1 > B_2 > G_2$) are produced by *Aspergillus*, the relative proportions depending on the species of mould. Jaundice, fever, ascites, oedema of the feet, and vomiting are the symptoms associated with aflatoxicosis. In 397 patients estimated to have consumed 2–6 mg aflatoxin daily for a month, 106 fatalities occurred. Fatalities also followed estimated intakes of 12 mg/kg of aflatoxin B_1. Five-year follow-up of survivors of acute poisoning (including liver biopsies) showed almost complete recovery. The principal concern with aflatoxin (particularly B_1) is the possibility of liver cancer associated with the chronic consumption of mouldy food.

Aflatoxin chemistry and metabolism are well described. Aflatoxin B_1 is metabolized to a range of metabolites by microsomal systems. The active metabolite is presumed to be aflatoxin B_1 8-9 epoxide. Inactivation is dependent on glutathione conjugation, with susceptibility to acute intoxication dependent on the activity of the enzyme glutathione-S-transferase. The B_1 epoxide binds covalently to a range of proteins that

have both structural and enzymic functions. Protein phosphorylation is also altered by aflatoxin B_1. All aflatoxins are genotoxic *(22, 23)*.

Trichothecene mycotoxins are a group of structurally related toxins produced by the *Fusarium* fungi found on many crops, and also by other mould genera such as *Stachybotrys*. They are sesquiterpinoids of low molecular weight, in the range 250–550 Da. Two of the better known toxins are T-2 and deoxynivalenol (or vomitoxin). Symptoms caused by the toxins are wide-ranging and include vomiting, diarrhoea, ataxia and haemorrhaging. The toxins are immunosuppressants and inhibit protein synthesis at the ribosomal level. They bind to the 60S subunit of eukaryotic ribosomes, altering peptidyl transferase activity. Inhibition of enzyme activity depends on toxin structure, and results in the failure either of polypeptide chain initiation or elongation. Toxicity of the toxins in in vitro test systems varies by as much as four orders of magnitude *(24)*.

In animals, the toxicity of T-2 is markedly species-dependent. Vomiting is induced in cats at 0.1–0.2 mg/kg after oral dosing. Guinea-pigs are unaffected at 0.75 mg/kg per day in the diet, but develop irritation and ulceration of the gut at 2.5 mg/kg per day. Immunosuppression is observed in rhesus monkeys at 0.5 mg/kg and in mice at 20 mg/kg. The LD_{50} in mice following intraperitoneal administration is reported to be 5.2 mg/kg. The toxicity of the trichothecenes in comparison with other toxins is therefore relatively low. They are, however, unusual among toxins in their ability to damage the skin, causing skin pain, pruritis, vesicles, necrosis and sloughing of epidermis.

The Joint FAO/WHO Expert Committee on Food Additives assessed the safety of aflatoxins and trichothecenes in food at its 56th meeting in February 2001 *(25)*.

2.4 Algal and other plant toxins

2.4.1 Saxitoxin

Saxitoxin is one of the phycotoxins that contribute to paralytic shellfish poisoning. It can also, though with difficulty, be synthesized. Consumption of seafood contaminated with marine algal toxins may cause either paralytic or diarrhoeal shellfish poisoning (PSP or DSP). In addition to their production by marine algae, PSP toxins can also be

made by certain bacteria, cyanobacteria and red algae. Depending on the substituent side-groups, these are small molecules of around 300 Da. The parent compound, saxitoxin itself, is a powerful neurotoxin that binds with high affinity to sodium channels on cell membranes, inhibiting influx of sodium ions into cells without altering potassium ion efflux. Cell action potentials are suppressed, and paralysis results, the extent of which is dose-dependent. Saxitoxin binding to sodium channels is reversible. The toxin is soluble in water and stable, and dispersal as an aerosol is feasible. Fatalities in adults have been reported following ingestion of 0.5–12.4 mg. Minimum lethal doses in children are estimated to be 25 µg/kg *(26, 27)*.

Sources

The PSP toxins, including saxitoxin, can be isolated from bivalve molluscs, such as the butterclam, *Saxidona giganteus*, that have accumulated PSP-producing dinoflagellates, such as *Gonyaulax catanella*, during feeding. In one reported experiment, about 8 tonnes of clams were processed to produce a single gram of saxitoxin *(28)*.

Main clinical features

Reported clinical symptoms describe the outcome of ingestion of saxitoxin. Onset of symptoms is typically within 10–60 minutes. Numbness or tingling of the lips and tongue (attributable to local absorption) spreads to the face and neck, followed by a prickling feeling in fingers and toes. With moderate to severe exposure, the paraesthesia spreads to the arms and legs. Motor activity is reduced, speech becomes incoherent and respiration laboured and subjects die from respiratory arrest. The terminal stages may occur within 2–12 hours. No cases of inhalation exposure have been reported in the medical literature, but animal experiments suggest that the entire syndrome is compressed, and that death may occur within minutes

Diagnosis and detection

Diagnosis is confirmed by detection of the toxin, using ELISA or mouse bioassay, in samples of, for example, stomach contents, water or food.

Medical management

No specific antidotes exist, and treatment is symptomatic. The toxin is normally cleared rapidly from the body via the urine, so that victims who

survive for 12–24 hours usually recover. Diuretics may help. Specific antitoxin therapy has been successful in animals.

Prophylaxis

No vaccine against saxitoxin exposure has been developed for human use.

Stability/neutralization

Saxitoxin maintains its activity in water heated to 120 °C.

2.4.2 Ricin

Ricin is a highly toxic glycoprotein (a lectin) of approximately 65 kDa that occurs in the seed of the castor oil plant, *Ricinus communis*. Ricin consists of two protein chains, the larger (B chain, 34 kDa) attaching to cell surface receptors and facilitating entry of the smaller (A chain, 32 kDa), which affects cellular ribosomal activity. It inhibits protein synthesis in eukaryotic cells, and is toxic by all routes, including inhalation, but least so by ingestion. Horses are the animals most susceptible to ricin, cattle and pigs less so, with ducks and hens the least susceptible. In mice, the systemic LD_{50} is 2.7 µg/kg *(12, 13)*.

Sources

Ricin can be extracted relatively easily from castor oil beans, about 1 million tons of which are processed per year in the production of castor oil. Ricin accounts for some 5% by weight of the waste mash.

Main clinical features

A latency period of many hours, sometimes days, follows exposure. After inhalation, significant lung pathology is evident, with increased cytokine concentrations, marked inflammation and pulmonary oedema. Ingestion results in severe gastroenteritis, often haemorrhagic. Convulsions, shock and renal failure may develop. Nerve cells, the heart and spleen are all affected by ricin. Ricin dust exposure will cause local irritation of eyes, nose and throat *(26)*. Sublethal lung pathology has been described in immunized mice following inhalation challenge with aerosolized ricin. Survivors of a ricin aerosol challenge may therefore experience some injury, particularly to the lungs.

Diagnosis and detection

The primary diagnosis is clinical and epidemiological. Specific ELISA testing on serum or immunohistochemical techniques for direct tissue analysis can be used to confirm the diagnosis.

Medical management

Management is supportive and should include maintenance of intravascular volume. No antitoxin is yet available.

Prophylaxis

There is no currently approved prophylaxis for human use, though both active immunization and passive antibody prophylaxis are under study. Formaldehyde toxoids against ricin have been used successfully to immunize rats. Toxoid was administered subcutaneously in 3 doses at 3-weekly intervals and prevented deaths in animals exposed to 5 LCt_{50} by inhalation challenge *(29)*.

Stability/neutralization

Ricin is soluble in water, the solution being less stable than the dry product. In the dry state, it is normally stable at room temperature but denatures at elevated temperature, the stability decreasing with increasing moisture content *(30)*.

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