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Threat Assessment of Mycotoxins as Weapons: Molecular Mechanisms of Acute Toxicity

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ABSTRACT

Mycotoxins are impractical as tactical weapons, but they can be used by small poor terrorist organizations to poison food and water sources or can be released in crowded, confined areas. Crude concentrated or dried extracts of readily grown fungal cultures can be used as weapons. The production of fungal weapons does not require elaborate facilities for the growth of fungi, sophisticated equipment for the purification of the toxins, or highly trained personnel. Aflatoxin B_1, fumonisin B_1, ochratoxin A, and the trichothecenes T-2 toxin and deoxynivalenol could be weaponized for bioterrorism. Knowledge of the symptoms of intoxication and the biochemical mechanisms of action of mycotoxins is necessary for the rapid identification of the toxins, the development of prophylactic antidotes, and the design of effective treatments of affected persons. All of these mycotoxins except deoxynivalenol are carcinogens (Stark, A. A., *Annu. Rev. Microbiol.* 34:235–262, 1980; Stark, A. A., p. 435–445, *in* P. S. Steyn and R. Vleggaar, ed., Mycotoxins and phycotoxins, 1986; Stark, A. A., p. 47–60, *in* C. L. Wilson and S. Droby, ed., Microbial food contamination, 2000; Stark, A. A., and N. Paster, p. 60–64, *in* M. L. Wahlqvist, A. S. Truswell, R. Smith, and P. L. Nestel, ed., Nutrition in a sustainable environment, 1994). Because immediate and widespread death, illness, or panic is the goal of bioterrorists, the mechanisms by which mycotoxins exert acute toxicity are the focus of this article.

The events that took place in the United States on 11 September 2001 taught us that machete-swaying armies, concentration camps and crematoria, and expensive bioweapons laboratories are not needed to cause global havoc. For example, the number of fatalities due to the dispersal of aerosolized potent toxins via the ventilation systems of the North and South Towers could have been larger than the number of people who actually perished in the attacks on 11 September. In the absence of alarming signs such as blast, fire, or suspicious odors and because of the lack of real-time detection and alarm systems for toxins, there would be no reason to escape, and it would be too late to do so when signs of intoxication become evident. Mycotoxins would be suitable for such actions of sabotage. The potent acute toxicity and chemical stability of aflatoxin B_1 (AFB_1), fumonisin B_1, ochratoxin A (OTA), and the trichothecenes T-2 toxin and deoxynivalenol (DON) make them likely to be weaponized for bioterrorism. The publicly available literature includes information for production of these mycotoxins by fermentation and for their extraction and purification.

Some mycotoxins may already have been used as weapons. The Soviet Union was alleged to have provided mycotoxins to the armies of Vietnam and Laos to use against resistance forces in Laos and Cambodia and to have used mycotoxins in combat operations in Afghanistan *(91)*. The indirect evidence was based on the ''yellow rain'' incidents in Southeast Asia and Afghanistan that were associated with toxicity syndromes typical for exposure to trichothecene mycotoxins *(41, 64, 79, 91, 95)*. Although illogical from the tactical point of view, aflatoxins (AFs) were loaded by the Iraqis into warheads and bombs in preparation for the Gulf War but were not used *(26, 70, 100)*.

THE BIOCHEMICAL BASIS FOR THE ACUTE TOXICITY OF MYCOTOXINS

Aflatoxins. AFs are toxic and carcinogenic to humans and animals. The liver is the primary target for the acute toxicity of AFs because this organ contains the highest concentration of activating enzymes *(80, 82)*. The main cause of death from acute intoxication is liver hemorrhage, fatty infiltration, and necrosis. Pulmonary edema is another complication induced by AFs *(92)*. AFB_1 was found in the liver, kidney, brain, and intestine of people who died from Reye syndrome, the features of which are identical to those of AF intoxication *(65, 74)*.

Ingestion of food contaminated with AF-producing fungi is the main route of intoxication. Increased incidence of death from various cancers and/or specifically lung cancer among peanut-processing workers who were exposed to grain dust particles contaminated with AFs *(30, 40, 76, 78)* indicates that inhalation may be an important route of exposure during attacks with AF-containing weapons.

Toxicity of AFs depends on activation by enzymes or UV light. AFs are nontoxic but are converted into highly toxic forms through oxidative metabolism by cytochrome P-450. The liver is the major AF-metabolizing organ. Hydroxylations of most positions in the AF molecule result in

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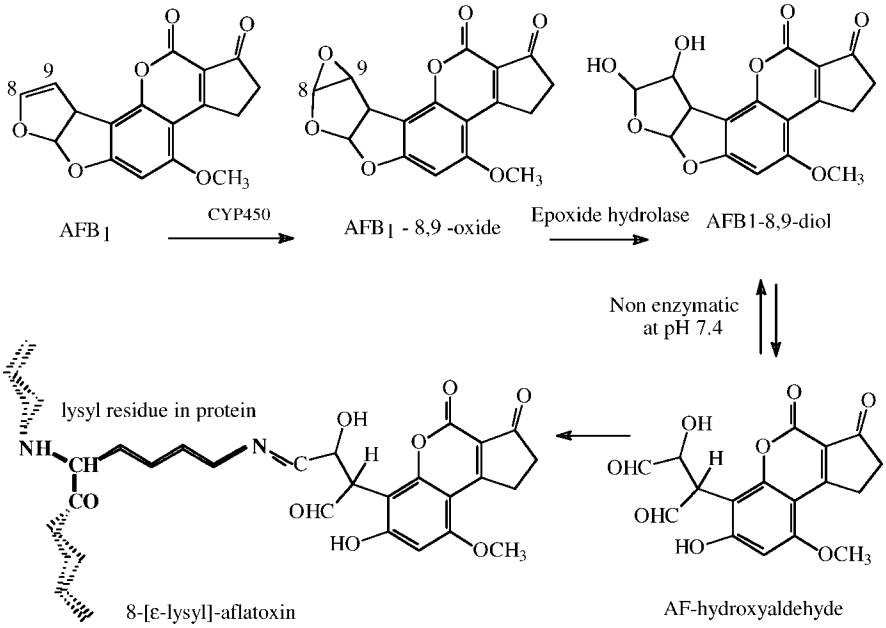

FIGURE 1. *Activation of aflatoxin B_1 to a protein-binding form.*

metabolites that are less toxic than the parental AFB_1. Epoxidation across the unsaturated 8,9 position yields AFB_1-8,9-oxide (Fig. 1). All of the acutely toxic and carcinogenic effects of AFs stem from covalent binding of AF-8,9-oxide to DNA, RNA, and proteins *(20, 81, 83, 97).* Whereas AF-8,9-oxide binds DNA and RNA directly, protein binding requires the conversion of the oxide to AFB_1-8,9-dihydrodiol by epoxide hydrolase. At physiological pH, the diol is in equilibrium with the hydroxydialdehyde, which readily forms a Schiff base with the ε-amino group of lysine on proteins (Fig. 1). Despite the presence of many nucleophiles in proteins, 8-lysyl-AF accounts for most of the protein-bound AF *(73).* The activation of AF in the rodent lung occurs mainly in Clara cells *(16, 22, 61)* and is similar to that occurring in the liver. AF activation in the human lung is performed mainly by alveolar type II cells *(3, 25).* AF is activated also by prostaglandin H synthase and lipoxygenase in lung macrophages *(3, 29, 55).* UV-irradiated AFs are converted into reactive forms, which bind DNA in a manner identical to that of biochemically activated AFs. Photoactivated mixtures of AFB_1 and AFB_2 act synergistically in DNA binding and mutagenesis *(43, 44, 75, 84–86).* Exposure of skin to weapon-delivered AFs in sunlit areas may add to the hazard of inhaled AFs.

Acute damage due to binding of AFs to DNA, RNA, and protein. Covalent binding of AFs to DNA and RNA results in inhibition of replication, transcription, and protein synthesis. Protein binding leads to inactivation of enzymes *(7).* DNA damage, such as replication blocks or strand scissions *(86),* can initiate p53-dependent apoptosis or impair the progression of the cell cycle *(99).* However, mutations in codon 249 of p53 (a hotspot for binding of AFB_1 *(68)*) render cells immune to p53-dependent apoptosis *(53).*

The major mechanism for detoxification of AFB_1 is conjugation of AFB_1-8,9-oxide with glutathione by glutathione-S-transferase, conversion of the adduct to mercapturic acid, and excretion via the urine. Oltipraz is a potent inducer of phase II detoxification enzymes *(56, 62).* It is effective in the chemoprevention of carcinogenesis and alleviation of acute toxicity.

Typical clinical signs of acute aflatoxicosis are hypolipidemia, fatty infiltration, fatty liver, and necrosis *(9, 37).* The exact mechanisms of toxicosis have not been elucidated. A recent hypothesis *(2)* states that binding of AFB_1-8,9-diol to lysine residues in protein B-100 of low-density lipoprotein renders the LDL unrecognizable by the LDL receptors on the membrane of extrahepatic cells. Modification of the lysine residues in LDL leads to their rapid clearance from the plasma by the hepatic Kupffer cells *(59)* and to hypolipidemia and fatty liver.

Immunosuppression often results from acute AF intoxication by inhalation. A single nose-only inhalation aerosol resulted in suppression of phagocytosis by alveolar macrophages that persisted for 2 weeks. Intratracheal instillation of AF that mimics inhalation produced the same result but at doses 10-fold higher than that used for aerosol inhalation, indicating that inhalation is the most effective and hazardous route of exposure *(46).*

Outbreaks of acute aflatoxicosis in humans. The most detailed incident of aflatoxicosis in humans occurred in southwestern India in 1974, where 397 persons in more than 150 villages were affected and 108 died. The major source of exposure was corn contaminated with 0.25 to 15 mg/kg AFB_1. The daily dose was estimated to be 3.85 to 15.6 mg per person, and exposure lasted for many days. The survivors recovered fully from the disease. In one village, an outbreak of acute aflatoxicosis in dogs preceded that in humans *(9, 50).*

Death of many local doves and then death of the local dogs was similarly reported to precede an outbreak of acute aflatoxicosis in Kenya. The daily intake of AFB_1 was estimated to be at least 2.7 mg per person, and the exposure lasted for many days. Twelve of 20 people died in this outbreak *(66).*

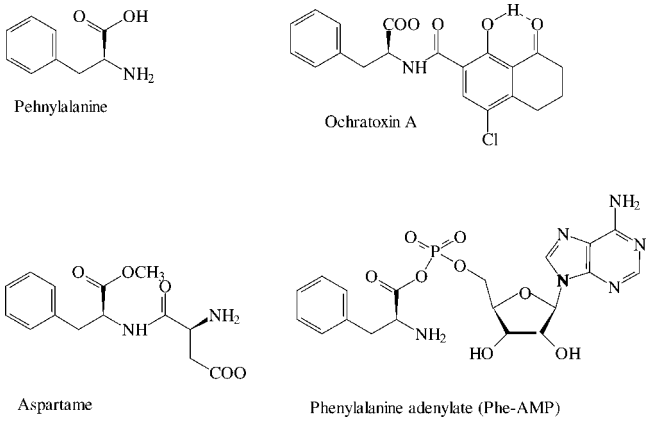

FIGURE 2. *Structural similarities among OTA, phenylalanine, and aspartame may explain the inhibition of phenylalanyl tRNA synthetase by OTA and its reversal by aspartame.*

TABLE 1. *Effect of OTA on he kinetic constants of phenylalanyl tRNA synthetases*

Constant[a]/ligand	Formation of: Aminoacyl adenylate	Aminoacyl tRNA	Reference
K_m for Phe (μM)			
Bacillus subtilis	28	28	*71*
Yeast	NT[b]	1.3	*19*
Hepatoma cells	30	5	*28*
K_i for OTA (μM)			
Bacillus subtilis	800	4,300	*71*
Yeast	NT	1,300	*19*
Hepatoma cells	1,500	1,500	*28*

[a] K_m, Michaelis constant; K_i, inhibition constant.
[b] NT, not tested.

The only known case of ingestion of pure AFB_1 by a human at amounts comparable to those estimated in Kenya did not result in a severe illness or in death. In 1966, a laboratory worker attempted to commit suicide by ingesting a total of 5.5 mg of AFB_1 over a period of 2 days. Six months later, she consumed a total of 32 mg of pure AFB_1 over a period of 2 weeks, after which she developed nausea and headache without other ill effects. Thus, exposure to 2.3 to 2.8 mg/day for up to 2 weeks may represent the no-effect level for AFB_1 in humans. At a 14-year follow-up evaluation, physical examination and blood chemistry results, including tests for liver function, were normal *(96).*

Ochratoxin A. OTA is suspected to be causative agent for Balkan endemic nephropathy, which affects renal tubules, and for various renal tumors. High levels (up to 600 ng/liter) of OTA have been found in the urine of patients with Balkan endemic nephropathy or with urinary tract tumors compared with 37 ng/liter in unaffected people in endemic areas *(13).* OTA is an analog of phenylalanyl adenylate and inhibits Phe-tRNA synthetase (Fig. 2), thus inhibiting protein synthesis but not RNA or DNA synthesis. Analogs of OTA such as Met-OTA and Ser-OTA inhibit the corresponding aminoacyl tRNA synthetases, and the addition of phenylalanine (Phe), methionine (Met), or serine (Ser) abolishes the inhibition, indicative of competition between OTA and the synthetase. Also indicative of competition is the inhibition of OTA toxicity by Phe at a concentration twice that of OTA *(28).* OTA is a kidney-specific toxin. The glomeruli and the proximal tubules incorporate aromatic amino acids into proteins at exceptionally high rates compared with other organs *(23, 87).*

These interactions seem to explain the effective protection from OTA intoxication by the artificial sweetener aspartame (aspartyl-phenylalanyl methyl ester; Fig. 2), a structural analog of OTA and Phe *(5).* Most of the nephrotoxic effects and the genotoxicity (mutagenicity) induced by OTA (289 μg/kg of body weight) were prevented by aspartame (25 mg/kg of body weight). In human terms, this dose is equivalent to the ingestion of 1.75 g of aspartame. Carbonated soft drinks sweetened with aspartame contain 600 mg/liter; thus ingestion of 2.9 liters of aspartame-sweetened soda provides protection from OTA toxicity. The maximum amount of aspartame that an adult weighing 60 kg can safely consume daily is 2.4 g, which is equal to 48 1-g sachets of sweetener containing 5% aspartame or 4 liters of carbonated soft drinks sweetened with aspartame. Aspartame is effective as a prophylactic and for flushing out the toxin even 2 weeks after intoxication *(18).*

Recent evidence based on biochemical *(19, 28, 71)* and molecular *(63)* modeling indicates that the high LD_{50} of OTA probably stems from its low affinity to Phe-tRNA synthetase because the kinetic constant of inhibition of the formation of phenylalanyl adenylate (Phe-AMP) and of phenylalanyl tRNA by OTA suggests very poor competition (Table 1).

OTA readily binds proteins; 95% of the OTA given orally or intraperitoneally was bound to plasma proteins, primarily albumin. Stable binding and very long half-lives in plasma are typical: 1.3 days in mice, 3 to 5 days in rats and pigs, 21 days in a macaque, and 35 days in a human volunteer *(88).* Free OTA is readily excreted in the urine *(36).* Phe or aspartame may protect against intoxication by binding to albumin, thereby rendering it unavailable to OTA, which in turn is readily excreted.

Fumonisin B_1. Almost all the toxic effects of fumonisin in the liver, kidney, lung, and nervous systems can be attributed to the disruption of the metabolism of sphingolipids. Sphingolipids function as second messengers for cytokines and growth and differentiation factors. Sphingoid bases inhibit the growth of many cells and induce apoptosis. Their concentration increases when the biosynthesis of ceramide is inhibited. Fumonisin B_1 and/or its hydrolyzed form, which are structural analogs of sphingosine and sphinganine (Fig. 3), inhibit ceramide synthesis and lead to the accumulation of sphinganine (Fig. 4), which kills the cells by the induction of apoptosis *(24).*

Sphingosine also is a mediator of apoptosis. It induces the release of cytochrome *c* from mitochondria. Cytochrome *c* activates the apoptosis executioner caspase-7. Fumonisin B_1 induces the expression of gamma interferon and tumor necrosis factor alpha, thus sensitizing cells to apo-

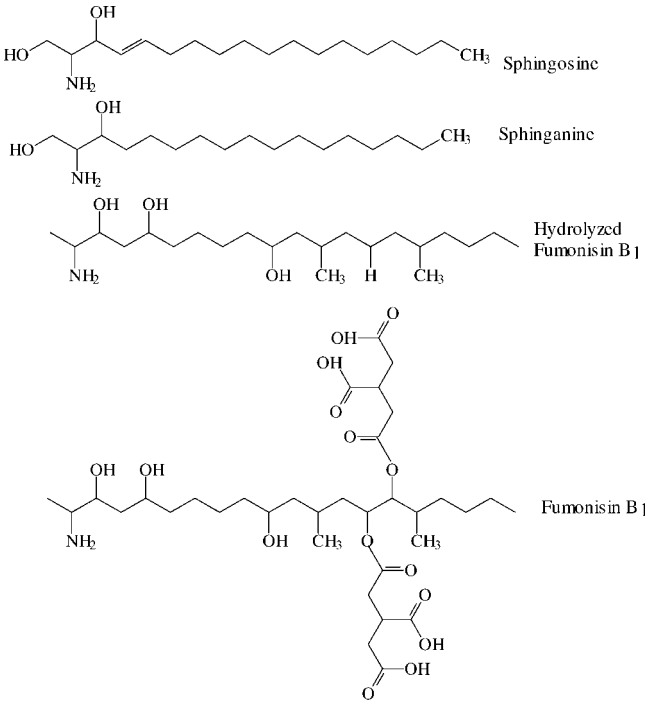

FIGURE 3. *Fumonisin and its metabolites are structural analogs of sphingolipids.*

ptosis *(6, 45, 47).* Special acute forms of fumonisin toxicity specific to pigs are cardiotoxicity and pulmonary edema. The accumulation of membranous material in capillary endothelial cells in the lungs of pigs exposed to fumonisin was thought to alter the permeability of the pulmonary capillaries and to cause the edema *(39).* However, fumonisin induced an increase in the concentration of sphingosine and sphinganine in the left ventricle and the plasma and decreased the functions of the left ventricle and the aorta, affecting cardiac output and decreasing arterial oxygen without changes in pulmonary capillaries *(10, 77).* The current theory is that the increased concentrations of sphingosine and sphinganine inhibit L-type calcium channels. Thus, the acute failure of the left side of the heart leads to the pulmonary edema and not vice versa *(38).*

T-2 toxin and DON. T-2 toxin and vomitoxin (DON) are trichothecenes produced mainly by *Fusarium* sp. Trichothecenes are highly toxic to dividing cells and specifically kill leukocytes. T-2 toxin causes alimentary toxic aleukia. Although it is primarily an immunotoxin, T-2 toxin may act as an immunostimulator. The chemically reactive epoxy moiety is important for toxicity of both T-2 toxin and DON (Fig. 5). Opening of the epoxy ring yields a strong electrophile that can bind nucleophilic centers in macromolecules. T-2 toxin is a potent inhibitor of protein synthesis that binds the 60S subunit of the ribosome, interacts with peptidyl transferase, and inhibits the elongation step. Unlike other trichothecenes, T-2 toxin also inhibits initiation of protein synthesis *(89).* T-2 toxin is a potent inducer of apoptosis in lymphocytes in the thymus and other organs *(42).* In humans, T-2 toxin induced apoptosis in progenitors of megakaryocytes *(35).* Animals exposed to T-2 toxin are much less resistant to bacterial and viral infections.

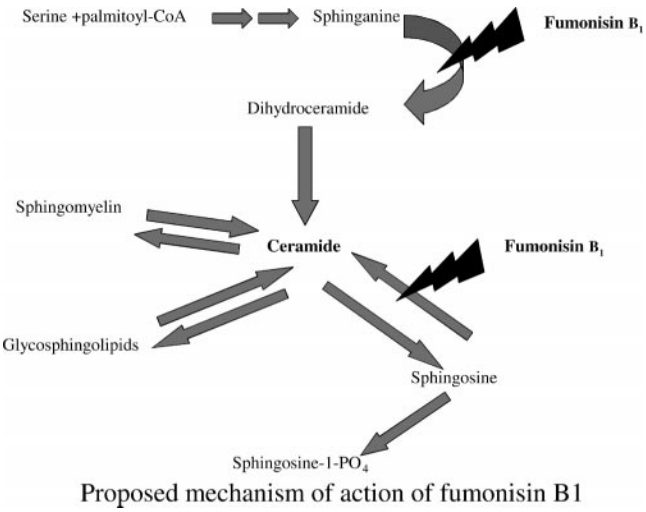

FIGURE 4. *Perturbations of the metabolism of sphingolipids by fumonisin B_1.*

The clinical signs of intoxication with T-2 toxin are diverse. In an outbreak of T-2 toxicosis in China, 60% of 165 people who ate rice contaminated by T-2 toxin suffered from nausea, dizziness, vomiting, chills, abdominal distension, abdominal pain, thoracic stuffiness, and diarrhea, with a latent period of 10 to 30 min *(94).* DON and T-2 toxin damage rapidly dividing cells such as those in the gastrointestinal tract; they cause degeneration and necrosis of the lymphoid tissues and the surface and crypt epithelium of the gastrointestinal mucosa *(98).* At low doses, DON causes anorexia, and at higher doses it induces vomiting by unknown mechanisms. However, because DON alters brain neurochemicals *(72),* anorexia and emesis could be due to neurotoxicity.

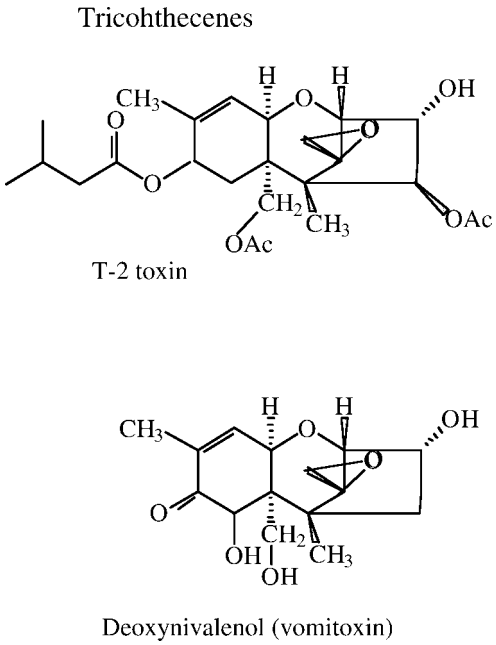

FIGURE 5. *T-2 toxin and deoxynivalenol contain a chemically reactive epoxide.*

TABLE 2. *Mycotoxins are impractical as tactical weapons*

Toxin	Species	LD_{50} (mg/kg)	10% of tactical amount[a]	Medium	Yield	Amount of culture needed to produce a tactical amount
AFB_1	Human	0.15–0.3 *(32)*	48–96 tons[b]	Liquid medium	300 mg/liter *(93)*	1.4×10^7 liters
OTA	Mouse	50 *(51)*	16,000 tons	Wheat solid culture	4 g/kg *(54)*	4×10^6 tons
Fumonisin B_1	Monkey	0.11[c] *(52)*	35 tons	Corn solid culture	32 g/kg mycelium *(57)*	1,100 tons
DON	Mouse	78 *(33)*	25,000 tons	Corn solid culture	175 mg/kg *(14)*	1.4×10^8 tons[d]
T-2	Mouse	0.25 *(34)*	80 tons[e]	Rice solid culture	357 mg/kg *(1, 21)*	2.2×10^6 tons
Ricin	Mouse	0.0025 *(34)*	800 kg[e]			
Botulinum toxin	Mouse	2.5 ng/kg *(34)*	0.8 kg[e]			

[a] The amount needed to cause 50% lethality over 10 km^2, assuming that the acute toxicity for humans is similar to that for mice. The calculation is based on the linear relationship between the LD_{50} in mice and that of Figure 1 of Franz and Zajtchuk *(34)*.

[b] Calculation according to LD_{50} in humans.

[c] No observable effect level in monkeys.

[d] 7.5% of the world annual grain consumption (1.904×10^9 tons).

[e] Values were adapted to 10 km^2 from information in Figure 1 of Franz and Zajtchuk *(34)*, where calculations were done for 100 km^2.

MYCOTOXINS ARE IMPRACTICAL FOR LARGE-SCALE WEAPONS

A linear relationship exists between the LD_{50} in the mouse and the amount of toxin necessary for dispersion as aerosol to induce 50% lethality in humans under optimal meteorological conditions in an area of 100 km^2 *(34)*. Assuming that the acute toxicity in humans is similar to that in mice, the mathematical model corrects for human parameters such as respiration *(34)*. Table 2 shows that the very large amounts of pure mycotoxin required to produce even 10% of an effective tactical weapon are dwarfed when compared with the even larger amount of fungal culture required for the production of mycotoxins, reaching absurdity in the case of DON (7.5% of the annual world grain consumption, which is 1.93×10^9 tons *(8)*).

Weapons alleged to contain toxins might be harmless but can effectively cause havoc. Distribution of gas masks and atropine syringes in Israel after the Iraqi invasion into Kuwait created the impression that chemical or biological attacks were imminent. Thirty-nine Iraqi Scud missiles containing conventional explosives landed in Israel during the Gulf War. Those that reached their targets and did not malfunction killed 2 people and injured approximately 200. These attacks caused 554 patients to suffer from anxiety and 230 patients to inject themselves with an overdose of atropine *(48)*.

CRUDE EXTRACTS OF FUNGAL CULTURES AS WEAPONS FOR BIOTERRORISM

Toxigenic fungi almost always produce several toxins at the same time. For example, *Aspergillus* species produce AFB_1, AFB_2, AFG_1, AFG_2, AFB_{2a}, and AFM_1 and occasionally sterigmatocystin; *Aspergillus* and *Penicillium* species produce OTA, OTB, and OTC; and some *Fusarium* species can simultaneously produce fumonisins B_1, B_2, and B_3. Other *Fusarium* species can simultaneously produce T-2 toxin, diacetoxyscirpenol, nivalenol, and DON.

In areas suspected of being affected by biological weapons (yellow rain) in Southeast Asia and Afghanistan *(41, 64, 79, 95)*, the detection of several related mycotoxins that are produced usually by one fungal species indicates that organizations as large and rich as armies prefer to use crude mycelial extracts rather than purified mycotoxins as weapons. Terrorists also probably would prefer crude extracts to purified mycotoxins. The advantages for the terrorist are the unsophisticated nature of the processes of fermentation and preparation of crude extracts, the relatively unsophisticated equipment and methods of production, and the requirement of only moderately trained technicians. The toxicology of mixtures of toxins is more difficult to evaluate and may complicate the design of countermeasures.

POISONING OF WATER OR FOOD

Poisoning of water or food might be used by bioterrorists to inflict damage. However, poisoning of crops in the field or of grains in granaries and poisoning of central water reservoirs probably would be ineffective because large amounts of mycotoxins would be required. Self-service salad bars were targets of bioterrorism attacks in 1984, in which *Salmonella* Typhimurium was used to contaminate food, affecting 751 persons *(90)*. Exposure of U.S. Postal Service workers to spores of *Bacillus anthracis* in letters resulted in 7 cases of cutaneous anthrax and 11 cases of inhalational anthrax, which caused more panic than actual damage *(4)*. Attacks involving mycotoxins seem to inflict damage and panic of similar or lesser magnitude.

INHALATION OF MYCOTOXINS IS MORE DANGEROUS THAN INGESTION

Dispersion of mycotoxins through the ventilation systems of, for example, public buildings and subway stations might be the method of choice for bioterrorism attacks because this approach is likely to result in the poisoning of many people within a short time. Despite the potential hazard of exposure to weaponized AF dust and despite the fact that inhalation is the most effective route of exposure to

weaponized toxins *(58)*, there is meager information about the acute toxicity of AF dust to humans. Intratracheal dosing of rodents with AF resulted in rapid uptake of the toxin into the lung parenchyma and alveolar macrophages, its appearance in the blood, translocation of a significant portion to the liver, and binding to lung and liver DNA. The lung retained AF adducts longer than did the liver *(7, 15)*. The serious effect of exposure to AF via the respiratory tract was demonstrated by the rapid appearance (30 min postexposure) of AF-DNA adducts in rat liver DNA. Nose-only inhalation of AF resulted in the appearance of DNA adducts in the liver as soon as 10 min after inhalation. The amount of DNA adduct was proportional to the concentration of AF and to the time of exposure *(15)*. In Czechoslovakia, two chemical engineers who had worked on a method for sterilizing peanut meal infected with *Aspergillus flavus* were reported to have died from lung cancer *(31)*.

There has been no report of acute Balkan endemic nephropathy caused by ingested OTA *(67)*, but inhalation of OTA was considered the reason for the development of acute renal failure within 24 h *(27)*. T-2 toxin is 10- to 50-fold more toxic when inhaled than when taken orally *(60)*. In mice, inhalation of T-2 toxin for 10 min was sufficient to induce death less than 5 h later *(17)*. T-2 toxin is readily absorbed through intact skin *(58)*.

The dispersal of mycotoxins through indoor air must be considered a possible route of bioterrorism attacks. Inhalation of mycotoxin-containing spores of mycotoxigenic molds has adverse effects on humans and animals. However, there is no evidence that exposure to spores at concentrations similar to those found in mold-contaminated indoor air of homes, schools, and offices results in adverse health effects *(69)*. The current theory is that the mycotoxin concentrations inhaled in mold-contaminated environments are too low to cause disease *(49)*.

A SIMPLE METHOD FOR THE CHEMICAL DECONTAMINATION OF AFs, OTA, AND T-2 TOXINS

Effective decontamination and destruction of AFs can be achieved readily by the use of household bleach (5.5% sodium hypochlorite in water). Wiping surfaces exposed to aerosolized AFs with a cloth impregnated with household bleach or soaking contaminated equipment in household bleach for 30 min almost completely destroyed AFs, reducing their concentrations to below the limit of detection *(12)*. T-2 toxin and OTA are also sensitive to standard household bleach (soaking for 30 min), especially when the solution is alkalinized *(11, 58)*.

SUMMARY

Mycotoxins are impractical for large-scale tactical weapons but are suitable for use in sabotage operations. Dispersal of mycotoxins in indoor air appears to be the most effective method for bioterrorism attack. A detailed understanding of the mechanism of acute OTA toxicity and the activation metabolism of AFB_1 resulted in the discovery that the ubiquitous and inexpensive sweetener aspartame is very protective against OTA intoxication *(18)* and that oltipraz effectively protects against AFB_1 acute toxicity and carcinogenicity. Further research could reveal antidotes for other mycotoxins.

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