

Sheehan

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
DEPARTMENT OF CHEMISTRY
CAMBRIDGE, MASSACHUSETTS 02139

JOHN C. SHEEHAN
PROFESSOR OF CHEMISTRY, EMERITUS

August 14, 1984

Professor Matthew S. Meselson
Department of Biochemistry and Molecular Biology
Harvard University
7 Divinity Avenue
Cambridge, MA 02138

Dear Matt:

It was good seeing you Sunday, August 12, 1984, at Woods Hole and Falmouth. Enclosed are copies of some of the correspondence with Frank Press concerning "yellow rain." As discussed, I am planning to send a draft copy of a letter to the "Wall Street Journal" for your comments. Hopefully this will be forthcoming within the next few days. I suspect that the other members of the Committee were not aware of the high toxicity of the nerve agents.

Sincerely,



John C. Sheehan
Professor of Chemistry
Emeritus

JCS:ep
enclosures

July 17, 1984

Dr. Frank Press, President
National Academy of Sciences
2102 Constitution Avenue
Washington, D.C. 20418

Dear Frank:

It was good to see you on July 5 at the dinner for Elkan Blout. As we discussed briefly I would be pleased to have my correspondence with you and the NRC staff made available to interested parties. My letters to you dated September 26, 1983 and to Dr. William M. Stigliani on September 9, 1983 are of particular interest. For example, I had a telephone conversation regarding "Yellow Rain" with Mr. Phillip Boffrey(sp?) of the New York Times, but did not feel free to inform him of the aforementioned letters.

My point was that Mycotoxin T-2 (purportedly the most toxic of the group) probably would not qualify as an effective antipersonnel agent, especially in a jungle setting. If one accepts this conclusion the question of whether Mycotoxins have been used is moot.

Hope to see you soon in Woods Hole.

Sincerely,

John C. Sheehan
Professor of Chemistry
Emeritus

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September 26, 1983

JOHN C. SHEEHAN
PROFESSOR OF CHEMISTRY, EMERITUS

Dr. Frank Press, President
National Academy of Sciences
2102 Constitution Avenue
Washington, D.C. 20418

Dear Frank:

I have signed the "Report of the Committee on Protection against Tricothecene Mycotoxins." However, I am taking this opportunity to convey to you personally some reservations which I have concerning this report.

My first concern is that the proposed program, especially the recommendations contained in Chapter VIII, are out of proportion to the challenge, either civilian or military, posed by the evidence. The research effort recommended still seems at an unrealistically high level, although the suggested actions have been moderated considerably in the revised version. The recommendations are open ended with no indication of size of effort in terms of time, budget, manpower and facilities, all of which are limited.

In order to obtain some perspective consider, in no particular order, the medical priority which should be accorded the tricothecenes as compared to cancer, heart, atherosclerosis, diabetes, arthritis, malaria, kidney and liver disorders, new infectious diseases, multiple sclerosis, muscular dystrophy, and so forth.

It is useful to compare the military effectiveness of tricothecene, especially Mycotoxin T-2, with standard chemical warfare agents.

First, omitting live micro-organisms, there are the microbiologically derived agents, such as botulinus toxin. It has been estimated that eight ounces of this substance, properly dispersed, would annihilate the world population. In addition, there is staphylococcal endotoxin, which is considered an incapacitating agent with some lethality.

Second, there are nerve gasses, such as GB, chemically $\text{CH}_3(\text{OC}_3\text{H}_7)_2\text{FPO}$ (Sarin). Related compounds are VX and the binary nerve agents. All are approximately equal as lethal chemicals. The lethal dose of Sarin has been estimated as one milligram per ~~50~~ ⁷⁰ kilogram person.

Third, there are harassing agents, usually vesicants, such as HD, distilled mustard gasses.

Fourth, there are the super tear gasses, such as CS (o-chlorobenzal-malonitrile).

Chapter VI-29, lines 15-17 of the report reads as follows: "De Nicola et al. (1978) reported necrosis of the myeloid tissue of the bone marrow of guinea pigs given T-2 toxin in doses of 2.5 or 5.0 mg/kg bw." Tables 6-2 and 6-3 list the LD₅₀ (mg/kg) of T-2 as approximately 5 mg/kg with various animals. Since GB has a toxicity of approximately 0.02 mg/kg assuming no

Dr. Frank Press, President

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species difference toxin T-2 would be between 100 fold and 1,000 fold less lethal than the nerve agents. If one were interested in lethality GB would be the obvious choice and HD would be the selection as a harrasing agent.

The tricothecene mycotoxins might be attractive for clandestine use in a jungle setting where it might be difficult technically to detect these compounds in the presence of the natural background of toxins. However, given the difficulty of dispersing the agents, it would seem that the use of tricothecene mycotoxins would be only of marginal effectiveness.

The Academy should recommend a greater role for non-military advice, not just feeding in new scientific information, but also expressing opinions on new technology transfer.

I hope the foregoing expresses some of my misgivings. I enjoyed serving on the Committee even though my evaluation of the situation differs from that of many Committee members.

Sincerely,



John C. Sheehan

JCS:lab

P.S. Also please consider my letter of September 9, 1983 to Dr. William Stigliani.

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JOHN C. SHEEHAN
PROFESSOR OF CHEMISTRY

September 9, 1983

Dr. William M. Stigliani
National Academy of Sciences
JH 651
2101 Constitution Ave., N.W.
Washington, D.C. 20418

Dear Bill:

As I discussed with you by telephone, I still have the same concerns expressed in my letter to you of August 12, 1983 concerning the Report of the Committee on Protection Against Tricothecene Mycotoxins. I am especially concerned over the content of the recommendations in Chapter 8 many of which I consider unrealistically broad, and if an attempt is made to implement them in anything like the present form would be unreasonably costly and time consuming and not cost effective.

I have no objections to recommendations 1, 2, and 3 if the size of the programs are kept at realistic levels.

Recommendation 4 is already being investigated in civilian situations.

Recommendation 5 is not only unnecessarily broad, but would require not only an extensive program but also a substantial period of time, presumably years to accomplish. Any study of persistence and study of the products of nonbiological and microbial degradation would clearly require an extensive and long-range project. The necessity for this recommendation is highly questionable. Perhaps the most objectionable in terms of breadth and potential commitment of resources is recommendation 6 which is almost a caricature. This would be a good candidate for the "Golden Fleece Award." This recommendation could be construed at best as an open-ended invitation for almost any type of proposal in this broad area. I had to read this section a number of times before I could believe my eyes. It is my opinion that the National Research Council and the National Academy would be subject to severe criticism by responsible members of the scientific community, if this recommendation is adopted in its present form.

Recommendation 7 would simply be a slight improvement of methodology dating back to World War II, taking advantage of newer fabrics and coatings.

Recommendation 8 does not make much sense to me. It is not clear technically how the recommendations could be implemented.

Recommendation 9 is potentially the most dangerous recommendation of all, since it would propose to "extend to protection against other potent biologically produced toxins." This would include the botulinus toxin, the staphylococcal endotoxin, among others. Historically, a study of methods of protection against chemical and biological agents has been used as an entry into research on offensive

Dr. William Stigliani
Washington, D.C. 20418

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September 9, 1983

military applications of these materials. In the late 1960s the U.S. signed an agreement against the use of biological materials for military purposes, and this recommendation might be used to weaken or circumvent this agreement.

Number 10 is the recommendation this Committee member agrees with most wholeheartedly. In some ways it is a recommendation in favor of applying, but it should be included since even this obviously essential procedure is being challenged.

In summary, I feel that I could not sign this report with the recommendations in their present form. I feel the matter needs to be explored further at an appropriate level and perhaps called to the attention of Dr. Bryce Crawford when the document is reviewed by the Academy itself. I would suggest as further outside reviewers among others Professor Paul Berg, Stanford University, Professor James Watson, Cold Spring Harbor, L.I., N.Y., Professor Paul Doty of the Kennedy School of Government, and Professor Bernard Davis of Harvard University, all Academy members. I am sorry that I feel it necessary to take this stand at such a late stage. You will recall that I was out of the country at the time of the June Committee meeting and by some unfortunate oversight was not sent this last copy and other material until September 7.

Sincerely,



John C. Sheehan

JCS:lab

Chapter 8

RECOMMENDATIONS

Of the many potentially fruitful areas of research described in this report the committee wishes to draw attention to 10 promising areas, which are listed below. The committee recognizes that there are important areas of research other than research on mycotoxins which deserve attention. Thus, the following research recommendations should be examined in light of the benefits and costs of each. An elaboration of these recommendations, and the rationale behind them, appear in the preceding chapters.

1. A systematic program should be undertaken to determine the global distribution of naturally occurring trichothecenes.

2. Efforts should be directed toward the development of protocols for sampling in the field. Further research is needed on the application of thin-layer chromatography (TLC) and the enzyme-linked immunosorbent assay (ELISA) for the identification and quantitation of various trichothecenes present in a variety of sample materials. Other methods that are less promising but nonetheless warrant attention include remote sensing techniques and assays based on the susceptibility of living organisms to trichothecenes.

Gas-liquid chromatography (GLC) and mass spectrometry (MS) should be used to validate new methodologies.

1 3. Chemical and enzymatic reactions that degrade trichothecenes
2 to form nontoxic products should be investigated. The chemistry of
3 the sterically protected epoxide should also be studied.

4 4. Methods of reclaiming trichothecene-contaminated commodities
5 by transforming them into useful foods, feeds, and products should be
6 developed.

7 5. Studies should be conducted to establish the persistence,
8 leaching, and products of nonbiological and microbial degradation of
9 trichothecenes in different types of soils and waters. The
10 persistence of these products should also be determined. Information
11 is required on the uptake by plants growing in contaminated soils and
12 on the behavior of trichothecenes in terrestrial and aquatic food
13 chains.

14 6. To determine the biological effects of T-2 toxin and other
15 trichothecenes, studies should be conducted on (1) the kinetics of
16 absorption, tissue distribution, and toxicity following topical and
17 inhalation exposures under a variety of environmental conditions; (2)
18 the effects produced by simultaneous exposure by multiple routes
19 (e.g., topical, oral, and inhalation); (3) the effects of continuous
20 and intermittent long-term exposures; and (4) the effects produced by
21 combined exposure to trichothecenes and other mycotoxins. These
22 studies should include clinical, clinicopathological, immunological,
23 morphological (i.e., gross, microscopic, and ultrastructural), and
24 functional evaluations. Effects on the cardiovascular, central
25 nervous, and immune systems should be examined in these studies as
26

1 should effects on known target organs and tissues, including the skin,
2 gut, lymphoid tissue, bone marrow, and gonads.

3 7. Investigations are needed to identify the best methods for
4 preventing exposure through the use of protective barriers and
5 decontamination procedures.

6 8. Research is needed to develop methods for reducing the toxic
7 effects of trichothecenes. Studies should be focused on processes
8 that will prevent absorption of the toxin, reduce its binding to
9 ribosomes, and increase its rate of degradation and elimination.

10 9. Studies should not be limited to protection against the
11 effects of trichothecenes but, rather, should extend to protection
12 against other potent biologically produced toxins.

13 10. The continued use of nonmilitary scientific advisors in
14 military research programs is encouraged. After reviewing new data
15 from current research efforts and examining new techniques, the
16 committee recommends that the military draw on the wide expertise
17 which is available in the scientific community, in order to take full
18 advantage of new scientific discoveries and techniques as they are
19 developed.