

MINUTES

TELEPHONE CONFERENCE CALL - NOVEMBER 4, 1980

Participants: Dr. Maas (Chairman)
Dr. Collier
Dr. Bernheimer
Dr. Mason
Dr. Levine
Dr. Gill
Dr. Milewski

Dr. Milewski began the discussion by defining the issue. She noted that the language currently in the NIH Guidelines (Section I-D-2) is ambiguous. She raised some points she thought might be pertinent to the discussion.

Dr. Gill suggested that toxins might be divided into two groups: (1) toxins with no effect on the gastrointestinal tract, and (2) toxins with an effect on the gastrointestinal tract. Dr. Collier asked if any experiments had been performed to determine which toxins had a deleterious effect on this tissue. It was agreed that data on this point did not exist for most toxins.

Several members voiced the opinion that cloning experiments involving toxins should be reviewed on a case-by-case basis. Each toxin is unique and each cloning situation would be unique. They suggested that a committee composed of RAC members and toxinology experts is necessary to evaluate each case.

Dr. Bernheimer advanced the proposal that cloning neurotoxins continue to be prohibited. Work with other toxins could proceed at P3 containment.

Dr. Levine said he found this proposal too restrictive for some toxins: in

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particular he thought the E. coli and Cholera toxins could be worked with at lower containment. He suggested that botulin is in a class by itself. Tetanus toxin, to produce an effect, apparently must be produced by an organism sequestered in the body; he pointed out that many animals carry C. tetani in the gut without suffering any deleterious effects. Dr. Gill said that no experiments have been performed to demonstrate that these organisms are actually producing toxin in the gut.

Dr. Levine objected to the inclusion of shiga toxin in the restricted category. He said he had done experiments in which human volunteers were fed (10^6 to 10^7 organism in sodium bicarbonate) attenuated toxin producing Shigella. He said no symptoms developed as long as the organisms were non-invasive.

Dr. Mason asked for a clarification of Dr. Bernheimer's proposal; he asked what toxins would be used at P3. The group suggested that Pseudomonas aeruginosa exotoxin and shiga toxin of Shigella might be included. It was noted that the gut toxicity of Pseudomonas exotoxin is greater than that of botulin.

Dr. Maas suggested that the committee focus on the pharmacological effect of the toxins themselves. He suggested that the group ignore the question of pathogenicity. He noted that in optimum conditions, a host-vector system might produce much more toxin than the pathogen itself might produce.

Dr. Milewski called the group's attention to the calculations made at the April 1980 NIAID Workshop on Recombinant DNA Risk Assessment in Pasadena, California by Dr. Walter Gilbert. There was some discussion of the numbers used by Dr. Gilbert. Some members felt that Dr. Gilbert's estimate of the number of E. coli in the gut might be low; in certain illnesses the numbers

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could increase. Dr. Milewski asked what the "worst case" scenario of 10^{11} bacteria producing 10^5 molecules of diphtheria toxin every twelve hours would mean for a colonized individual. Dr. Gill replied that this amount is a lethal dose; the tissue of the lower GI tract would be destroyed.

It was suggested that Section I-D-2 should be modified into three categories: (1) prohibited toxins, (2) case-by-case considerations, and (3) toxins which present no significant risk and could be cloned at P2. Cholera toxin and the E. coli enterotoxins LT and ST would be included in the third category. Members also inquired as to the feasibility of including language which would require that the case-by-case proposal be reviewed by experts in toxicology. Several members also asked whether the requests to clone Pseudomonas aeruginosa exotoxin A in E. coli could be re-evaluated by the NIH.

The committee members asked whether NIH would fund a risk-assessment program to examine some of the effect of toxins on the G.I. tract. Dr. Milewski noted that NIAID was letting a contract to study the effect of hormones on the tract, but said that the results might not be available for two or three years. Dr. Gill asked if NIAID might consider combining a contract on the effect of toxins with the study of the effects of hormones.

Dr. Gill proposed a criterion for determining whether a toxin was potent: if 100 micrograms/kilogram of body weight can kill or paralyze the animal. It was suggested that three species of animals would have to be tested both intravenously and intraperitoneally. There were some discussion of this proposed criterion. Dr. Gill agreed to work further on it, and construct language.

Dr. Milewski suggested that the committee members evaluate the discussion and if possible attempt to construct some language. The members agreed to study various aspects of the issue. Everyone agreed to a second conference call to continue the discussion on Friday, November 21, 1980. Dr. Maas suggested in closing that at the minimum the word "potent" be deleted from Section I-D-2.