

# DRAFT

MINUTES - FEBRUARY 23, 1981  
CONFERENCE CALL

Dr. Milewski began the discussion by calling the group's attention to the revised language, contained in a memorandum dated February 2, 1981, concerning the ad hoc group's proposal on toxins (Attachment I). She noted that this language, which was proposed for publication in the Federal Register, had been modified administratively and differed significantly from the language given to RAC at the January 8-9, 1981 meeting (Attachment II). She offered some explanations for the changes.

Dr. Gottesman noted that the language did indeed differ from the ad hoc group's original language. She noted that certain points, addressed by the ad hoc working group, had not been included in the revised language. Dr. Gill agreed. He said NIH had asked the ad hoc working group "what is a potent toxin." The ad hoc working group had replied "it depends" and had attempted to address the question of potency in various situations. He said the revised language (Attachment I) did not include any definition of either potent or toxin. He felt these definitions were indispensable.

Dr. Gottesman asked the group whether they would prefer the Guidelines to provide more guidance for PIs and IBCs in the area of toxins. She asked if the ad hoc working group would prefer an operational definition of a toxin be included in the language. She noted this definition was lacking entirely in the proposed Federal Register language (Attachment I). She questioned whether the hierarchy of containment conditions, originally proposed by the group (Attachment II), should be included in the Federal Register language.

Dr. Gill said that section A and B in the proposed language (Attachment I), were acceptable, but section C as it stands is useless. He said the document

lacked a definition of how innocuous a protein should be to be exempted from consideration as a toxin.

Dr. Gill, noting that section C of the proposed language (Attachment I) would permit cloning of certain enterotoxins under Section III-O, asked Dr. Gottesman to explain the procedural requirements of Section III-O. Dr. Gottesman replied that Section III-O required the use of P1 + EK1 containment conditions. She noted that experiments covered by Section III-O were not reviewed by the IBC prior to initiation. She added that Saccharomyces cerevisiae was included under III-O as a host-vector system and asked if the ad hoc working group accepted that toxin genes could be cloned in S. cerevisiae. Dr. Gill replied that the group had not had the opportunity to consider use of host-vector systems other than E. coli K-12.

Dr. Gill noted that the proposed language (Attachment I) did not provide procedures for evaluating the toxicity of unknown toxins. Dr. Gottesman surmised that the proposed language (Attachment I) was intended to provide greater flexibility in interpretation. She noted, however, that some mechanism of alerting investigators to procedures and toxicities in dealing with new toxins might be necessary. Dr. Milewski suggested that an article in the Recombinant DNA Technical Bulletin might be an appropriate mechanism to publicize known toxicities, and to disseminate information on determining toxicities of new toxins.

Dr. Gottesman asked whether the ad hoc working group felt the Guidelines should contain a list of toxicities and procedures for determining toxicity. She

noted that in approach, the ad hoc group's original proposal (Attachment II) most closely approximates the procedure currently followed in the Guidelines in certifying host-vector systems. She agreed that specific language defining the level at which proteins cease to be potent is necessary. She asked if any special attention need be paid to "non-potent" toxins. The group agreed that "non-potent" toxins may be treated like any other protein under the Guidelines. Dr. Gill said minimally a statement defining "non-toxic" proteins should be published in the Federal Register. Dr. Gottesman agreed that PIs required such language. She suggested that a footnote added to the proposed language (Attachment I), might be appropriate.

Dr. Gottesman questioned which administrative procedure, of those currently used in the Guidelines, would be preferred by the ad hoc working group in determining toxicity. She noted that the Guidelines provided three mechanisms for determining appropriate containment: (1) the PI alone decides, (2) the IBC makes the determination and (3) ORDA and/or RAC evaluates the proposal. She asked the ad hoc working group which procedure they felt to be appropriate for dealing with toxins. Dr. Collier felt the ad hoc working group should have an active input. Dr. Levine and the other members agreed.

Dr. Levine noted that a good concensus had been reached by the ad hoc working group concerning the original proposal (Attachment II). He felt that the historical route, i.e., to begin conservatively and to relax containment conditions as precedent and data become available, is a reasonable way to approach the problem. Dr. Levine agreed with Dr. Gottesman's procedural analogy of

reviewing recombinant DNA proposals involving toxins as one would review and certify host-vector systems.

Dr. Talbot, who had been detained, then joined the conversation. Dr. Gottesman summarized the discussion. She said the ad hoc working group agreed that the proposed Federal Register language (Attachment I) lacked (1) a procedure for handling new toxins and (2) a definition of potency.

Dr. Talbot presented his argument in support of the proposed language (Attachment I). He said footnote 2A in Section I-D-2 referred the reader to a statement indicating that the PI would make the original determination on toxicity. He hoped that under that statement the PI, if doubtful about toxicity, would contact ORDA. An internal guidance document would then be supplied to the PI, who might then perform toxicity testing. He felt the alternative document, with the Federal Register language including toxicity testing instructions, would be complicated and unwieldy.

Dr. Gottesman suggested that the known toxins should be listed in the Guidelines. As other toxins are discovered, the ad hoc working group would evaluate them, and add them to the list.

Dr. Gill suggested that the Federal Register language should accurately reflect the original ad hoc working group language (Attachment II). He felt explicit statements on toxicities would be most helpful to PIs and IBCs. Dr. Gottesman agreed; she said many points developed by the ad hoc working group are not explicitly stated in the February 2, 1981 proposed language (Attachment I). For example, the ad hoc working group had not considered host-vector systems

other than E. coli K-12. Thus they had restricted cloning to E. coli K-12 systems. This point is not clear in the February 2, 1981 memorandum (Attachment I). Dr. Talbot called the group's attention to Section I-D-2. In his interpretation, I-D-2 explicitly states those toxins that are prohibited. If a toxin is not prohibited, it would fall naturally into the other sections of the Guidelines. To restrict cloning to EK systems would essentially be a "tightening" of the Guidelines concerning toxins. He added that self-cloning would also be restricted by the ad hoc working group's original language (Attachment II). Dr. Levine said it was not the intent of the group to restrict self-cloning. He said the committee, because of time constraints, only considered cloning in E. coli K-12. Dr. Gottesman noted that self-cloning permits transfers among organisms on the exchanger lists in Appendix A. She felt the committee had not addressed that question. Dr. Gill pointed out that Section I-D-2 does not actually define "potent" but only offered examples of toxins. Dr. Gottesman agreed. She said the situation requires clarification. The ad hoc working group agreed that some ranges of toxicity should be included in the Federal Register language.

Dr. Collier asked Dr. Gottesman to explain the procedures by which proposals can be reviewed by the NIH. Dr. Gottesman replied that one mechanism requires publication of the proposal in the Federal Register and subsequent action by RAC. A second method does not require publication of the proposal in the Federal Register, but does require RAC action. In a third procedure, ORDA, in consultation with recognized experts, handles the evaluation internally. She noted that the third procedure was the least time consuming and most flexible.

Dr. Gill suggested that a list of information on toxicity be included in the Federal Register language. The list would be constantly updated as additional information became available. In the case of new toxins, the data would be evaluated by ORDA in consultation with the ad hoc working group. Dr. Levine supported Dr. Gill's position. He said PIs should be advised of the existence of this table. Subject to the availability of new data, a toxin may be moved up or down on the toxicity list. Such a table would overcome a great deal of ambiguity.

Dr. Talbot asked the ad hoc working group which of two possibilities they would prefer: (1) the list be published as part of the Guidelines or (2) ORDA maintains a registry and PIs are instructed to contact ORDA. Dr. Gottesman said that the second option would provide greater flexibility. Dr. Gill supported the second option. He suggested, however, that the language in the Federal Register should be as explicit as possible.

Dr. Talbot noted that the ad hoc working group position was reflected in earlier language drafted by Dr. Milewski. He suggested that he, Dr. Gottesman and Dr. Milewski would rework that draft language.

Dr. Levine thanked Dr. Talbot for participating in the conference call. He said he had obtained a better understanding of the administrative problems involved with drafting language for the Guidelines. He hoped Dr. Talbot had been sensitized to the concerns of the ad hoc working group. He agreed that the language proposed by the ad hoc group might be more restrictive than the current Guideline situation but as it is less ambiguous, it may actually encourage more work to be done on toxins.

Dr. Milewski asked the group what time in the next week might be convenient for a follow-up conference call. The group agreed to a call scheduled on March 2, 1981 at 10:30 a.m.