

# STANFORD UNIVERSITY MEDICAL CENTER

## DEPARTMENT OF GENETICS

September 25, 1978

Dr. Maxine Singer  
National Institutes of Health  
Bethesda, Maryland 20014

Dear Maxine:

Here is a summary of my views of the non-E. coli HVL problem, and my proposed solution:

As we have discussed, the proposed NIH Guidelines prohibit the use of any and all host-vector systems (no matter how non-pathogenic the organism) that have not been specifically approved by the RAC. In addition to requiring an unwieldy case-by-case review of each and every instance where someone wants to use a non-E. coli K12 host, this procedure makes the assumption that all non-E. coli systems are dangerous and places the burden of proof for establishing safety on the scientist who wants to use such a system. Omission of a non-E. coli HV system from the "approved" list thus places the system in the prohibited category.

The modification I propose in the Guidelines is a minor addition which addresses the issue of organisms that have not been specifically dealt with by the committee. It does not, in my opinion, represent any substantive change in what the RAC has done; it simply sets forth conditions for carrying out experiments with organisms that the RAC has not previously considered. There is a need for this addition, since as noted above, simple experiments involving introduction of genes from non-pathogens into other non-pathogenic non-E. coli hosts would otherwise be placed in the "too dangerous to be done" category, despite the fact that most scientists would agree that such experiments are among the safest of all.

My suggested wording for this addition is: "Host-vector systems involving organisms that have not undergone review and approval for HVL status, and which are not in etiologic agent class 2 or higher, shall be designated as HV0 systems. Such host-vector systems may be used as recipients for recombinant DNA molecules provided that the physical containment conditions employed are at least one level higher than those required for introduction of the DNA into an HVL host-vector system. Notwithstanding the above, the RAC shall be empowered to specifically designate any host-vector system, regardless of the etiologic agent class, as unsuitable for use for any or all recombinant DNA experiments."

This addition makes unnecessary a strain by strain or organism by organism consideration of host-vector systems that involve non-pathogenic organisms, while still allowing the RAC to preclude use of any specific system that it considers to be unsuitable. It follows the basic principle that an HV system is innocent unless there is a specific reason for anticipating a problem, rather than being guilty unless innocence has been established by a specific vote of the RAC. This presumption of innocence for certain prokaryotic HV systems is based on rational judgment and scientific considerations; a similar presumption has been applied in the proposed Guidelines to experiments involving the cloning of eukaryotic viral DNA, and thus there is an established precedent for it. In addition, the principle of requiring a higher level of physical containment when biological containment is reduced is also well-established in the Guidelines, and has been followed for all sections except those where the committee has specifically recommended otherwise.

The wording I propose would assume that an HV0 organism provides no biological containment whatsoever, and would accordingly require higher physical containment than an HV1 system. If an investigator believes that an organism does in fact provide some biological containment, he then would have the burden of proving this to the committee, in order to have the organism designated as HV1. In that case, the physical containment level could be lowered.

Because of the ambiguity in the current Guidelines that permits non-E. coli non-pathogenic organisms to be considered as equivalents to E. coli K12, experiments that employ B. subtilis, yeast, Neurospora, Streptomyces species, and perhaps some other organisms as recipients have been carried out with the approval of the NIH, NSF, or other granting agencies. In some instances, the timing and standards applied by the different agencies in allowing experiments to be done have been different. The wording of the new Guidelines removes ambiguity, and because of this the Guidelines will require cessation of ongoing investigations that involve the above organisms as recombinant DNA recipients. The wording I suggest will deal with this problem.

A "fall back" position would be to modify the end of my addition to read, "such host-vector systems may be used as recipients for recombinant DNA molecules that include components from organisms below etiologic agent class 2 under physical containment conditions, etc....". I believe the fall back position is far less satisfactory, and hope that you will try for the first wording. The Guidelines already require higher levels of physical containment for DNA from organisms and etiologic agents classes 2 and 3, and a further increase in containment level when HV0 hosts are used should be more than adequate to deal with biosafety concerns, regardless of the source of the DNA being cloned.

Dr. Maxine Singer

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I hope these comments will be useful to you. Please telephone me if you want to discuss this further, and let me know what happens.

Best regards,

Sincerely yours,

A handwritten signature in black ink, appearing to read "Stan", written in a cursive style.

Stanley N. Cohen

SNC:kl