

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH

1321

RECOMBINANT DNA ADVISORY COMMITTEE  
WORKING GROUP ON TRANSGENIC ANIMALS

MINUTES OF MEETING<sup>1</sup>

MARCH 28, 1988

The Working Group on Transgenic Animals, Recombinant DNA Advisory Committee, was convened at 9:00 a.m. on March 28, 1988, at the National Institutes of Health, Building 31, Conference Room 9, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Mitchell Cohen was Chair. The following were present for all or part of the meeting.

Working Group members:

|                 |                 |                       |
|-----------------|-----------------|-----------------------|
| Mitchell Cohen  | Ronald Luftig   | William J. Gartland   |
| Susan Gottesman | Robert McKinney | (Executive Secretary) |
| A. Lynn Harding | Paul Neiman     |                       |
| C. Max Lang     | Fred Rapp       |                       |

The working group roster is attached.

Other National Institutes of Health staff:

Becky Lawson, NIAID  
Dinah Singer, NCI

Others:

Carter Blakey, Federation of American Societies for Experimental Biology  
Alan R. Goldhammer, Industrial Biotechnology Association  
Daniel D. Jones, Department of Agriculture  
Ann Rose, Bionetics Research, Inc.  
Ilga Semeiks, Blue Sheet  
George P. Shibley, Department of Agriculture  
William Szkrybalo, Pharmaceutical Manufacturers Association  
Allan Shipp, Association of American Medical Colleges  
Robert G. Zimbelman, American Society of Animal Science

---

<sup>1</sup>The working group is advisory to the Recombinant DNA Advisory Committee, and its recommendations should not be considered as final or accepted.

Dr. Cohen called the meeting to order and asked Dr. Gartland to summarize the charge to the working group. Dr. Gartland responded that the working group was being asked to consider two issues regarding transgenic animals. The first issue involves transgenic animals that do not technically fall under the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules because the DNA introduced into the animal is not recombinant DNA as defined by the NIH Guidelines. The other issue concerns containment guidelines for experiments involving introduction of recombinant DNA into the genome of animals, particularly experiments involving introduction of DNA from human pathogens.

Dr. Rapp stated that in effect one is doing a recombinant DNA experiment when DNA is introduced into an animal, and these experiments probably should be covered by the NIH Guidelines. He said that essentially the experiment is being done in an animal rather than in a test tube. Dr. Lang agreed and said there will be many more projects of this sort.

Dr. Gottesman noted that the NIH Guidelines generally have not addressed non-recombinant DNA experiments. However, she noted that Section III-A-4, which refers to human gene therapy, covers "recombinant DNA or DNA or RNA derived from recombinant DNA." She said this kind of extension could be considered for transgenic animals.

Dr. Neiman questioned what other review mechanisms are in place for these kinds of experiments. Dr. McKinney responded that oversight committees for experiments involving animals are generally not constituted to review safety. Dr. Lang said an animal committee may not see the entire experimental protocol.

Dr. Gottesman noted that introduction of recombinant DNA into animals is covered by the NIH Guidelines. She said there are two issues here: (1) the experiments involving introduction of non-recombinant DNA into animals, and (2) review procedures for these experiments.

Dr. Singer, chair of the NIH Institutional Biosafety Committee (IBC), noted that a piece of DNA excised from a vector is not considered to be recombinant DNA. She said there is a need to consider transgenic animal experiments as recombinant DNA experiments.

Dr. McKinney said he is unaware of any document other than the NIH Guidelines that could be used to provide guidance to IBCs regarding transgenic animal experiments. Dr. Gottesman said there is concern about broadening the definition of recombinant DNA and again suggested the approach used for human gene therapy, i.e., including DNA derived from recombinant DNA.

Dr. Neiman noted that there are other techniques in which there is no involvement of recombinant DNA, and the field of transgenic animals will have to be monitored as it develops. Dr. McKinney stated that the non-recombinant experiments should fall under the NIH Guidelines.

Dr. Cohen said that he sensed a consensus that certain types of non-recombinant transgenic animal experiments should be covered by the NIH Guidelines.

Dr. Gottesman suggested that the working group work from the proposed changes to the NIH Guidelines recommended by the Recombinant DNA Advisory Committee at its meeting on September 21, 1987. These changes have not yet been promulgated by the NIH.

Dr. Gottesman proposed that the working group recommend a narrow change to cover DNA derived from recombinant DNA, and addition of wording regarding production of potential undesirable traits in the host animal. She noted that changing the definition of recombinant DNA in Section I-B would be a very broad change. Dr. Neiman felt Dr. Gottesman's proposal went a long way to cover the types of experiments under discussion.

After further discussion, the working group recommended that the following proposed changes in the NIH Guidelines be published for comment and considered by the RAC on June 3, 1988.

- A. On September 21, 1987, the RAC recommended that paragraph 7 as published for comment in the Federal Register of August 11, 1987, be incorporated into Section II of the NIH Guidelines as follows:

"Biosafety Level 1 for animals (BL1-N) describes containment which is used for animals in which the germ line has been modified through recombinant DNA techniques (transgenic animals) and is designed to eliminate the possibility of sexual transmission of the modified genome or transmission of recombinant-DNA-derived viruses known to be transmitted only vertically (i.e., transmitted from animal parent to offspring only by sexual reproduction). Procedures, practices, and facilities follow classical methods of avoiding genetic exchange between animals."

The working group recommended that "(transgenic animals)" be deleted from this paragraph.

- B. The working group recommended that the following new sentence be added at the beginning of Section III-B-3 before the paragraph entitled "Caution":

"Experiments involving the introduction of eukaryotic viral genomes into the germ line of animals are covered in Section III-B-4."

- C. On September 21, 1987, the RAC recommended that the title of Section III-B-4 as published for comment in paragraph 32 in the Federal Register of August 11, 1987, be changed to read as follows:

"Recombinant DNA Experiments Involving Whole Animals."

The working group recommended that the title of Section III-B-4 be amended to read as follows:

"Experiments Involving Whole Animals, Including Transgenic Animals."

- D. On September 21, 1987, the RAC recommended that paragraph 34 as published for comment in the Federal Register of August 11, 1987, be incorporated into Section III-B-4 of the NIH Guidelines as follows:

"This section covers experiments involving whole animals, both those in which the animal's genome has been altered by recombinant DNA techniques and experiments involving viable recombinant-DNA-modified microorganisms tested on whole animals. For the latter, other than viruses which are only vertically transmitted, the experiments may not be carried out at BL1-N containment; a minimum containment of BL1 or BL2-N is required."

The working group recommended that this section be amended to read as follows:

"This section covers experiments involving whole animals, both those in which the animal's genome has been altered by stable introduction of DNA into the germ line (transgenic animals) and experiments involving viable recombinant-DNA-modified microorganisms tested on whole animals. For the latter, other than viruses which are only vertically transmitted, the experiments may not be carried out at BL1-N containment; a minimum containment of BL1 or BL2-N is required.

"Caution: Special care should be used in the evaluation of containment conditions for some experiments with transgenic animals. For example, such experiments might lead to the creation of novel mechanisms or increased transmission of a recombinant pathogen or production of undesirable traits in the host animal. In such cases, serious consideration should be given to increasing the containment conditions."

- E. On September 21, 1987, the RAC recommended that a modified paragraph 37 as published for comment in the Federal Register of August 11, 1987, be incorporated as Section III-B-4-a of the NIH Guidelines as follows:

"Recombinant DNA, or RNA molecules derived therefrom, from any source except for a eukaryotic viral genome may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study [2]. Animals containing sequences from viral vectors, if the sequences do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment

comparable to BL1 or BL1-N and appropriate to the organism under study. For experiments involving recombinant DNA modified Class 2, 3, 4, or 5 organisms (1) using whole animals, see Section III-B-1."

The working group recommended that this section be amended to read as follows:

"Recombinant DNA, or DNA or RNA molecules derived therefrom, from any source except for a eukaryotic viral genome may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study [2]. Animals containing sequences from viral vectors, if the sequences do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study. Experiments involving the introduction of other sequences from eukaryotic viral genomes into animals are covered under III-B-4-b. For experiments involving recombinant DNA modified Class 2, 3, 4, or 5 organisms (1) using whole animals, see Section III-B-1."

- F. On September 21, 1987, the RAC recommended that paragraph 41 as published for comment in the Federal Register of August 11, 1987, be incorporated as Section III-B-4-b of the NIH Guidelines, as follows:

"For experiments involving whole animals and not covered by Section III-B-1 or Section III-B-4-a, the appropriate containment will be determined by the IBC (22,23)."

The working group recommended that this section be amended to read as follows:

"For experiments involving recombinant DNA, or DNA or RNA derived therefrom, involving whole animals, including transgenic animals, and not covered by Section III-B-1 or Section III-B-4-a, the appropriate containment will be determined by the IBC (22)."

Dr. Singer asked whether limits should be placed on numbers of animals in the cautionary note. Dr. Rapp responded that numbers would depend entirely on the animal species under consideration. Dr. Gottesman said that IBCs could be advised that scale is an option.

Dr. Rapp recommended that the changes, when adopted, be highlighted in the Recombinant DNA Technical Bulletin.

The meeting was adjourned at 12 noon.

  
William J. Gartland, Jr., Ph.D.  
Executive Secretary

I hereby certify that, to the best of my knowledge, the foregoing Minutes and Attachment are accurate and complete.

Date: \_\_\_\_\_

\_\_\_\_\_  
Mitchell Cohen, M.D.  
Chair  
Working Group on Transgenic Animals  
Recombinant DNA Advisory Committee

---

RECOMBINANT DNA ADVISORY COMMITTEE  
WORKING GROUP ON TRANSGENIC ANIMALS

---

CHAIR

COHEN, Mitchell L., M.D.  
Division of Bacterial Diseases  
Center for Infectious Diseases  
Centers for Disease Control  
Atlanta, Georgia 30333  
404 639-3683

-----  
GOTTESMAN, Susan K., Ph.D.  
Laboratory of Molecular Biology  
National Cancer Institute, 37/4B09  
National Institutes of Health  
Bethesda, Maryland 20892  
301 496-3524

McKINNEY, Robert W., Ph.D.  
Division of Safety, 31/1C02  
National Institutes of Health  
Bethesda, Maryland 20892  
301 496-1357

HAPDING, A. Lynn, M.P.H.  
Office of Biological Safety  
Harvard University  
46 Oxford Street  
Cambridge, Massachusetts 02138  
617 495-2090

NEIMAN, Paul E., M.D.  
Division of Basic Sciences  
Fred Hutchinson Cancer Research Center  
1124 Columbia Street  
Seattle, Washington 98104  
206 467-4417

LANG, C. Max, D.V.M.  
Department of Comparative Medicine  
Milton S. Hershey Medical Center  
500 University Drive, P.O. Box 850  
Hershey, Pennsylvania 17033  
717 534-8462

RAPP, Fred, Ph.D.  
Department of Microbiology  
Pennsylvania State University  
Hershey, Pennsylvania 17033  
717 534-8253

LUFTIG, Ronald B., Ph.D.  
Department of Microbiology, Immunology,  
and Parasitology  
Louisiana State Univ. Medical Center  
1901 Perdido Street, Room 6206  
New Orleans, Louisiana 70112  
504 568-4063

-----  
EXECUTIVE SECRETARY

GARTLAND, William J., Jr., Ph.D.  
Office of Recombinant DNA Activities  
National Institutes of Health  
12441 Parklawn Drive, Suite 58  
Rockville, Maryland 20852  
301 770-0131

-2-

---

LIAISON REPRESENTATIVE

---

McCARTHY, Charles, Ph.D.  
Office for Protection from Research  
Risks  
National Institutes of Health, 31/4B09  
Bethesda, Maryland 20892  
301 496-7005