Exemptions from or modifications of the requirements would be allowed for arms transfers, disaster relief, intelligence activities, and for various reasons such as national security, and commercial and competitive factors.

The draft order spells out several areas of disagreement between CEQ and State: by far the greatest difference is over nuclear exports. The State Department wants all exports of nuclear fuel to be exempt from the order. It fears that environmental assessments would cause interminable delays (compounded by possible court suits) and that our nuclear clients would decide we were unreliable and turn to other sources. This sentiment is backed up by a conglomeration of forces including the export and international trade community, the defense and intelligence people, and those opposed to nuclear proliferation (who, in the words of one official, "are increasingly hard to distinguish from the nuclear exporters").

The CEQ proposes that exemptions for nuclear exports be decided on a case-by-case basis and be applied only where nonproliferation objectives appear to be jeopardized, although CEQ chairman Charles Warren has contended that "there is no conceivable way that the preparation of appropriate environmental reviews for fuel shipments could have adverse effects on the Administration's nonproliferation policy."

Another difference between State and CEQ is over environmental assessments of physical facilities that produce toxic chemicals. State only worries about the export of chemicals; CEQ maintains that, in the words of chairman Warren, "We must be as concerned about the federal involvement in the export of a DDT plant as we are about federal involvement in the export of DDT."

Other matters await resolution. The State Department, in what CEQ regards as a last minute rug-pulling maneuver, wants to eliminate the EIS option altogether, leaving only the two less rigorous procedures. It objects to CEQ's desire that agencies involved in actions abroad be required to share their environmental information with other government agencies, and it has added wording under "rights of [legal] action" intended to discourage courts from thinking that the order creates a right to bring lawsuits to enforce compliance.

On the whole, the document would be a cautious one even if CEQ won out on all the disputes. Applying NEPA principles abroad would not necessarily result in the cancellation or alteration of any actions; nor would they apply at all to most environmental depredations carried on *within* a country with the aid of U.S. dollars.

The Environmental Protection Agency, which participated only marginally in the development of the regulations, is supposed to keep its official mouth shut until the White House has worked out a final version of the order. However that agency has always contended that NEPA does apply abroad (the Justice Department is supposed to issue an opinion on that soon) and there is reportedly a good deal of dissatisfaction at EPA with the loopholes, exemptions, and opportunities for agency discretion that are contained in the draft order.

Many observers believe the order would not precipitate a flurry of new lawsuits; on the contrary, some feel there will be even fewer after the Administration comes up with an explicit stand on this long-disputed subject.

—CONSTANCE HOLDEN

New Rulebook for Gene Splicers Faces One More Test

The gene splicing and cloning technique, first invented in 1973, is now in use in some 350 research projects financed by the National Institutes of Health (NIH). The researchers are subject to the safety guidelines drawn up by an NIH committee in June 1976, but for more than a year have been anxiously awaiting a major revision of the rules.

The proposed new rulebook was published in the 28 July issue of the *Federal Register*, but with it was the news that there is to be one more round of review before the rules become final. Secretary of Health, Education, and Welfare (HEW) Joseph Califano says he plans to hold a public hearing on 15 September. Comments received then and in writing will be reviewed by a four-man group chaired by HEW general counsel Peter Libassi. Other members are NIH director Donald Fredrickson, and two assistant secretaries of HEW, Julius Richmond and Henry Aaron.

Since Fredrickson has already conducted a public review of most of the revisions (*Science*, 6 January 1978), Califano's intention of repeating the exercise unavoidably looks like second guessing the NIH's judgment. (Libassi says that no second guessing is intended although the review group will inevitably be covering some of the same ground.) Libassi's review will also constitute the first time that anyone other than the NIH and its committees has had the power to change the guidelines. In return for accepting another round of review, the NIH seems to have persuaded Califano to promise that the final guidelines will be issued promptly and that there will be no extension of the 2-month period for public comment that started on 28 July.

The proposed new rules assume particular importance now that it seems increasingly possible that Congress will once again fail to pass any bill governing gene splicing research. The bill prepared by the House health subcommittee has yet to reach the floor, while the Senate is still awaiting a reply to the letter sent by six senators to Califano on 1 June.

If no bill is passed, and if Califano declines the senators' invitation that he invoke existing statutory powers to govern gene splicing, the present "voluntary" system would continue under the aegis of the revised rulebook. Features included in the new guidelines—such as a voluntary registry for industry—seem designed to make the NIH rulebook an arguably sufficient instrument for national governance of the research.

The new guidelines differ from the old in both scientific and procedural aspects. The three main scientific changes concern thinking about the bacterial host system for gene splicing, experiments with viruses, and "shotgun" experiments.

• *E. coli* K12. Many gene splicing experiments consist of splicing DNA from the organism of interest onto a virus or plasmid which can replicate in the human gut bacterium *Escherichia coli*. The inserted DNA is, as it were, xeroxed

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each time the bacterium divides, a process known as cloning. A major reason for drawing up safety rules was the suggestion that the bacteria might in some circumstances gain pathogenic features from the foreign DNA sequences being cloned in them. At the time the original guidelines were issued, in June 1976, the NIH committee believed that *E. coli* K12, the enfeebled laboratory variety of the bacterium, was unlikely to be converted to a pathogen by any random insert of DNA. Just in case, however, the committee set up an elaborate system of safety rules based on physical containment (graded from P1 to P4) and the use of genetically disabled forms of *E. coli* K12 (graded from EK1 to EK3).

The NIH committee's belief in the safety of *E. coli* K12 has since been corroborated. New data is often stressed in political forums as the reason, but perhaps of equal importance has been a process of discussion and consensus-making among biologists. Because of the new confidence in the bacterium, the two topmost grades of safety in the present guidelines, P4 physical containment and EK3 biological containment, would be effectively abolished for research involving *E. coli* K12.

• *Viruses.* The present guidelines require gene splicing experiments with animal virus DNA to be conducted largely at the P3 and P4 levels of containment. Most such experiments could be carried out at the P1 and P2 levels under the revised guidelines. The basis for this change is not new data but a decision by a group of American and European virologists that cloning the whole or any part of a virus must logically be less dangerous than working with the whole virus itself, which is done routinely. "The probability that K12 organisms carrying viral DNA inserts could represent a significant hazard to the community was so small as to be of no practical consequence," the group concluded at its meeting in January this year in Ascot, England.

• *Shotgun experiments.* Genuinely new data, much of it obtained by gene splicing methods, has changed the perception of shotgun experiments from comparatively hazardous to comparatively quite a safe category of gene manipulation. The reason has to do with genetic "expression," the process whereby, in the central dogma of biology, the cell makes RNA copies of the genes constituted by the DNA, and the RNA segments, or "messengers," direct the synthesis of the particular protein specified by each gene.

In a shotgun experiment, the entire gene set of an organism is broken into segments, and each segment is cloned in host cells. Because of the wide range of genetic material being sampled, there seemed a relatively high chance that at least one of the *E. coli* clones might contain a harmful gene, particularly if the organism being shotgunned was in evolutionary terms close to man. But for its harmful effects to be realized, the gene must at some stage be expressed. The surprising discovery now beginning to emerge is that the genes of higher organisms seem not always to consist of continuous runs of DNA but to possess intervening sequences of uncertain purpose. What is certain is that the sequences must be excised, apparently at the messenger-RNA stage, before protein synthesis begins. Bacterial cells, whose DNA seems not to possess intervening sequences, have no need for and do not possess the excision machinery. The consequence is that the DNA of higher cells seems not to be properly expressed in *E. coli*, a situation that relieves much of the concern about shotgunning higher cell DNA.

In the light of this finding, the revised rulebook would reduce the required containment levels for most shotgun experiments by a considerable margin. Shotgunning the human gene set, which at present must be done in the highest containment levels, would be permissible in P2 conditions, which requires not too much more than standard laboratory equipment and good microbiological practice.

Proponents of gene splicing sometimes appeared inconsistent in talking up the possible practical benefits of the technique (some of which depend on expression taking place) and talking down the hazards by saying it was not even certain that expression occurred. But it now seems possible to have it both ways. Expression of higher cell DNA in bacteria does not occur naturally, which reduces the hazards, but probably can be made to occur by appropriate manipulations, which should allow the benefits to be realized. One such manipulation is to program bacteria with DNA copies, made in the test tube, of messenger-RNAs from which the intervening sequences have already been excised by natural or other means.

The revised rulebook contains several new procedural features, some of which are clearly designed to broaden, perhaps to the extent of making universal, the application of the NIH's safety rules. The rules at present have bite only for researchers supported by NIH money. The proposed rules would demand that institutions receiving any NIH money see to it that all their research activities meet the standards of the NIH rules regardless of the source of funding. Another new feature would permit industry to register its gene splicing projects with the NIH provided the NIH rules are followed; the NIH would preserve the confidentiality of proprietary information submitted to it.

To cut bureaucratic delays in approving new experiments, the proposed rulebook would delegate considerable powers of decision to local biohazards committees. The committees could approve single step reductions in the containment level of an experiment without waiting for NIH say-so. HEW general counsel Libassi says that his review panel will pay particular attention to the procedural aspects of the rulebook since they propose "a considerable amount of delegation and deregulation."

One critic who has declined to climb aboard the consensus is Robert Sinsheimer, editor of the *Proceedings of the National Academy of Sciences* and chancellor of the University of California, Santa Cruz. In a letter to the NIH of 4 January, Sinsheimer raises various criticisms of the proposed rules.

In his view the guidelines are informed by a perspective which is "extraordinarily anthropocentric" (the safety rules are biased toward protecting man rather than the plants, microbes, insects, and other species which play vital ecological roles), "extraordinarily confident of the completeness of our knowledge of micro-organisms," and "dangerously narrow" in their preoccupation with gene splicing to the exclusion of other forms of genetic research. Such a perspective "may indeed represent the political 'center' but it does not to my mind reflect the objectivity with which we are familiar in everyday science," Sinsheimer says.

Sinsheimer does not agree with the downward revision of the containment requirements because he is as yet unconvinced by the argument that *E. coli* K12 cannot be made pathogenic. The current strains of *E. coli*, being ubiquitous in man, would not be expected to be highly pathogenic, "but that does not prove they lack the potential." As for K12 itself, as long as the exact genetic basis of its enfeeblement is unknown, "We cannot know how difficult the introduction of pathogenicity would be by the appropriate route."

Libassi says his review panel is likely to pay more attention to the procedural rather than scientific content of the new rulebook. Final rules should be published within 90 days of the 15 September hearing.—NICHOLAS WADE