

EXHIBIT F

**TO DECLARATION OF
JENNIFER A. SORENSON**

Excerpt from National Academy of Sciences 1980 Report

The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds

Committee to Study the Human Health Effects
of Subtherapeutic Antibiotic Use in Animal Feeds
Division of Medical Sciences
Assembly of Life Sciences
National Research Council

NATIONAL ACADEMY OF SCIENCES
WASHINGTON, D.C. 1980

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

A relatively small proportion of the research that has been conducted on the subtherapeutic or therapeutic use of antimicrobials in animal feeds is truly epidemiological. Much of the information on this subject has been generated by poorly controlled studies of small numbers of subjects observed for brief periods.

An ideal study of the effects on human health resulting from the subtherapeutic use of antimicrobials in animal feeds would be able to relate, without conjecture or speculation, antimicrobials in feed to changes in morbidity or mortality or to treatment complications caused by resistance to antimicrobials in humans who had been exposed to animals or meat products during processing, handling, or, especially, consumption. Changes in morbidity and mortality could be used to quantitate the risk of the potential hazards posed by increased prevalence of resistant bacteria, by the development of plasmids conferring multiple resistance, or by the evolution of especially efficient transfer mechanisms within the reservoir of bacteria in animals.

Because the literature provides only isolated fragments of information relating to various components of the meat production system, it is insufficient for assessing the direct relationship between the use of subtherapeutic levels of antimicrobials in animal feeds and the health of humans. A major deficiency in much of the literature is the lack of a clear differentiation between the consequences of subtherapeutic and therapeutic uses of antimicrobials in animals. Moreover, data gathered in the United Kingdom, the Federal Republic of Germany, and the Netherlands do not indicate clearly whether restrictive regulations have actually reduced or averted the postulated hazards to human health. Restrictions on the use of antimicrobials in the United Kingdom may well have altered the patterns of their use without significant alteration in the total amounts used or their consequences. Therefore, it is not possible to conclude from the literature that restricting only the subtherapeutic use of antimicrobials will cause a decrease in the overall prevalence of R^+ organisms in humans or animals. Furthermore, there is little information on qualitative changes in resistance in the enteric bacteria of animals or humans. For example, no data exist to indicate the extent to which new resistance combinations or more efficient transfer mechanisms have

been brought about by the subtherapeutic use of antimicrobials in feeds.

After reviewing the evidence, the committee concluded that the postulations concerning the hazards to human health that might result from the addition of subtherapeutic antimicrobials to feeds have been neither proven nor disproven. The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definite risk has not been conducted and, indeed, may not be possible.

The committee gave considerable thought to the necessary elements of the ideal study to measure accurately the effects on human health resulting from the subtherapeutic use of antimicrobials in animal feeds and how such a study should be designed.

It concluded that a comprehensive, all-encompassing study could not be realized or even approximated because of insurmountable technical difficulties. This decision reflected a number of facts:

- There are marked differences in both the therapeutic and subtherapeutic use of antimicrobials in the various major species of animals raised for their meat and in the different regions of the country.
- It is not clear how much the subtherapeutic use of antimicrobials, as compared to the therapeutic use, contributes to the prevalence of resistant bacteria in animals.
- Animals with different histories of exposure to antimicrobials are known to exchange bacteria during normal rearing and shipping prior to slaughter. Consequently, the types and amounts of antimicrobials received by a particular slaughterbound animal or its companions cannot be determined.
- Household members consume meats from animals that have been exposed to different antimicrobial agents during the course of different regimens, both subtherapeutic and therapeutic. Thus, ~~it is not practical to determine the original selective pressure~~ for resistant bacteria that may occur on a particular piece of meat.
- ~~It is difficult to determine the relative contributions~~ made by subtherapeutic and therapeutic levels of antimicrobials in animals or in humans to the pool of resistant bacteria that may affect human health.

The committee concluded that less comprehensive approaches, although more feasible, could not provide direct evidence of a consistent chain of events from animal production to meat consumption. However, it did outline a sequence of four possible studies on individual aspects of the transmission chain. The results of these studies, if interpreted with the recommended precautions, would provide a useful scientific background for policymakers. At best, however, the remaining gaps in our knowledge will still have to be bridged by conjecture or speculation.

The committee also discussed some nonepidemiological aspects of the subtherapeutic use of antimicrobials. A better understanding of the mechanisms through which subtherapeutic levels of antimicrobials produce beneficial effects may lead to development of other substances or other treatments of equal or greater effectiveness, thereby rendering this entire issue moot. For example, if the beneficial effect is caused primarily by controlling infections, then other preventive techniques such as new vaccines may yield equal benefit. If the mechanism is nutritional, i.e., nutrient sparing or an alteration of nutrient absorption, then new nutritional supplements may yield the desired result.

Plasmids in isolates from animals and humans must be characterized to assess the possibility that subtherapeutic levels of antimicrobials in animals produce qualitative changes in resistance to antimicrobials in the enteric flora of animals, changes that might subsequently affect human health.

RECOMMENDATIONS

The committee RECOMMENDS that future epidemiological studies, whether the ones suggested here or others, be carefully planned to fill gaps in our present knowledge and, especially, to avoid the errors of ambiguous design and small sample size that have caused such difficulties in interpreting the data. The proportionate contributions to resistance made by subtherapeutic and therapeutic uses of antimicrobials in animals and in humans urgently need resolution.

~~The committee~~ RECOMMENDS increased and continued monitoring and surveillance of the occurrence of antimicrobial resistance in bacteria in animals, in meat and meat products, and in humans, especially in cases of human illness due to Salmonella and pathogenic E. coli. ~~If restrictions on antimicrobial use are adopted,~~ the committee RECOMMENDS that monitoring be continued in order to determine the effect of such restrictions.

The committee RECOMMENDS further research on:

- the mechanism of action of subtherapeutic levels of antimicrobials in feed (BARR, Appendix K) including characterization of the composition and interactions of the gastrointestinal flora (Savage, Appendix D),
- factors that inhibit the development and transfer of resistance in vivo (Jacoby and Low, Appendix C), and
- studies on the epidemiology of plasmid-mediated resistance to antimicrobials in both animals and humans (O'Brien, Appendix I).