# REGULATION OF DIETHYLSTILBESTROL (DES), 1972



## HEARING

BEFORE THE

## SUBCOMMITTEE ON HEALTH

OF THE

## COMMITTEE ON LABOR AND PUBLIC WELFARE

## UNITED STATES SENATE

NINETY-SECOND CONGRESS

SECOND SESSION

ON

## S. 2818

TO AMEND THE FEDERAL FOOD, DRUG, AND COSMETIC ACT TO PROHIBIT THE ADMINISTRATION OF THE DRUG DIETHYLSTILBESTROL (DES) TO ANY ANIMAL INTENDED FOR USE AS FOOD, AND FOR OTHER PURPOSES

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JULY 20, 1972

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# REGULATION OF DIETHYLSTILBESTROL (DES), 1972

THURSDAY, JULY 20, 1972

U.S. SENATE,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON LABOR AND PUBLIC WELFARE,
*Washington, D.C.*

The subcommittee met, pursuant to notice, at 9:40 a.m., in room 4232, New Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittee), presiding.

Present: Senators Kennedy and Javits.

Committee staff present: LeRoy G. Goldman, professional staff member; Dr. Larry Horowitz, professional staff member; and Jay B. Cutler, minority counsel.

Senator KENNEDY. The subcommittee will come to order.

Diethylstilbestrol—DES—is a synthetic estrogen which is widely used in beef cattle and sheep to stimulate more rapid weight gain with less feed.

DES is also, however, a well-recognized carcinogen and has been directly linked to the appearance of vaginal cancer in young women whose mothers had taken large doses of DES during their pregnancy. At significantly lower doses, DES causes cancer in mice.

These two sets of facts present a classic policy dilemma—under what conditions can an economically useful agent, which has some potential to do grave harm to human beings, in this case by causing cancer, be used in the food industry?

The Congress has considered this dilemma in the past, and with administration concurrence, has resolved it very clearly.

The Delaney clause of the Food, Drug, and Cosmetic Act forbids the appearance of any residues of known cancer-causing agents in the food people eat.

That fact is not in dispute. The law does not require that cattle, for example, not be fed cancer-causing agents. But it does require that all such agents be completely eliminated from those cattle by the time they are slaughtered and sent to market.

The intent of Congress here is clear—whether by banning such substances or by assuring their disappearance before slaughter, cancer-causing agents must not be found in the meat that appears on America's dinner tables.

We are here today because DES, a known cancer-causing agent, is appearing on thousands of American dinner tables. It appears four times more frequently today than it did 6 months ago. The latest figures released by the Department of Agriculture this past Tuesday show that 2.27 percent of all cattle tested contained DES residues after slaughter. Considering that we slaughter in excess of 30 million

cattle each year, that means that more than 660,000 head of cattle probably reach American dinner tables, in various forms, with a known cancer-causing agent in them.

The Food and Drug Administration is the regulatory body which is responsible for controlling DES. Six months ago, when the reported incidence of DES was 0.5 percent, FDA took the position that the residues could be eliminated by tightening administrative procedures. They did just that, extending the period for withdrawal of cattle from DES to 7 days from the previous 2-day period. At that time, FDA Commissioner Charles C. Edwards stated:

> The FDA will not permit DES residues in the food supply. Should the new control procedures prove unsuccessful in application—we are prepared to ban its use entirely from animal feeds.

There was considerable controversy 6 months ago about whether the new control procedures could be successful. Dr. Roy Hertz, senior physician at the Rockefeller University, formerly of the National Cancer Institute, said:

> I think that administratively, this would be totally impractical. I think the hazards of additional exposure would be increased by such a practice rather than reduced, and I believe that on the face of it, knowing regulatory practices, particularly on a national scale, notwithstanding the possibility of criminal action against violations, that the impracticability of protecting the public from exposure to these materials in foodstuffs is very, very great and really a foolhardy undertaking. What has been proposed by * * * FDA is unfeasible and impractical and ill-advised.

It now seems that the control procedures are unenforceable. In 6 months, the incidence of DES has risen from 0.5 to 2.27 percent. And yet, DES is, at the present moment, still not banned and still is part of many Americans' daily diet.

FDA has called for public hearings to "gather all the facts" in this matter. To do that, it has explained that the only mechanism available is to propose a formal action to withdraw approval of the drug which would automatically, in their words, "* * * bring about an opportunity for an official hearing." Such hearings have in the past, however, been far from automatic—on March 31, 1971, 15½ months ago, FDA published a similar hearing notice for Nihydrazone and there has still been no hearing.

The facts in this case are clear. So clear that 21 countries, including the two leading cattle producers, Argentina and Australia, have banned DES; and Sweden and Italy have banned the importation of U.S. meat from cattle fed with DES.

The law is also clear. What is not clear is why the FDA has not followed the friendly advice of Dr. Frank L. Rauscher, the Director of the National Cancer Institute, who has said he would ban the use of DES in cattle feed now, and then, if warranted, conduct hearings.

My distinguished colleague, Senator William Proxmire of Wisconsin, is the principal sponsor of S. 2818, which would bar DES from use in animal feed. At this point we will enter a copy of the bill, S. 2818.

(A copy of S. 2818 follows:)

92D CONGRESS
1ST SESSION

# S. 2818

IN THE SENATE OF THE UNITED STATES

NOVEMBER 8, 1971

Mr. PROXMIRE (for himself, Mr. BAYH, Mr. CASE, Mr. MCGOVERN, Mr. MOSS, and Mr. RIBICOFF) introduced the following bill; which was read twice and referred to the Committee on Labor and Public Welfare

# A BILL

To amend the Federal Food, Drug, and Cosmetic Act to prohibit the administration of the drug diethylstilbestrol (DES) to any animal intended for use as food, and for other purposes.

*Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,* That section 301 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331) is amended by adding at the end thereof a new subsection as follows:

"(q) The administering of the drug diethylstilbestrol (commonly known as DES) to any animal intended for use as food or to any animal the product of which is intended for use as food."

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SEC. 2. Section 409 (a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 348 (a)) is amended by inserting "(1)" immediately after "SEC. 409. (a)"; by redesignating clauses (1) and (2) as clauses (A) and (B), respectively; and by adding at the end of such section a new paragraph (2) as follows:

"(2) A food shall be deemed to be unsafe for the purposes of the application of clause (2) (C) of section 402 (a) if it contains the drug diethylstilbestrol (commonly known as DES)."

Senator KENNEDY. This morning's hearing will consider the impli a-tions of S. 2818 and the entire DES question.

Senator Javits.

Senator JAVITS. Thank you, Mr. Chairman.

First I would like to state my support of the chairman in calling these hearings and my gratification for his having agreed to have as the opening witness FDA Commissioner Edwards who will express his views, which I understand are to be that DES is safe if used as directed and, as to the question of "imminent hazard" and whether the evidence is adequate to support that legal requirement.

For myself, I believe, with my colleagues, that if DES residues cannot be eliminated—and that seems to be the evidence of the Department of Agriculture—then we have to prohibit the introduction of DES into the food supply, unless we are shown some very good reason why not;

I am very gratified, Mr. Chairman, that we are having these hearings, and we will get right down to business on the practicalities of the situation.

Mr. Chairman, I would like at this moment to express my appreciation for the appearance here of a top scientific witness, Dr. Peter Greenwald, director of the Cancer Control Bureau of the New York State Department of Health.

His tremendous background, training, and experience concerning this issue, and his investigations relating to the possible cause-and-effect relationship between DES administered to pregnant women and cancer of the vagina, to which the chairman referred, occurring years later in their daughters.

This will be discussed with us, and I am sure will have a great bearing on how we handle this matter in the future.

I want to mention also my appreciation for the appearance of Dr. Rauscher of the National Cancer Institute, who has shown a remarkable sensitivity to the need to deal with this issue in a most decisive way.

(The prepared statement of Senator Javits follows:)

PREPARED STATEMENT OF HON. JACOB K. JAVITS, A U.S. SENATOR FROM THE STATE OF NEW YORK

Mr. Chairman, it is a matter of great scientific importance and serious social implication as to whether we should ban the use of diethylstilbestrol—commonly known as DES—a synthetic drug. While DES promotes rapid weight gain in beef cattle with its cost savings and better quality meat for the consumer, it has been determined to be a carcinogen capable of causing cancer in experimental animals and is also reportedly linked to human cancer.

Dr. Frank J. Rauscher, Jr., the Director of the National Cancer Institute, which has as its mission the conquest of cancer, recently indicated that the prudent course is to prohibit DES in livestock feed pending the outcome of the FDA public hearings on the matter.

Dr. Rauscher has publicly defined his mission as Director of the National Cancer Institute as being "to protect the people from cancer." I believe our commitment as legislators is to help him fulfill that goal. If legislatively reasonably possible, we should eliminate from the environment anything that increases man's carcinogenic burden.

Apparently the FDA voluntary regulatory control program—withdrawal of DES from livestock feed for greater periods prior to slaughter, for example, from 48 hours to 7 days—has not been successful; the DES detection rate has increased. I understand FDA Commissioner Edwards views DES safe if used as directed and at this point does not believe there is sufficient evidence to declare it an "imminent hazard" which would enable the Secretary to ban the use of DES pending the outcome of the FDA hearings. However, I believe that if DES residues cannot be eliminated—and that appears likely according to the evidence found by recent Agriculture Department samplings of beef and lamb livers—then we would have to prohibit the introduction of DES into the food supply.

In closing, Mr. Chairman, I am pleased to welcome as a witness Dr. Peter Greenwald, director of the Cancer Control Bureau of the New York State Department of Health. Dr. Greenwald has an outstanding background of training and experience concerning this issue and has investigated the possible cause-and-effect relationship between DES administered to pregnant women and cancer of the vagina occurring years later in their daughters.

Senator KENNEDY. I want to welcome this morning as our first witness Senator Proxmire, who is perhaps best known for his very effective work as Chairman of the Joint Economic Committee.

He introduced this legislation a number of months ago. I believe it was on November 8 of 1971, so he was very much aware of this problem and concerned about it a long time go, before it was really brought forth for a full airing.

## STATEMENT OF HON. WILLIAM PROXMIRE, A U.S. SENATOR FROM THE STATE OF WISCONSIN, ACCOMPANIED BY TOM VAN DER VOORT AND DAVID EPSTEIN

Senator PROXMIRE. Thank you, Mr. Chairman.

I have with me Tom van der Voort and David Epstein of my staff.

Let me first thank you very much for you and your Subcommittee on Health convening these hearings; and I see that you and Senator Javits have both anticipated part of what I intend to say this morning, and I appreciate that very much.

Congress must devote serious attention to a cancer-causing drug which has shown up in the food supply of the American people with alarming frequency in recent months.

My reading of the record indicates that Congress has, on numerous occasions in the past, devoted its serious attention to this very issue, and has already resolved it through the Delaney amendment.

According to that provision, no residue-producing carcinogens may be added to American food supplies. But for whatever reasons, the FDA has not seen fit to apply the Delaney amendment to DES.

Accordingly, I have proposed specific legislation on that subject.

To my knowledge, no one expresses the slightest doubt that DES is carcinogenic. An expert from the National Cancer Institute told Congressman Fountain's Intergovernmental Relations Subcommittee that DES is "one of the chapters in a textbook" on cancer.

Laboratory experiments have proven it to be carcinogenic to animals. And a 1970 study established a clear link between use of DES by pregnant women and vaginal cancer in their daughters.

Yet, DES is currently being added to livestock feed to increase the growth rates of cattle and sheep.

To the best of my knowledge, more than half of our beef is being fed DES.

Residues of DES have been detected in beef and lamb tissue samples tested by the Department of Agriculture since 1965. As of last December, residues were being found in about one-half of 1 percent of samples tested.

At that time, the Food and Drug Administration claimed that these residues were attributable only to violations of the procedural guidelines set down for use of DES.

Therefore, the agency made their guidelines mandatory, lengthened the period for withdrawal of livestock from DES-medicated feed from 2 to 7 days, and promised stricter enforcement.

At that time, the FDA was confident that this would solve the problem of the persistent one-half of 1 percent residue rate. But FDA Commissioner Edwards repeatedly assured Congressman Fountain's House Subcommittee about FDA's intentions if the new controls failed.

On page 203 of the hearing record, he said:

> Should the new control procedures prove unsuccessful in application, or should new evidence on DES be developed, we are prepared to ban its use entirely from animal feeds.

And on page 251:

> The fact of the matter is, if we find that our new program is not working, there is just one recourse for us and that is to ban its use totally.

The new procedures went into effect January 1. What has happened since that time?

From the beginning of January to the middle of April, the residues continued at about one-half of 1 percent. But between April 15 and the most recent report on July 8, the residues showed up at a startling average rate of 3.60 percent. That is over seven times higher than the old figure.

If that rate continued for a year, it would mean over 1,200,000 cattle would be slaughtered in this country with residues of DES. This rate, I remind you, is with the new FDA procedures in effect. I do not believe anyone would deny that these controls are, to use the Commissioner's phrase, "unsuccessful in application."

As it happens, April 15 was the date that the USDA began reporting results of more sensitive tests which detect DES levels below two parts per million. So part of the increase is attributable to improved detection—but only part of the increase.

To be precise, 2.06 percent of the samples showed residues under two parts per million; and the other 1.54 percent showed residues over two parts per million.

This means two things: first, the lower level residues were presumably present before April. So there were in the past more residues than we had known about.

Second, the residues above two parts per million have themselves tripled; which means that regardless of measuring techniques, the absolute number of DES residues seems to have increased markedly. Neither of those conclusions is at all comforting.

With a 7-year history of residues, why hasn't the FDA banned DES under the Delaney clause?

The answer they gave last winter was to insist that there is in theory no reason for there to be residues. The FDA said its experiments persuaded it that DES, used in accordance with the regulations, leaves no residue. Therefore, even though there was no evidence of procedural violations in a number of the cases the FDA reported to the House subcommittee, they argued that if there were residues, there must have been procedural violations.

If the problem is indeed one of enforcement, it is no less a problem. I understand that at the present time, the FDA has filed one court case and has two more in process. There have been 54 residues reported since January. This subcommittee should find out what has happened in each of those cases.

If FDA thinks the regulations can be enforced, why are not violators prosecuted?

But frankly, I will not be satisfied if FDA manages to bring a few more cases to trial. The purpose of controlling DES is to protect American consumers; and even a more vigorous prosecution program will not achieve this. The primary grounds for prosecution rests on finding DES residues.

The USDA inspection program for DES tests about one out of every 10,000 cattle slaughtered each year. That is apparently enough to give us an idea of how widespread DES residues are.

But that also means that the chance of an individual violation being detected and prosecuted is extremely small.

Many violations are apparently unintentional, resulting from cross-contamination of feed supplies, human error, or animals uncooperatively eating feed intended for other animals. Even under laboratory conditions, according to the testimony of Dr. Roy Hertz, it is difficult to prevent accidental contamination with an agent as potent as DES.

Unintentional violations, in all but the tiniest fraction of cases, will not even be called to the farmer's attention. And there is certainly no particular incentive to scrupulously follow the regulations. The point is that such a plan of controls is simply unworkable. It will continue to detect the presence of residues in our food, but it will do almost nothing to stop the residues.

It is not enough for the FDA to assert that their procedure should prevent all residues. It cannot comfort Americans to know that their meat is uncontaminated in theory, while it, in fact, may contain carcinogenic residues.

Whether the FDA regulations are inadequate, or whether they are adequate but violated—in either case, the result is residues of a carcinogen in livestock destined for American dinner tables. In either case, it is unacceptable. In either case, the solution is a ban on the use of DES.

Some who have opposed a ban on DES have managed to be quite equivocal in their assessment of its dangers. The FDA throughout last winter's hearings insisted that it agreed with the Delaney clause that no amount of carcinogenic residue in meat is tolerable.

But again and again they explained that, well, if there just happened to be a little bit that slipped through, it wouldn't be so intolerable. But experts agree that there is no level that can be called safe for a carcinogen—nor do we know how to go about establishing such a level.

For this reason, Congress has again and again resolved that no carcinogen may be added to our food supply. According to FDA internal staff memoranda, even our most advanced techniques do not have anything near the sensitivity required to detect significant levels of residue. In fact, in one memorandum, two top FDA scientists recommended that consideration be given to "withdrawing DES from use in medicated feed until such time that an analytical method sensitive to one part per trillion is developed."

The two largest beef producing nations outside the United States—Argentina and Australia—have already banned the use of DES—and you can imagine the economic price that this constitutes with respect to those nations that depend far more on beef than we do as far as their balance of trade is concerned—as have the Common Market nations.

I recently received a letter from a spokesman from Canada's National Farmer's Union, indicating that organization's advocacy of a ban in Canada.

I am fully aware of estimates claiming that a ban on DES would cost the American consumer an additional $3.85 a year. That is not a trivial amount, but it is not extravagant, either.

The total national cost is less than the Federal Government will spend for the National Cancer Institute this year. It is a drop in the bucket of our gross national product.

This assessment of cost, I believe, also reflects a limitation of imagination. There should be an intensive effort to explore alternative

means of cutting the costs of producing wholesome—and I emphasize the word "wholesome"—meat. Getting our meat cheaply but with the potential of causing cancer is a bad bargain. By banning DES, we would provide the consumer with a bargain his dollars cannot now buy—the assurance that the beef and lamb he eats is uncontaminated by an artificial carcinogen.

Mr. Chairman, in great part owing to your leadership, our Nation has resolved to combat cancer. Surely controlling the hazards of carcinogens in our food supply is a necessary part of that effort.

For 7 years, we have permitted residues of DES to reach the American consumer. We will not know the full impact on the health of our people for many years, if we will know then. But with the evidence about DES we already have, a ban on the use of this drug in livestock feeds is simply a matter of prudence.

Mr. Chairman, I addressed a beef producers' meeting in Wisconsin on this subject a few months ago. You can imagine that there was a natural concern about this and an opposition to banning DES on the part of the beef producers.

At that meeting, the Lilly Co., which is the largest present producer of DES, was represented; as was the Department of Agriculture of the State of Wisconsin, and the U.S. Department of Agriculture.

What I found was that the beef producers find themselves in a competitive situation. As long as DES is permitted, they are almost compelled to use it because they are in competition. If an individual beef raiser should not use it, his losses are considerable under these circumstances.

If it is banned, however, there is not any question that within a short time their collective situation will be ajdusted to the market, and their losses would not be significant; and I found that they understood that.

I talked to a number of them privately about this, and they told me if DES were found to be cancer producing, they certainly wanted it banned.

Senator KENNEDY. Thank you very much, Senator Proximre.

Your last comment is certainly very interesting. Your feeling then is that if the meat producers themselves were convinced that inclusion of DES in the feed would significantly threaten the health and well being of the American people, they would not want a part of it?

Senator PROXMIRE. Yes, indeed; but, as I say, they are in a position where they have to continue feeding DES because of the competitive situation.

Senator KENNEDY. Yes; but if it were banned and no one could use it, at least they could recognize the value of that step if they were convinced that it did pose a threat.

In the FDA release of June 16, they point out a beef animal will reach a market weight of about 1,000 pounds 35 days sooner using 500 pounds less feed than a comparable animal not fed DES.

That is in their Department press release. That seems to be to be an economic issue, not an FDA issue.

Senator PROXMIRE. That is true; but you also have a situation where this is not an economic problem for the country as a whole because we have a surplus of feed. In fact, we have a situation where we have to store it, take it off the market, in order to hold up the price.

Senator KENNEDY. I thought FDA was going to be looking at the health issues rather than the economic. It seems to me the Department of Agriculture would be making that argument rather than the Food and Drug Administration, which is charged with protecting the health and well-being of the people.

Tell me, what is your reaction to the Delaney amendment? Do you think that is strong enough? Do you agree with me that with the passage of the Delaney amendment by the Congress, the Congress thought it was doing the job that we want to be done in this circumstance; or do you think that it is full of loopholes?

Senator PROXMIRE. In this case, it seems to be a very clear loophole. It is obvious to me this is not being administered in the spirit in which Congress intended it, at least not in the spirit which this Senator intended.

There is not any question that DES is a carcinogen; there is not any question the purpose of the Delaney amendment was to prohibit or prevent meat or food containing carcinogens from being sold to the public, and they are being sold to the public.

Senator KENNEDY. I want to thank you again for your appearance here. You are a real leader in the Congress on this issue.

I think particularly that because you come from a meat-producing State, you have shown a considerable amount of courage on this issue, as well as on many others.

Senator PROXMIRE. May I add, Mr. Chairman, there are, I think, three issues which might arise on the part of those who oppose this amendment, and I would like to leave the answers to some of the questions with you.

One claim is that DES residues are only apparent in livers. Since what we eat is mostly muscle tissue, why worry? Why not just ban the livers?

I have some very interesting information indicating that DES residues are present in other parts of the animal.

Senator KENNEDY. Certainly if it is in the blood stream it would naturally contaminate the other parts of the animal.

Senator PROXMIRE. Yes, indeed; and we found when we got this more sensitive test it is at a somewhat lower level, one-quarter to one-ninth of the concentration that is found in the liver, but is is found in the kidneys, the musculature.

A second claim is that DES produces more healthful meat because it reduces the amount of fat.

The answer there, I think, is a convincing answer, but as far as health is concerned, DES makes no contribution that is significant.

The third claim is that estrogenic hormones are naturally present in the human body as well as in many plants and animals which humans eat, and the answer is that natural hormones are vastly different from DES in level and potency.

I have this documented, and I would appreciate it if this information could be included in the record.

Senator KENNEDY. It will be included in the record.

(The information referred to follows:)

## LIVERS--FEED SURPLUS

Claim: DES residues are only apparent in livers. Since what we eat is mostly muscle tissue, why worry? Why not just ban the livers?

First, liver is a useful nutritious food. Why ban it?

Second, in the two cases where DES residues were found in parts of the carcass other than the liver (the musculature and the kidney) it was at levels 1/4 and 1/9 the consentration in the liver. Thus if we assume, conservatively, that DES occurs in the musculature at 1/10th the levels in the liver it would show up in the musculature at a level of 1/5th part per billion when it was present in the liver at 2 parts per billion. This one-fifth level is too low to be detectable but too high to be acceptable according to FDA's own scientists who urge withdrawal of DES until it can be detected at one part per ~~x~~ trillion.

## FATS

Claim: The use of DES produces more healthful meat because it reduces the amount of fat.

Reply:

~~A~~ study in the Journal of Animal Science, November 1960, reported that DES-fed cattle actually had more fat at age 6 months than cattle not fed DES.

A USDA study in 1955 (number 2444-55 (42) ) concluded that while the non-DES cattle were slightly fatter than the DES-fed cattle, there was no difference between the two groups in either marbling or intra-muscular fat. This is important, since external, removable fat is not eaten. The only fat with any relation to the healthfulness of the meat is that which is found within the meat itself. And the USDA study found no difference in the amount of internalized fat between DES and non-DES cattle.

## HORMONES PRESENT IN THE HUMAN BODY

Claim: Estrogenic hormones are naturally present in the human body, as well as in many plants and animals which humans eat.

Reply: Those natural hormones are vastly different from DES in level and potency.

(1) ALL plant hormones are significantly lower in activity than DES. One of the most potent, coumestrol, found in alfalfa and clover, has 1/10,000th the activity of DES.

(2) The estrogen naturally present in animals and humans is estradiol. Since it is natural in man, it is rapidly metabolized and excreted. But DES is a synthetic estrogen having ten times the potency of estradiol and is much more slowly metabolized and excreted.

(3) Recent studies* have quantified the estradiol level in meat.
In the serum, total estrogens range from
0.5 to 10 parts per trillion
rising just before the onset of estrus to
20 to 30 parts per trillion.
Even that highest figure is 1/17 the lowest level of DES that has been detected. And bear in mind that DES is 10 times as potent.

(4) The estradiol level in post-menopausal women is about
15 parts per trillion
Assuming one of these women ate 4 ounces of liver containing 1 part per billion DES, this could be the equivalent of almost tripling the physiological level of estradiol on a body weight basis, or assuming these estrogens exist only in the blood, of raising the level to 22 times normal.

In short, introduction of DES is clearly on quite a different scale than naturally-present hormones. Indeed, it would be quite surprising if the results were otherwise, since DES dramatically stimulates livestock growth, it surely should be expected to have other dramatic effects.

*Hendricks, et.al., Endocrinology, Vol. 89, No. 6, December 1971 and Dr. Hafs, Michigan State University, unpublished data.

EXPLANATION OF STATISTICS

RESIDUES

"From the beginning of January to the middle of April, the residues continued at about one half of one percent."

January 1 - April 15 1046 samples, 5 residues = .48%

"But between April 15 and the most recent report of July 8, the residues showed up at a startling average rate of 3.60 percent."

April 15 - July 8 1360 samples, 49 residues = 3.60%

NOTE: Latest data thru July 15: 1504 samples, 53 residues = 3.52%
This data leaves the [redacted] succeeding statements unchanged.

"If that rate continued for a year, it would mean over 1,200,000 cattle would be slaughtered in this country with residues of DES."

35,354,000 cattle slaughtered in 1970 (USDA statistics)
3.60 %
1,272,744 (or using 3.52, 1,244,461)
both exceed 1,200,000.

"2.06% of the samples showed residues under 2 parts per billion; and the other 1.54% showed residues over 2 parts per billion."

April 15 - July 8 1360 samples
28 under 2ppb = 2.06%
21 over 2ppb = 1.54%
49 total = 3.60%

ARE THE STATISTICS SIGNIFICANT?
Yes. The weekly report figures are subject to fluctuation due to bunching of results. But a USDA spokesman agreed that analysis of trends over several months is possible. Our figures from April to July include 12 weeks of results, and more than 1300 samples, easily enough to be significant.

FDA MEMORANDUM. From Leo Friedman, Ph.D., Director, Division of Toxicology. To: Dr. Virgil O. Wodicka, Director, Bureau of Foods. February 8, 1972



The dose of DES, 0.1 mg twice weekly, represents about 2 µg/kg at the time of administration and on a weekly basis averages about 0.5 to 0.6 µg/kg/day. Considered in terms of dietary intake, this is approximately 20 ppb of the total daily diet.

1) PLANT HORMONES → Comments have been made that we are continually exposed to naturally occurring exogenous and endogenous hormones in greater amounts than we would encounter from DES. The plant hormones which may be consumed by either man or animal vary widely in estrogenic effect but all are significantly lower in activity than DES. One of the most potent plant hormones, coumestrol, found in clover and alfalfa, has only 1/10,000th of the activity of DES. Genistein and genistin, estrogenic compounds derived from clover and soybeans, have about 1/200,000th the potency of DES.

3) ESTRADIOL IN MEAT → The principal source of estradiol and its metabolites in our foods would be from meat. Data currently available (Hendricks et al., Endocrinology, Vol. 89, No. 6, December 1971), using a radioimmunoassay has, for the first time, really quantified this source. His data indicate that in the bovine female, total estrogens present in serum range from 0.5 to 10 parts per trillion in the diestrus state, and rises to between 20-30 parts per trillion about 24 to 48 hours prior to the onset of estrus, then falls rapidly (during the 6-8 hour period) following the onset of estrus. We have no reason to believe muscle levels would be above these amounts and would more likely be somewhat less than the serum levels. It is interesting to note that a 350 kg heifer needs only an increase of approximately 300 nanograms within the whole volume of her circulating blood to go into heat. A kilogram of liver with 1 ppb would contain 1000 nanograms. (Dr. Hafs, of Michigan State University, unpublished data, has checked the serum level of estradiol in steers and finds it in the same range as has been published by Hendricks for the diestrus female).

2) DES PERSISTS IN MAN LONGER THAN ESTRADIOL. The estradiol is a natural hormone in man, and the metabolic pathways are already established so that in the event any is absorbed, it will be rapidly metabolized and excreted. DES, on the other hand, is a synthetic estrogen having ten times the potency of estradiol and is much more slowly metabolized and excreted, thus exerting its effect on target organs for a much longer period of time. Dr. Umberger has estimated the half-life of DES to be 12 hours, while Hendricks' (Clemson University) work would indicate the half-life of estradiol is much less, probably somewhere between 6 and 8 hours.

4) NATURAL LEVEL OF ESTRADIOL IN HUMANS The level of circulating estradiol in serum of post-menopausal women is about 15 parts per trillion (Korenman et al, Journal of Clinical Endocrinology, 29:879, 1969). Assuming one of these women ate 4 oz. of liver containing 1 ppb DES, she would consume about 0.125 mcg or

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0.0025 mcg/kg body weight, which is equivalent to 2.5 parts per trillion. Since DES has ten times the activity of estradiol, this could be the equivalent of adding 25 ppt estradiol to that already normally present, almost tripling the physiological level on a whole body weight basis. If we assume that the DES and estradiol exist only in the circulating blood, the increase would be 22 times normal.

If violations of the 7-day withdrawal period should occur, the probability that muscle as well as kidney and liver, will be above what we now would consider an "acceptable" level, would be real. Furthermore, one must consider that such exposures would not be limited to an occasional piece of liver or that they would be equivalent to the natural exposure from the occasional slaughter of a pregnant cow, because:

1. Many people buy meat in quantity and store it in lockers or home freezers.

2. Liver is still considered a hematinic and, in some cases, consumed daily.

3. If violations of the withdrawal period do occur, it would not be limited to a random animal, but would more likely involve all the cattle marketed at that time by that producer.

4. Until sufficient time has elapsed to clear the animal's metabolic pool of DES, we are dealing with a population of hyperestrogenized animals that cannot be considered normal in this regard. We should like to have better evidence than we have now to conclude that 7 days are sufficient time to reduce the DES to the low physiological levels of estrogenic activity normally found.

The study by Mitchell et al in Agriculture and Food Chemistry, Vol. 7, No. 7, July 1959, is practically the only evidence to support the 7-day withdrawal period. By our current standards, this study is weak scientific justification for the conclusion:

1. Only one animal was used in this study.

2. Only a single dose of tritium labeled DES was given. The animal had not been equilibrated by feeding unlabeled drug.

3. Only 51% of the administered drug was recovered in urine and feces (29.3% in feces and 21.8% in urine), while 49% of the administered drug was not accounted for. Yet when untreated fecal material was spiked with radioactive material, from 73% to 83% could be recovered.

Senator KENNEDY Thank you very much, Senator Proxmire.

I want to welcome now Dr. Charles Edwards, the Commissioner of the Food and Drug Administration.

Dr. Edwards, I think you are aware of the order of scheduling witnesses. We had you a little later in the morning in order to hear from some of the scientific witnesses first.

I recognize full well the procedures controlling the hearing of administration witnesses first. I always feel it is sometimes better to have some of the information laid out before we get the final position.

I followed that procedure with the Refugee Committee business.

We did not intend any disrespect either for you or for the position you hold, and we welcome you here. We hope you will be able to remain so that in the course of the morning if there are some questions, which I am sure there will be, we will be able to have an opportunity to gather your comments on those questions.

We welcome you now; and I want the record to be quite clear on why we had arranged the order we had.

**STATEMENT OF CHARLES C. EDWARDS, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY DR. HENRY SIMMONS, DIRECTOR, BUREAU OF DRUGS, PETER HUTT, ASSISTANT GENERAL COUNSEL, FOOD, DRUGS, AND ENVIRONMENTAL HEALTH DIVISION, DR. C. D. VAN HOUWELING AND GERALD F. MEYER, DIRECTOR, OFFICE OF LEGISLATIVE SERVICES, FOOD AND DRUG ADMINISTRATION**

Dr. EDWARDS. Thank you, Senator.

I do appreciate this opportunity of appearing after Senator Proxmire, because I think it is important that we get the "real" FDA position on the table in the course of your deliberations this morning.

Senator KENNEDY. Good.

Dr. EDWARDS. At any rate, we do appreciate this opportunity to appear before you to discuss the Department of Health, Education, and Welfare's position on S. 2818, which would prohibit the administration of diethylstilbestrol (DES) to food-producing animals and provides that food containing DES shall be "adulterated" under the Federal Food, Drug, and Cosmetic Act.

Diethylstilbestrol is a synthetic drug with estrogenic activity which was first approved for use in animal feed in 1954. It effectively causes cattle and sheep to grow more rapidly and with less feed consumption. For example, a beef animal will reach a market weight of about 1,000 pounds, 35 days sooner using 500 pounds less feed than a comparable animal not fed DES. Additionally, this increase in body weight is reflected in additional protein and less fat in edible tissues

DES has been shown to induce tumors in certain species of laboratory animals when included in their diets for extended periods of time. Some reports have recently been developed which show an apparent association of vaginal cancer in girls whose mothers were treated with large doses of DES over a period of weeks or months to prevent a threatened abortion.

I would first like to address myself to those specific aspects of the use of DES, which are the responsibility of and subject to the legal actions of FDA.

As I am sure you know, Mr. Chairman, the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act included the so-called Delaney clause, which prohibits the use in the food supply of any food additive found to produce cancer in man or animals.

The 1962 Drug Amendments, however, exempted from the Delaney clause those drugs or chemicals added to animal feed, which are shown to be safe for the animal, and which leave no residue in edible tissue at the time of slaughter if used in accordance with label directions that are "reasonably certain to be followed in practice."

It should be pointed out that Congress enacted this exemption from the Delaney clause explicitly to permit the use of DES in cattle and sheep. DES was the major subject of the congressional debate. At the time, Congress knew that DES was a carcinogen and that misuse could result in illegal residues.

The data submitted in support of a regulation providing for the use of from five to a maximum of 20 milligrams of DES per day for beef cattle establish that no DES residues were detectable in edible animal tissues when the medicated feed is withdrawn 48 hours prior to slaughter. This determination was made using the officially approved assay method which is sensitive to at least two parts per billion. The regulations authorizing the use of DES, therefore, required that it be withdrawn at least 48 hours prior to slaughter.

It should be noted that, under the Delaney clause, as amended, the finding of residues of DES in the livers of some animals does not, in itself, require disapproval of the drug. Illegal residues should result in enforcement action and punishment of the offender if misuse of the drug is proven, rather than withdrawal of approval of the new animal drug application. Such withdrawal is indicated only if it is determined that the label directions are not—and I quote from the law—"reasonably certain to be followed in practice."

As I am sure you know, because of reports of misuse of DES resulting in illegal residues, more than 6 months ago, the U.S. Department of Agriculture and the Food and Drug Administration instituted new controls over the use of DES in animal feed to further assure that DES residues would not be found in the livers of animals fed DES. No new restrictions were instituted for DES administered by implant because no violations were or have been found when used in that way. Livers are the only edible tissue in which DES has been detected after misuse of medicated animal feed. This is so even though the USDA examines flesh tissues whenever a positive liver sample is found.

These controls were instituted after USDA's monitoring program disclosed DES residues in approximately one-half of 1 percent animal liver samples collected in 1971. At that time, we extended the withdrawal period for DES to 7 days before slaughter. The additional withdrawal period was believed to be more practical and offered an additional margin of safety. USDA, at the same time, established a mandatory certification program, requiring livestock producers to provide written certification that they complied with the 7-day withdrawal period.

Despite these precautionary steps, USDA has continued to detect residues of DES in the livers of animals offered for slaughter. During the first 6 months of 1972, DES residues have been found in 58 livers or 2.3 percent of samples analyzed. These tests show that the drug is not always being used as required by the regulations.

Mr. Chairman, there has been substantial publicity and confusion concerning FDA's position with respect to DES. When we instituted our new controls earlier this year, I stated unequivocally that if the new and increased restrictions failed to reduce the incidence of violative residues of DES, FDA would withdraw approval for the use of DES in animal feeds. On finding the incidence of violations increasing, late last month we commenced appropriate proceedings to withdraw the approval for the use of DES.

Senator KENNEDY. Does that mean you have banned it or not banned it?

Dr. EDWARDS. I will explain that as I move along, Mr. Chairman. We have proposed withdrawing approval of the new animal drug applications which in essence will be to ban the use of the drug in animal feeds.

Senator KENNEDY. Can they feed the animals today or can they not?

Dr. EDWARDS. They can feed DES to animals today.

Senator KENNEDY. How long will they continue under the procedures to be able to feed animals DES?

Dr. EDWARDS. We proposed withdrawing approval for DES. Under the procedures, there is a 30-day period for comments, and this period expires as of Friday of this week.

After evaluating the comments that are received by the manufacturers, we have to make a determination of whether or not to ban or whether there is sufficient evidence that has been adequately explored to call for a hearing on it.

Senator KENNEDY. The Secretary could declare it an imminent hazard, could he not, and stop it today?

Dr. EDWARDS. That is correct. If we found and so advised the Secretary that DES was an imminent hazard, it could be banned immediately.

Senator KENNEDY. And halt it right away?

Dr. EDWARDS. That is correct.

Senator KENNEDY. And you are not prepared to make that recommendation to the Secretary?

Dr. EDWARDS. We are not, nor is the National Cancer Institute, nor any of the authorities we have consulted, willing to categorize this as an imminent hazard.

Senator KENNEDY. In spite of all the information and the research and the studies that have been made to indicate there is an increase in DES residues in the liver of cattle generally? You are still not prepared to make such a recommendation to the Secretary that it is an imminent hazard?

Dr. EDWARDS. That is right, Mr. Chairman, because we have absolutely no evidence that the use of DES in animal feed has caused harm to human health.

Senator KENNEDY. Your hearing procedures have taken up to 15 months, have they not, before a final decision was made, and they have been taking that long in the past in some instances?

Dr. EDWARDS. There have been some prolonged hearings. But I assure you, if the hearing route is the way we go, it will not take 15 months. We anticipate the hearings lasting somewhere between 2 and 3 months.

Senator KENNEDY. When you say in your testimony, "We commenced appropriate proceedings to withdraw the approval for the use of DES," you really have not taken the final step, have you, Mr. Commissioner, the final step being the urging of the Secretary to ban it? You are unwilling to take that final step?

Dr. EDWARDS. We have not taken that step under the route we are going. We have to allow time for comment.

Senator KENNEDY. If you made the recommendation that he ban it, he could ban it within the law.

Dr. EDWARDS. If we declared it an imminent hazard; that is correct.

Senator KENNEDY. But you are either not sufficiently concerned or the evidence presented to you is not sufficiently convincing to the point you think you ought to take that important step. This is just so I understand your position.

Dr. EDWARDS. I would not want to suggest for one moment we are not concerned, but we feel there are many, many hundreds of other chemicals in which we have equal concern.

Senator KENNEDY. How often have they done that in the past? How often has the Food and Drug Administration recommended to the Secretary that he ban a drug?

Dr. EDWARDS. As an imminent hazard, you mean?

Senator KENNEDY. Yes.

Dr. EDWARDS. I am not sure. Maybe Mr. Hutt can answer that.

Mr. HUTT. Senator, we would have to provide that information for the record. Neither of us has been here long enough to go back in history.

The Food and Drug Administration cannot identify any occasion in which the Secretary of the Department of Health, Education, and Welfare immediately banned a drug under the "imminent hazard" to health provisions of the Federal Food, Drug, and Cosmetic Act.

Senator KENNEDY. You must have made a study of this. This ought to be one of the alternatives that you were considering in your recommendations to the Commissioner.

Mr. HUTT. We certainly did consider it.

Senator KENNEDY. What were the factors that you considered?

Mr. HUTT. The question of whether something is an imminent hazard is a scientific determination involving the danger to human health. It is specifically laid out in the statute.

We consulted the scientists, as the Commissioner mentioned. We talked to the National Cancer Institute. No one thus far has been able to come up with a rationale for saying DES is an imminent hazard to health.

Senator KENNEDY. As I understand from reading the newspaper reports, the head of the Cancer Institute said it would be prudent to ban it now.

Mr. HUTT. Senator, we have talked to Dr. Rauscher about that. He obviously will speak for himself on that. He has informed us that at the time he made that statement, he obviously had no information about the legal requirement for a finding of imminent hazard.

Senator KENNEDY. Wait a minute. The legal? What about the health? Are we getting bottled up on legalities, or are we talking about the health issue to the American people?

Mr. HUTT. There is a requirement in the law that there be a determination by health authorities that there is an imminent hazard to health. As a health authority, the Commissioner has no evidence on which to base such a determination; therefore, as a matter of law, we cannot order a ban pending a hearing.

Senator KENNEDY. You mean as a health issue, you would like to ban it, but somehow the legalities of the statute under which you are operating do not give you the power to do so? Is that what we are presenting to the American people?

The head of the Cancer Institute will speak for himself, and you feel he would recommend that it be banned; but you cannot find the legal justification to do so?

Mr. HUTT. Senator, no; that is incorrect. If there were no statutory requirements for finding an imminent hazard to health—if in short one could just arbitrarily say that DES is a chemical we would just as soon not have in the food supply—I think anybody would say let us take it out.

However, the statute which Congress enacted specifically precludes us from doing that unless there is a finding of imminent hazard to health, and neither he nor the others with whom we have consulted have been willing to go that for.

Senator KENNEDY. I did not understand his statement to be, "We would just as soon not have it." I thought he said in his statement if it were up to him as a health issue—as a health issue—as the person who is in charge of the National Cancer Institute, he would ban it.

As I understand from your point of view, he was unaware of the legal acrobatics that had to be gone through; therefore, as a health issue, he would like to ban DES but because of the legalisms, either you do not feel you have the power to do so or the legal justification therefore, it is not being done; we are following this other procedure.

Mr. HUTT. Senator, just to recap, he has advised us in his judgment there is no imminent hazard to health.

Now, he must speak for himself, and he will apparently testify shortly.

Senator KENNEDY. But he still recommended that it be banned as a health matter, did he not?

Dr. EDWARDS. I think Dr. Rauscher should speak to this.

Senator KENNEDY. We will get back to that.

All right; do you want to continue?

Under the Federal Food, Drug, and Cosmetic Act, there are two possible courses for withdrawing DES from use in food animals. If an "imminent hazard" to health can be demonstrated, the Secretary of the Department of Health, Education, and Welfare, can issue an immediate ex parte ban on the shipment of DES in interstate commerce. It should be noted that in this case, an opportunity for an expedited hearing must be provided to the affected parties.

A decision that DES is an "imminent hazard" would require immediate removal from the market of all meat from animals fed DES and all feed containing DES.

An "imminent hazard" under the Federal Food, Drug and Cosmetic Act is defined as being a condition so hazardous that the article involved cannot continue on the market during the pendency of administrative proceedings. There is no evidence of harm to humans from the use of DES as a growth promotant in food animals, and conse-

quently, we cannot substantiate a finding that it constitutes an "imminent hazard" to health.

Senator KENNEDY. How much of a hazard is it—not "imminent"—legally?

Dr. EDWARDS. At this point in time, Mr. Chairman, I think all we can say is that it represents a potential hazard.

Senator KENNEDY. If you had a piece of steak in front of you right now, would you let your wife eat it if it had 0.5 percent residues of DES?

Dr. EDWARDS. Absolutely.

Dr. SIMMONS. Mr. Chairman, I think it is important to point out that the hazard we are talking about here is small compared to other hazards which are around us all the time.

Dr. EDWARDS. Mr. Chairman, speaking of the steak, I think the potential hazard in eating a charcoal broiled steak is much greater than the hazard posed by these DES residues, which are minimal, to say the least.

Dr. SIMMONS. There also is evidence, Mr. Chairman, if your wife were going to eat steak, it would probably be better to eat steak with DES in it since DES produces a meat with less fat.

A meat with less fat, when broiled, may produce less of a substance which is a potent carcinogen.

Senator KENNEDY. We will hear from some others on that.

Dr. EDWARDS. Mr. Chairman, I might say at this point that this is an extremely complex issue.

Senator KENNEDY. Everything is complex.

Dr. EDWARDS. That is right.

Senator KENNEDY. If we just leave it to the experts, we will be all right.

Dr. EDWARDS. I think the experts likewise have a responsibility to look at all aspects of all the problems. Unfortunately, I do not think this has always happened.

Continuing, however, thus the only alternative available is to follow the formal procedures of the act to withdraw approval of applicable new animal drug applications—NADA's. This has been done.

As required by law, FDA published a notice of opportunity for a hearing on DES in the Federal Register on June 21, 1972. This notice initiated the procedure to withdraw approval for use of DES in food-producing animals. I would like to insert that proposal at this point in the record.

Senator KENNEDY. It will be included.

(The information referred to follows:)

[From the Federal Register, vol. 37, No. 120—Wednesday, June 21, 1972]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[Docket No. FDC–D–494; NADAs 9525, etc.]

ELANCO PRODUCTS CO. ET AL.

Diethylstilbestrol; Notice of Opportunity for Hearing on Proposal To Withdraw Approval of New Animal Drug Applications

Substantial public interest has been raised about the continued approval of diethylstilbestrol for use as a growth-promotant for cattle and sheep. A Subcommittee of the Committee on Government Operations of the House of Represent-

atives held extensive hearings on this matter during 1971. The Natural Resources Defense Council has filed a lawsuit to compel the Food and Drug Administration to withdraw approval of diethylstilbestrol. In December 1971 the Food and Drug Administration and the U.S. Department of Agriculture instituted a joint program to extend the withdrawal period for diethylstilbestrol containing feeds from 2 days to 7 days and to require written certification of withdrawal (36 F.R. 23292, 24928). At the same time, a new and more sensitive method of detecting diethylstilbestrol was put into widespread use. Using this more sensitive method, the number of reported illegal residues of diethylstilbestrol in animal livers has increased rather than decreased.

In light of this increase in reported diethylstilbestrol residues the Commissioner of Food and Drugs is considering whether it is appropriate to withdraw approval of diethylstilbestrol, to institute new more effective restrictions to reduce illegal residues, or to take other action. The Commissioner has concluded that, prior to making a final decision as to the appropriate course of action to be taken, additional information is needed from all segments of the public, including consumer organizations, the animal husbandry industry, the pharmaceutical industry, the academic community, members of Congress, and other governmental agencies and departments.

The Commissioner has concluded that the most appropriate forum for public consideration of this matter is a public hearing, to develop on the public record the information necessary for a conclusion as to the proper handling of this matter. Under section 512 of the Federal Food, Drug, and Cosmetic Act, an opportunity for a hearing on a proposal to withdraw approval of a new animal drug application is provided to the holder of the application. The Commissioner has discretion in permitting other interested individuals and organizations to participate in any subsequent hearing. Accordingly, the Commissioner has concluded that it would be appropriate to propose withdrawal of the approval of the new animal drug applications for diethylstilbestrol in order to utilize the hearing mechanism provided in the statute for this purpose.

The Commissioner has not yet concluded that withdrawal of approval for diethylstilbestrol is the appropriate course of action. Requests for a public hearing may be accompanied by proposals for additional and more effective restrictions on diethylstilbestrol that would obviate such withdrawal of approval. Alternative restrictions that could be considered include prohibition of use for human food of livers from animals receiving diethylstilbestrol, or requiring such livers to be tested prior to marketing, or requirements limiting the persons who may use the drug.

In the event that a hearing is held, the Commissioner will wish to obtain data and information from all interested persons with respect to such relevant matters as the current rate of illegal residues and ways in which this might be reduced, the potential effect upon the public health and safety of a low rate of illegal diethylstilbestrol residues, the likely effect on the environment of withdrawing approval of diethylstilbestrol, the availability of alternative growth-promotant drugs and their safety and effectiveness as compared with diethylstilbestrol, the need for growth-promotant drugs in the animal husbandry industry, differences or similarities between administration of diethystilbestrol by feed or by implant with respect to the potential for residues, the accuracy and reliability of present detection methods for diethylstilbestrol, the potential availability of more sensitive detection methods for diethylstilbestrol and the likely result of their use, and any other relevant information.

Accordingly, notice is hereby given to the following listed holders of new animal drug applications that the Commissioner of Food and Drugs proposes to issue an order under section 512(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(e)) withdrawing approval of the following listed new animal drug applications which provide for use of diethylstilbestrol as a growth promotant for cattle and sheep:

Elanco Products Co., Post Office Box 750, Indianapolis, IN 46206. NAD Nos. 9525, 11090, 42162.

Pfizer, Inc., New York, N.Y. 10017. NADA Nos. 9757, 9783, 11356, 9770.

Walnut Grove Products, Division of W. R. Grace Co., Atlantic, Iowa 50022. NADA No. 10132.

Dawes Laboratories, Chicago, Ill. 60632. NADA Nos. 10421, 11485, 34916.

Simonsen Manufacturing Co., Quimby, Iowa 51049. NAD No. 10566.

Vineland Laboratories, Inc., Subsidiary of Damon, Vineland, N.J. 08360. NADA No. 10964.

Hess & Clark, Division of Rhodia, Inc., Ashland, Ohio 44805. NADA Nos. 11295, 12553, 44344, 45982, 45981.
Peter Hand Foundation, Inc., Waukegan, Ill. 60085. NADA No. 14773.
O. M. Franklin Serum Co., Denver, Colo. 80216. NADA No. 15274.
Fort Dodge Laboratories, Fort Dodge, Iowa 50501. NADA No. 31446.
Thompson-Hayward Chemical Co., Kansas City, Kans. 66106. NADA Nos. 35019, 35017.
Feed Additives, Inc., Fremont, Nebr. 68025. NADA Nos. 36313, 37869.
Dale Alley Co., St. Joseph, Mo., 64501. NADA Nos. 36671, 36554.
Standard Chemical Manufacturing Co., Omaha, Nebr. 68103. NADA Nos. 36976, 34735.
National Oats Co., East St. Louis, Ill. 62205. NADA Nos. 37148, 37541.
Texas Nutrition & Service Co., Fort Worth, Tex. 76108. NADA Nos. 38507, 38510, 39509.
Bresley-Koelling, Inc., Ord, Nebr. 68862. NADA No. 39491.
Feed Products, Inc., Denver, Colo. 80211. NADA Nos. 39716, 39718, 39717, 39715.
Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N.J. 07065. NADA Nos. 39772, 42840, 10261.
Chemetron Corp., Chicago, Ill. 60611. NADA No. 42355.
Farmland Industries, Kansas City, Mo. 64116. NADA No. 42702.
Western Farmers Association, Seattle, Wash. 98111. NADA No. 44526.
E. R. Squibb & Sons, New Brunswick, N.J. 08902. NADA No. 11365.
Western Feed Supplements, Ellensburg, Wash. 98926. NADA No. 40014.
Ultra Life Laboratories, Inc., East St. Louis, Ill. 62201. NADA No. 38682.
Square Deal Fortification Co., Kouts, Ind. 46347. NADA No. 39161.
Falstaff Brewing Corp., St. Lousi, Mo. 63166. NADA No. 44795.
Feed Products, Inc., Denver, Colo. 80211. NADA No. 39715.
American Cyanamid Co., Princeton, N.J. 08540. NADA No. 10259.
S. B. Penick Co., New York, N.Y. 10008. NADA No. 36479.

The Commissioner, based on an evaluation of new information before him with respect to such drugs together with the evidence available to him when the applications were approved, concludes that there is a question as to whether the drugs are shown to be safe under the conditions of use upon the basis of which the applications were approved.

Information available to the Commissioner establishes that use of such drugs has resulted in illegal residues of diethylstilbestrol in animal livers.

In accordance with the provisions of section 512 of the act (21 U.S.C. 360b), the Commissioner hereby gives the applicants an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of the above listed new animal drug applications should not be withdrawn. Promulgation of the proposed order would cause any such drug containing diethylstilbestrol to be a new animal drug for which no approved new animal drug application is in effect. Any such drug or any animal feed bearing or containing such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the Federal Register, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Product Safety Division, Room 6–88, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner, without further notice, will enter a final order withdrawing approval of said applications.

Failure of such persons to file a written appearance of election within 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing concerning a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance. Interested persons who are not parties may intervene to present evidence and file pleadings, and may cross-examine witnesses when in the judgment of the hearing examiner their interests are not adequately protected otherwise or it is required for a full and true disclosure of the facts.

If such persons elect to avail themselves of the opportunity for a hearing, they must file a written appearance requesting the hearing and giving the reasons why the approval of the new animal drug applications should not be withdrawn together with a well-organized and full-factual analysis of the data they are prepared to prove in support of their opposition to the Commissioner's proposal. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the applications, the Commissioner will enter an order stating his findings and conclusions on such data. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

Responses to this notice may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

Pending consideration of responses to this notice, no action will be taken on the notice of opportunity for hearing pertaining to diethylstilbestrol liquid premixes, published in the FEDERAL REGISTER for March 11, 1972 (37 F.R. 5264). Both notices will be acted upon at the same time.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343–51; 21 U.S.C. 360b) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: June 16, 1972.

CHARLES C. EDWARDS,
*Commissioner of Food and Drugs.*

Dr. EDWARDS. Our proposal to withdraw approval of DES must by law allow time for affected parties to submit objections and request a public hearing. Requests for a hearing must be justified on the basis of a genuine and substantial issue of fact. If no hearing is requested, or if objections filed do not support the need for a hearing, prompt action will be taken to issue a final order withdrawing approval for use of DES in food-producing animals. Time for objections and requests for a hearing will end on July 21, 1972—this Friday.

If a request for a hearing is justified based on reasonable grounds establishing genuine issues of fact relevant to this decision, we will immediately proceed to announce and schedule the hearing. If a hearing is held, a final decision must be based on evidence adduced at the hearing. It would, of course, be inappropriate for me to further address the question of whether or not a hearing should be held, or DES banned, until I have had the benefit of reviewing the data submitted in response to our proposal.

Senator KENNEDY. You have had a pretty good opportunity. Tomorrow is the last day.

Dr. EDWARDS. That is correct.

Senator KENNEDY. You must have examined all of these data pretty well if you have only 1 more day.

Has anything come in to date that you can tell us about?

Dr. EDWARDS. Mr. Hutt is more familiar with this aspect.

Mr. HUTT. We have received no formal objections as of yesterday noon. The way the time limit runs under the regulations they must be mailed with a postmark no later than midnight Friday.

It is quite often the case that all the objections are mailed on the last day, and we would therefore not receive them until next Monday. In any event, we have received none as of yesterday.

Senator KENNEDY. You have not received any?

Mr. HUTT. None. If none is received, that will be the end of the matter.

Senator KENNEDY. What do you mean by that?

Mr. HUTT. There would be an immediate order issued withdrawing approval of the drug, and it could no longer be used.

Senator KENNEDY. By when? When would you know? If your mail does not come in on Monday, will we get something Monday afternoon?

Mr. HUTT. The notice would have to be drawn up, and we would have to go through the proper procedures, Senator. But it would certainly be an expedited matter, I assure you.

Senator KENNEDY. Help us out a little.

Mr. HUTT. A week.

Senator KENNEDY. Why does everybody wait until the end?

Mr. HUTT. Presumably, Senator, we have made it clear that we are not going to grant a hearing unless there is good cause shown. We have made that very clear, as the Commissioner has said.

Therefore, the industry is on notice if they do wish to have a hearing—and we do not know that at this moment—they must do a first-rate job on their presentation.

Senator KENNEDY. They have not indicated to you, though, that they want a hearing at this time?

Mr. HUTT. There was an initial press release that one company would submit objections. That was when we initially announced the opportunity for the hearing.

Senator KENNEDY. Can one company delay this?

Mr. HUTT. Yes. Let me qualify that. The notice in the Federal Register lists a number of new animal drug applications. If any one of the individuals involved does not submit an objection and request for a hearing, we may withdraw that particular NADA if any hearing is to be held on the other NADA's.

Senator KENNEDY. If you do not get any mail tomorrow, can you tell us whether you are planning to ban it?

Mr. HUTT. If we get no mail whatever?

Senator KENNEDY. Yes.

Mr. HUTT. We will ban it.

Dr. EDWARDS. Even if we get mail, as Mr. Hutt has pointed out, and as I did in my testimony, the respondents to our proposal have to demonstrate some reasonable issues on which to hold a hearing, or we will obviously ban it.

Mr. Chairman, let me now shift for just a moment from the specific issue of DES to other subjects of broader concern which I also believe are pertinent to this hearing.

Quite candidly, judging the safety of any substance used in food is not a simple matter. A number of considerations and issues cannot be ignored in determining whether a substance is suitable for use in food.

In making a judgment to withdraw approval for a useful substance in food, we must be mindful of other ramifications which can result from such action. A theoretical or potential risk to the public health may well be sufficient reason for moving against a particular food ingredient.

On the other hand, where the use of a substance substantially increases the availability of a food, affects its nutritional value, or

lessens the possibility of other hazards to health, a potential problem may not be sufficient to justify completely removing the product from the market.

We are concerned about the extent to which our decisions may affect the nutritional value of our food supply, and I am certain this committee and every consumer is concerned with the impact of decisions which may influence the availability of nutritious food to large segments of our population.

Many decisions affecting our food supply may also have a significant impact on the environment, and could present as difficult a health problem as the potential direct effect of ingesting minute traces of the substance. Indeed, under the National Environmental Policy Act, we are required to consider the environmental effect of our actions.

Perhaps the most critical scientific consideration is the as yet unresolved question as to whether extremely low levels of a substance actually represent a potential risk for the induction of cancer in man. It is this concern that was a preeminent consideration in our decision to develop the research resources at Pine Bluff, Ark., the National Center for Toxicological Research.

All of these factors are considerations for which the answers are extremely difficult to obtain; and in certain instances, we are only able to give them limited attention because of the law.

For example, the all-or-nothing philosophy of the Delaney clause sounds eminently reasonable to the consumer because he wants absolute assurance that no harm will come from anything he eats. And yet, we must regulate in the certain knowledge that absolute safety is impossible and science nearly always incomplete. We are certainly opposed to carcinogenic substances entering our food supply, as well as other harmful substances. We must keep in mind, however, that a statistical association of substances causing tumors in experimental animals may not have any relationship to the induction of cancer in humans. This must be considered for many substances both natural and synthetic that enter man's environment.

Mr. Chairman, DES will not be the only substance to generate these kinds of issues. This is why we cannot recommend enactment of S. 2818. We do not believe piecemeal legislation directed at any given substance is appropriate for making regulatory decisions that are to be based on scientific evidence. We now have sufficient regulatory authority to act effectively on behalf of the consumer. In this sense, S. 2818 is unnecessary.

I do appreciate the opportunity to discuss these issues with your committee, and I will be pleased to answer any questions you or members of your committee believe will be helpful.

Senator KENNEDY. I do have some questions, but what I would like to do is hear from our next witnesses. Then I would have some brief questions and release you. We will not delay you terribly long.

I would like next to welcome Dr. Peter Greenwald, Director of the Cancer Control Bureau of the New York State Department of Health.

Dr. Greenwald received his M.D. from the State University of New York at Syracuse, his M.P.H. from the Harvard School of Public Health. He is also clinical assistant professor of medicine at Albany Medical School.

## STATEMENT OF PETER GREENWALD, M.D., DIRECTOR OF THE CANCER CONTROL BUREAU, NEW YORK STATE DEPARTMENT OF HEALTH

Dr. GREENWALD. In New York State, nine teenage girls are known to have developed vaginal cancer 15 to 19 years after their mothers took DES or another synthetic estrogen during pregnancy. Six of these girls have died of advanced disease.

I plan to summarize our study of these nine patients, present the reasons we believe there is a cause-and-effect relationship between DES and vaginal cancer, and briefly discuss our continuing studies of DES in relation to other human tumors.

Physicians, hospitals and laboratories throughout New York State, exclusive of New York City are required by State law to report all patients with cancer to a registry maintained by the health department.

Senator KENNEDY. Do you think there ought to be a national registry maintained?

Dr. GREENWALD. Yes.

Senator KENNEDY. Why do you believe this?

Dr. GREENWALD. I believe it is essential for a number of reasons.

One is that we have to have detailed information, as much as possible, on what the risk is, the number of people exposed; and in this instance with DES the details about the dosage, and whatever we can learn as to how to prevent cancer, and the best mode of treatment.

There have been some steps taken in this direction, although this has not been formalized.

Senator KENNEDY. Registration of this kind of research would be extremely difficult, would it not? It would be virtually impossible?

Dr. GREENWALD. That is right.

The initial observation is possible, but to completely follow through on it as completely as we might wish would be impossible.

New York City was recently added to our State reporting system. Among their many uses, cancer reporting systems allow for rapid identification of people with specific tumors for study of possible causative factors.

In this instance, we believe that all diagnosed vaginal tumors in women under 30 years old and from a wide geographic area—upstate New York and Long Island—were reported for further study.

The nine patients were studied in detail for history of drug use by their mothers during pregnancy. DES therapy was definitely given to mothers of seven patients. Obstetricians used the therapy to prevent threatened spontaneous abortion.

The mother of the eighth patient told us herself that she had received therapy during pregnancy in order to avoid "a miscarriage like the last time."

Destruction of records, however, prevented definite ascertainment of whether DES was used. The ninth patient took another synthetic estrogen, dienestrol, which is very similar to DES.

Details on dosage, the period during which DES was taken by the mothers, and the age and year at diagnosis in the daughters are shown

in table 1 appended Place of birth varied widely with four patients being born in upstate New York, four in New York City, and one in Pennsylvania

All patients were single and had no children Their menstrual periods 1 year before the first symptoms were described as normal, and none had hormone or contraceptive therapy before the onset of first symptoms

I believe that the following facts demonstrate the cause-and-effect relationship between therapeutic use of DES by mothers and vaginal cancers in their daughters:

(1) The mothers of all patients studied had definitely or probably taken DES or another synthetic estrogen during pregnancy;

(2) None of the mothers of a comparison group of girls had taken DES This difference between patients and a comparison group of girls of the same age and born at the same hospitals is statistically significant;

(3) All nine patients were born during the period 1951 through 1955, the time of peak clinical use of DES to prevent miscarriages;

(4) There is an absence of vaginal cancer in girls of this age group born before the time of common use of DES;

(5) The rather uniform microscopic pattern of these tumors supports the possibility of a common cause;

(6) The observations are consistent with our biologic knowledge of DES, and particularly with the fact that DES can be shown to produce cancer in a variety of animals; and

(7) Similar observations were made by two independent investigators. Our studies confirmed and expanded upon those by Doctors Herbst, Ulfelder, and Poskanzer in Boston.

It should be pointed out that I believe, as do most cancer investigators, that cancer is generally not the result of a single cause, but rather of a chain or web of causes which interplay with each other.

By "cause-and-effect relationship," I mean that the DES was a necessary factor, and the cancer would not have developed without it. There are undoubtedly additional factors affecting susceptibility and resistance, which are yet to be uncovered.

It should also be noted that as we have studied all vaginal cancer patients in the State, and as the mothers of all had been treated therapeutically, there is no reason to suspect that DES in food caused any of the tumors

The depth of the investigation was important here. In one instance, neither the obstetric nor the hospital record showed evidence that DES had been taken It was only after a local pharmacist had searched his records from 1952, which he had fortunately maintained, that we could demonstrate that this mother had been prescribed 100 5 mg DES tablets at 2½ weeks of gestation, and 50 25 mg DES tablets at 11 weeks of gestation

Senator KENNEDY. Does this not really show just on another issue, a quality-of-care issue, the importance of maintaining a record of all prescriptions?

Dr. GREENWALD. Yes; this was very valuable.

Senator KENNEDY. This is certainly not required now, and I would assume it would be a serious administrative burden to the pharmacists all over the country. Probably that is a burden on which they ought

to get some kind of assistance or relief; but it does raise the quality-of-health issue, which I think all of us are trying to deal with. This is a good example of the importance of maintenance of records.

Dr. GREENWALD. It is very dependent on records. A retrospective study such as this always is, and we felt we were just lucky that this pharmacist kept this record.

Senator KENNEDY. What is his name; do you remember?

Dr. GREENWALD. No; he is from the town of Lyons, N.Y.

As for other tumor types, in persons of both sexes, we have obtained prenatal drug use histories on mothers of all females born after 1947—when DES began to be used to prevent miscarriage—reported with cancers of the breast, uterine cervix—adenocarcinoma—uterine corpus, fallopian tubes and urethra, and all males born in the same period with cancers of the breast, prostate, penis, epididymis, spermatic cord and urethra.

A number of patients with cancers of the ovary, testis, bladder, and kidney were also studied. These sites were chosen primarily because they derive embryologically from the same general area as the vagina or because they are hormone-dependent organs.

DES was taken during pregnancy by the mother of only one patient, an 18-year-old girl with adenocarcinoma involving both the cervix and vagina; she is case No. 6 on the table.

Time trends in incidence for the 0 to 24 year age group, born at a time when DES might have been used in pregnancy, were compared to the unexposed 25 to 34 year age group. There were no increases that could be attributed to DES use. There is thus far no indication that maternal use of DES contributes to the development of tumors other than those of the lower female genital tract.

Dr. Hollis S. Ingraham, our State commissioner of health, 1 full year age took the lead in responding to this evidence of DES and vaginal cancer.

Dr. Ingraham alerted all of the State's physicians to this problem, and suggested that the Food and Drug Administration do likewise on a national scale. We are recommending intravaginal examination of girls whose mothers were treated with DES, and are helping mothers who aren't sure whether they received DES to find out if they were so treated and the dosage level.

Senator KENNEDY. Do you know what the results of Dr. Ingraham's request of the Food and Drug Administration were? Do you know what response he received?

Dr. GREENWALD. Yes.

We wrote the Food and Drug Administration in June of last year, and then there were Congressman Fountain's hearings the following fall.

About that time, the Food and Drug Administration did alert all the physicians in the country. I am not sure to what degree our own information caused the action, but they did follow through.

With respect to DES in foods, it is difficult to assess the relative significance of large therapeutic doses as compared to the trace levels in foods. My personal opinion—and it is an opinion—is that it would be prudent to insure that DES is not in food when it reaches the table.

Past actions on sweetening agents—cyclamates—and pesticides may also have some bearing on the DES question, and incidentally, we

used the New York State Cancer Registry to evaluate both cyclamates and pesticides.

I have some reluctance in comparing different situations, but it is clear that with DES we have direct evidence of a cancer-producing effect in humans, while with the other compounds, we do not.

Senator KENNEDY. Are you saying that there is more evidence available that DES causes cancer in human beings than was available on cyclamates?

Dr. GREENWALD. Yes.

As far as I know, there is no evidence whatsoever that cyclamates cause cancer in humans.

Senator KENNEDY. They have been banned; have they not?

Dr. GREENWALD. Yes; but with diethylstilbestrol there is evidence in humans. I did not comment on whether the ban on cyclamates was the right action, but in a comparative sense, the DES is more of a threat to humans, to pregnant women.

Senator KENNEDY. As a researcher or as one who has studied this area, you are convinced there is more evidence that DES causes cancer in human beings?

Dr. GREENWALD. Yes; and I would say evidence is limited to ingestion by pregnant women at this point.

Senator KENNEDY. Very good.

Thank you very much.

(Additional information supplied by Dr. Greenwald follows:)

Table 1. Vaginal Cancer and Maternal Use of Synthetic Estrogen in Patients Reported in the New York State Cancer Registry, 1950-1972.

| Case No. | Date of Birth | Age (Year) at Diagnosis | Maternal Synthetic Estrogen Therapy During Pregnancy | | |
|---|---|---|---|---|---|
| | | | Time Started* | Time Ended* | Drug & Dose |
| 1 | 2/9/51 | 15 (1966) | 5 wk | Delivery | Stilbestrol (oral), 5 mg/day initially, increased 5 mg/wk to 125 mg/day |
| 2 | 4/5/52 | 19 (1971) | 2½ wk | 3½ - 4 mo | Stilbestrol (oral), 5-mg tablets initially & 25-mg tablets later (exact dose unknown) |
| 3 | 9/28/52 | 15 (1968) | Conception | Delivery | Stilbestrol (oral), 0.1 mg/day until 3d week, then 5 mg/day to 100 mg/day |
| 4 | 10/2/52 | 17 (1970) | 3 mo | 6 mo | Dienestrol (oral), 5 mg/day; also estrone (intramuscularly) for 2 doses at 3d mo; progesterone & thyroid 3d mo to delivery |
| 5 | 4/20/53 | 17 (1970) | 2½ mo | 5 mo | Stilbestrol (oral), possibly 65 mg/day; also, 28 "estrogen" shots from 2½ mo to 4½ mo |
| 6 | 4/5/52 | 18 (1970) | 2½ mo | 5½ mo | Stilbestrol (oral), 25 mg/day; from 2½ mo to 5½ mo |
| 7 | 8/18/53 | 17 (1971) | 3 mo | Delivery | Possibly stilbestrol, dosage unknown |
| 8 | 2/3/52 | 19 (1971) | 3 mo | 9 mo | Stilbestrol (oral), 75 mg/day from 3 mo to 7 mo, decreased beginning 7 mo to 50 mg/day and at middle of 8 mo to 25 mg/day |
| 9 | -/-/55 | 17 (1972) | 3 mo | 9 mo | Stilbestrol (oral), dosage unknown |

*Time of gestation

Senator KENNEDY. We welcome Dr. Arthur L. Herbst, head of the department of gynecology at Massachusetts General Hospital.

**STATEMENT OF ARTHUR L. HERBST, M.D., ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY, MASSACHUSETTS GENERAL HOSPITAL, HARVARD MEDICAL SCHOOL, BOSTON, MASS.**

Dr. HERBST. Thank you, Senator Kennedy.

At the outset, I would like to acknowledge the invaluable contributions to these studies of Dr. Howard Ulfelder, professor of gynecology; Dr. Robert E. Scully, professor of pathology; and Dr. David C. Poskanzer, who serves as our epidemiologist. All are from the Massachusetts General Hospital and Harvard Medical School.

Prior to 1966, there had not been one case of adenocarcinoma of the vagina in a woman under age 25 years at our hospital, and only a very few rare case reports existed in the medical literature.

Then between 1966 and 1969, six women under 25 years of age with adenocarcinoma of the vagina were seen and treated at the Vincent Memorial Hospital, Department of Gynecology, Massachusetts General Hospital.

During that period, we had the opportunity to review the findings of a seventh similar case treated elsewhere. These young girls had sought medical advice because of excessive vaginal bleeding and were found to have vaginal cancers.

Six of the seven young patients were able to be treated and all six are living and well today.

The seventh patient had advanced disease when first seen and has since died. During this time, we also heard of an eighth identical case treated at another Boston hospital and these eight cases were more than had been reported in the medical literature up to that time.

A case control retrospective epidemiologic study was carried out to compare in detail the patients with carcinomas and other families with an appropriate control group of young ladies of similar age who did not have these cancers.

Four matched controls were obtained for each patient with carcinoma by examining the birth records of the hospitals in which the patients were born.

Females were identified who were born within 5 days of each girl with carcinoma, and we then contacted the women who gave birth to the daughters closest in time to each of our patients with carcinoma. In this way, 32 control families; that is, four for each patient with cancer, were obtained whose replies to our detailed epidemiologic questionnaire were compared to the replies of the families of the girls with carcinoma.

There was no significant differences to the replies obtained from these two groups for most of the topics covered. However, there was a highly significant association between the treatment of the mothers with diethylstilbestrol during pregnancy and the subsequent development of adenocarcinoma of the vagina in their young daughters years later.

Other factors found to be significant were bleeding during the study preganancy and a history of previous pregnancy losses. The fact that

these were so-called high-risk pregnancies was the indication for stilbestrol administration.

Six of the seven mothers interviewed volunteered the information that stilbestrol had been prescribed for them. The seventh was uncertain, but her physician identified the drug as diethylstilbestrol.

For one of the eight mothers, whose daughters had this carcinoma, there was no evidence that stilbestrol was administered during pregnancy. She had not experienced prior pregnancy loss or bleeding during the study pregnancy. As mentioned previously, these tumors were known to occur, though very rarely, in women of this age group prior to the availability of stilbestrol. It is thus possible that factors other than maternal stilbestrol ingestion are operative in the development of these cancers.

After the publication of our findings last year, we heard of additional cases of cancer identical to the ones that we studied; and you have already heard a description of some of these by Dr. Greenwald.

Because it was obvious that many more of these tumors would develop in the future, and since definitive statements on tumor behavior and therapy are not yet warranted, my colleagues and I established a registry for clear-cell adenocarcinoma of the genital tract in young women to help centralize this important information and rapidly obtain data on a large number of cases.

Senator KENNEDY. Do you think it would be worth while to have a national registry on this?

Dr. HERBST. That is exactly what we are trying to do. We have been in touch with physicians all over the country in the medical centers, and in the departments of obstetrics and gynecology, in order to study this.

Senator KENNEDY. Is there a role for the Federal Government in this on developing legislation?

Dr. HERBST. For legislation?

Senator KENNEDY. Yes.

Dr. HERBST. I think accurate records could be kept, and we are making data from our records available to the Food and Drug Administration so that they can carry through with what additional record-keeping they want.

Senator KENNEDY. Maybe you can think about that and let us know if you think there is a need for this at the national level. I am convinced of the importance of it, and we would welcome your thoughts about a role that we might be playing in this.

Dr. HERBST. The registry contains varying amount of information on over 80 cases of adenocarcinoma of the vagina or cervix in young women under age 25 years.

This information has been made available to the registry thanks to the generous cooperation of many physicians throughout the United States. The details of a few of these cases have been published in the medical literature by different investigators, and I have cited that in the references in the prepared statement, in Nos. 1, 2, 3, 4, and 5.

Maternal histories are not available in all cases entered in the registry, but stilbestrol, dienestrol, or hexestrol have been implicated in most of the cases for which we have been able to obtain a history.

Dienestrol and hexestrol are chemically similar to stilbestrol. All three are potent nonsteroidal synthetic estrogens. Thus far, we know

of no cases which have been associated with steroidal estrogens. It must be remembered, however, that the nonsteroidal compounds were the ones most frequently prescribed to support pregnancies in the past.

We have, from the beginning of our investigations, been interested in the relation of the dosage and time of administration of stilbestrol during pregnancy to the appearance of these cancers. Our information in these categories obviously varies depending upon the mother's recollection of past medication, the availability of doctors' records, et cetera.

Such data are often difficult to obtain since we are dealing with pregnancies that for the most part occurred 15 to 25 years ago.

Nevertheless, we do know of one case for which the record indicates the mother received only 1.5 milligrams of stilbestrol daily. Her daughter developed cancer.

In a different case, the patient's record reports the use of stilbestrol for only 12 days during the first trimester of pregnancy.

It is my impression that there is wide variation both of the doses used and the duration that the mothers of the girls with cancers were treated. I do not think we can define with confidence the smallest dose or shortest duration of exposure to these compounds that might endanger the fetus.

Senator KENNEDY. Really, we cannot define the smallest safe dose for a carcinogen either, can we?

Dr. HERBST. That is right; I do not believe we can.

Our studies to the present time do not permit us to estimate the risk of cancer development in any young girl whose mother took stilbestrol during pregnancy.

We do not know the number of women in this country or elsewhere who have been treated with stilbestrol or similar drugs during pregnancy. It probably is many thousands or perhaps even millions.

Only a few cases of carcinoma have been uncovered so far. Although we cannot specify the risk of cancer development, present status suggests the risk is small. Nonetheless, the results of our study indicate that intrauterine exposure to stilbestrol and similar compounds increases the risk of development of these adenocarcinomas years later.

Senator KENNEDY. Very good. I have just a few questions, Doctor. In your study, do you consider DES to have been a major factor in the development of vaginal cancer?

Dr. HERBST. A major factor? Yes, we do.

Senator KENNEDY. Would you be concerned if pregnant women were exposed to trace levels of DES in food over the course of their pregnancies?

Dr. HERBST. As I mentioned during my testimony, I do not think we can find what levels of exposure would be safe. I just do not think we know.

Senator KENNEDY. As I understood, you could not determine what would be dangerous, but you cannot say either what would be safe?

Dr. HERBST. That is correct. I would agree with that.

Senator KENNEDY. Nonetheless, you are satisfied that some DES—and you are not prepared to state at what level—is also a factor in development of vaginal cancer?

Dr. HERBST. Yes.

Senator KENNEDY. In your medical opinion, is there a possible risk to humans if they are continually exposed to trace levels of DES in their daily diet for over a long period of time?

Dr. HERBST. From our studies, one really cannot answer that question because we are dealing with a limited situation; namely, a woman who is pregnant with a female fetus.

I think if she is exposed to stilbestrol in her diet, the risk of development of cancer increases, and our studies up to the present time have not yet related the increase in risk to dosage.

It has occurred with high doses, small doses, long exposure, and short exposure; so I would have to say we do not know.

Senator KENNEDY. Can you give us any help as to what the parameters are regarding high dosage, low dosage? What can you tell the laymen?

Dr. HERBST. The high doses that were used and were often publicized in the medical literature would go up to as much as 125 milligrams a day in the latter part of pregnancy.

As I mentioned, the lowest dose we know is 1.5 milligrams per day. These are doses where there is definite association with carcinoma development, so there is really a wide difference of dosage associated with carcinoma development.

I have to again emphasize we have a small number of cases where the dosage of stilbestrol is known.

Senator KENNEDY. But you are satisfied that with trace levels over a period of time in pregnant women, the incidence of cancer is increased?

Dr. HERBST. We have documented it for 1.5 milligrams. Whether a dosage smaller than that can do it, we obviously do not know.

Senator KENNEDY. Thank you very much.

If your wife were pregnant, would you have any reluctance in seeing her take DES for the period of pregnancy?

Dr. HERBST. I would not want her to take DES if she were pregnant.

Senator KENNEDY. Dr. Edwards, could you come back?

We are going to vote at 11. I think we could recess just very briefly, and we will go over and vote and then come back.

I would like to have your own thinking about the administrative procedures that can be followed.

I do not think we will be gone a long period of time. We will recess for about 10 or 12 minutes.

(Short recess.)

Senator KENNEDY. Mr. Commissioner, you appeared before the Fountain committee several months ago. You indicated, in response to a question:

We will investigate all reported residues. Immediately upon receipt of such reports, appropriate legal action will be taken against offenders if residue reports are substantiated by field investigation; and should these measures prove unsuccessful, we will be prepared to ban its use entirely in animal feed.

Do you remember that comment?

Dr. EDWARDS. Absolutely; yes.

Senator KENNEDY. Can you tell us about how many cases have actually been prosecuted?

Dr. EDWARDS. With your permission, I would like to have our General Counsel speak to that.

Mr. HUTT. There is one criminal suit that has been filed against a person who used the product illegally, resulting in an illegal residue.

There were a number of criminal investigations that were terminated at an earlier stage—18 in number, I believe—for failure of the Department of Agriculture to keep the necessary duplicate samples which, under our statute, are required to be given to any defendant, so that he may conduct appropriate tests himself.

There have been, I believe, five new citations recently, although Dr. Van Houweling can correct me on the precise number, and an additional two that are in a stage of investigation right now.

What we have done, Senator, is instead of bringing a criminal citation under section 305 of the act, which is an order to show cause why the individual should not be criminally prosecuted, in every instance of an illegal residue, we have first sent out investigators to determine whether it appears that there was illegal activity.

If there is an appearance of illegal activity, then we institute the so-called section 305 citation.

Senator KENNEDY. How many reports have been brought to your attention?

Mr. HUTT. Dr. Van Houweling, I believe, can answer that.

Dr. EDWARDS. Dr. Van Houweling, Mr. Chairman, is Director of our Bureau of Veterinary Medicine.

Dr. VAN HOUWELING. I believe the USDA has reported residues in 58 instances up to the present time.

We have reports from investigations of 34 at the present time. There are 24 that we have not yet received a report.

Senator KENNEDY. Just so I understand, there have been 58 allegations or charges; is that right?

Dr. VAN HOUWELING. No. For the record, we should state that the U.S. Department of Agriculture does the sampling. They have reported 58 instances where they detected DES in the liver of slaughtered animals.

Senator KENNEDY. They detected it in 1958. You must have investigated all of those, did you not?

Dr. VAN HOUWELING. They are all under investigation. We have received the reports of the investigations on 34.

Senator KENNEDY. And you are waiting for the others?

Dr. VAN HOUWELING. They are in process.

Senator KENNEDY. The other 24?

Dr. VAN HOUWELING. When we received the notification from Agriculture by telephone that they have liver in which they found DES residues, we immediately phone our field office, and the investigation is begun. We follow this up with TWX instructions.

Senator KENNEDY. So you have received back investigative reports on 34, and 24 you are waiting for; is that right?

Dr. VAN HOUWELING. That is right.

Senator KENNEDY. Of the 34 that you have received, how many of those did you decide to move ahead with criminal prosecution?

Dr. VAN HOUWELING. As Mr. Hutt indicated, we have filed one case.

Senator KENNEDY. When was that filed?

Mr. HUTT. Approximately 3 weeks ago.

Senator KENNEDY. So you have filed that one case. What about the other 33?

Dr. VAN HOUWELING. There are four more in which we are still considering prosecution. They are in various stages of evaluation, either in our Bureau or in the General Counsel's office.

As we indicated, we have two other citation instructions we are considering at the present time.

Senator KENNEDY. So you are considering four more; is that right?

Dr. VAN HOUWELING. That is right.

Senator KENNEDY. What about the other 29?

Dr. VAN HOUWELING. The reports have not been completed, and we have not received the final recommendation from the field as a result of their investigation.

Mr. HUTT. Senator, perhaps I could clarify that.

Are you referring to the other 24 that are still in the field, or are you referring to the 29?

Senator KENNEDY. Let us take the 29.

Mr. HUTT. There were a number, as I mentioned, 18 of which I am aware of, and there may well have been all 29, in which we concluded that the case was legally defective and that we could not file, or where investigation showed that there was no history of use of DES by the individual involved that we could determine.

Senator KENNEDY. What do you mean by "legally defective"?

As I understand, there was DES in the liver.

Mr. HUTT. Yes. To the best of our methodology, yes. But the difficulty was, as I stated earlier, that the Department of Agriculture did not retain a sample of the illegal liver.

The Federal Food, Drug and Cosmetic Act provides that we provide a duplicate sample to the potential defendant.

This problem has been overcome. The Department is now retaining the samples.

Senator KENNEDY. You mean because they did not have a duplicate sample, you could not move ahead on the prosecution?

Mr. HUTT. That is entirely correct. It is unfortunate.

Senator KENNEDY. Are there other reasons besides the duplicate sample?

Mr. HUTT. That was the controlling reason.

As I mentioned, there were some cases where the duplicate sample issue was moot because our investigation indicated that there was no wrongdoing on the part of the individual.

Senator KENNEDY. You mean the people are feeding DES to cattle and you cannot prove the wrongdoing even though they are feeding it? You cannot halt it or you are not equipped to halt it?

Mr. HUTT. No.

Perhaps I can break these cases down once again.

Senator KENNEDY. Before you do, I apologize, but the last vote was 46 yeas and 46 nays, and there in another vote now.

I do not want this next one to be 46 to 45. We are going to have to recess and take a vote and come back.

(Recess.)

Senator KENNEDY. The subcommittee will come to order.

We were talking about the number of cases that were brought to the attention of the FDA and the procedures that they followed to investigate the various cases and what action had been taken.

And as I remember, we saw that one of the cases had been filed for criminal prosecution, and there were four others, I believe, that were under immediate consideration for filing.

There were 34 that had been investigated and returned and there were 24 still under investigation.

Mr. HUTT. I perhaps should correct that record somewhat. Of the 58, it is correct, one was filed; it was in the latter part of May, which was about 6 weeks ago now.

Four were recommended for prosecution to my office, and the criminal information is in the process of being put together and typed up for transmittal to the U.S. attorney.

In two, the section 305 citation has been recommended, and that will go forward through our field offices.

In 27, there has been only a preliminary report from the field, not a final report, and thus, at this moment, no prosecution, citation, or anything has been recommended. And in 24 there has been no report whatever because it has been too recent to even get a preliminary report.

Senator KENNEDY. Now, as I understand, you indicated previously that one of the principal limitations in carrying forth a filing for prosecution was the fact there had not been a reserve sample that had been retained and that the procedure had been changed now so they will maintain——

Mr. HUTT. Yes, sir.

Senator KENNEDY. Were there any other reasons?

Mr. HUTT. There was the basic reason, other than the possibility that in some instances, we have not found any use of DES whatever by the individual involved, in which case our investigation leads us to the conclusion that it was a false positive, or naturally occurring estrogen may have been picked up through the chemical analysis, or cross contamination of a kind that we are unable to track down in any way and certainly not the fault of the farmer himself.

Senator KENNEDY. Was another reason that the chemical method was not legal?

Mr. HUTT. No, sir.

We considered whether that would be a legal disability and concluded it would not prevent us from filing prosecutions.

Indeed, the one prosecution filed depends upon the new chemical method. We did consider, as I mentioned, from a legal standpoint, whether it would be permissible to use the new method even though it is not yet the formal legal requirement, and we concluded that we could do so.

Senator KENNEDY. You remember the February 9 memorandum which you offered, in the fourth paragraph, that although the former section 305 hearing was not in itself a legal impediment, the lack of 70T samples, especially in light of the fact that the residues were not determined by the method legally designated in regulations, required the conclusion that prosecution must be refused as legally defective.

Can you explain that to me?

Mr. HUTT. Yes; there were two factors.

Senator KENNEDY. Let me just tell you how it appears to me and maybe you can indicate to me why the methods which you were using to detect this were, you felt at that time, legally defective in a criminal prosecution.

Am I wrong in that interpretation?

Mr. HUTT. I believe, Senator, the conclusion was, as I mentioned, there were two factors involved there.

One was a lack of a sample. The other was the question of the test methodology.

We concluded the lack of the sample was the critical factor that prevented the prosecution. We have concluded that the test methodology is not controlling and will not prevent filing of a criminal information or successful prosecution.

Senator KENNEDY. Well, the courts ruled——

Mr. HUTT. The courts in the past have ruled that a sample is required, a duplicate sample. The courts have not ruled on the question of the methodology and we believe we can be sustained on that.

Senator KENNEDY. Why should there be any confusion about methodology? Why can you not have a valid means for the testing?

Mr. HUTT. Well, what we have been trying to do before publishing this new method, official method, in the Federal Register is to validate it with a collaborative program involving the Food and Drug Administration and the U.S. Department of Agriculture.

We have preliminary results back from that validation, which indicate that we can go ahead now and publish it in the Federal Register.

Senator KENNEDY. Isn't part of the reason that there has not been a greater administration oversight on this, is because you did not have a validated procedure for the investigators?

Mr. HUTT. To my knowledge, no, sir.

Senator KENNEDY. Did you have one?

Mr. HUTT. Yes, we do.

Senator KENNEDY. Was it published in the Federal Register?

Mr. HUTT. It is not yet——

Senator KENNEDY. Is it legal?

Mr. HUTT. It is not a disability for a prosecution, Senator. As to whether it is the official method——

Senator KENNEDY. Let us talk about the health of the American people on this. You were using a system that had not been validated, had not followed the Administrative Procedures Act?

Mr. HUTT. Senator, I think we had better step back one step and go through the history of this.

Senator KENNEDY. I am just reading from your memorandum here, so you understand.

Mr. HUTT. I understand.

Senator KENNEDY. I am going to include the memorandum, and maybe you can explain your way out of it, and I am glad to hear the explanation. In an earlier paragraph, you said: "With the result we cannot corroborate the DES residue." That is part of it.

In the fourth full paragraph on the first page, you point out: "Were not determined by methods legally designated in the regulations."

Mr. HUTT. That is correct. We have concluded that that is not a disability of our prosecuting an individual where there is an illegal residue.

Senator KENNEDY. How about the part where it is refused as legally defective?

Mr. HUTT. That was based upon the conclusion that there was not statutorily required reserve sample, which the courts have held is a legal disability. The courts have not said that the failure to use the

method specified in the Federal Register precludes us from prosecution where there is an illegal residue by any method.

Senator KENNEDY. In the next paragraph: "This underscores the fact that the new chemical method must immediately be validated and promulgated in the Federal Register."

Mr. HUTT. Yes. We are proceeding to do this in order to bolster our case.

Again, it is our legal conclusion it is not necessary. Let me explain the reason for the methodology. The reason for the methodology is set out in section 512 of the Federal Food, Drug, and Cosmetic Act.

Senator KENNEDY. Well, this memorandum is dated February 9, and the date today is July 20. Were they ever put into the Federal Register?

Mr. HUTT. It has not yet been put in the Federal Register.

Senator KENNEDY. Why not?

Mr. HUTT. The validation process is in its final stages now. I would like to ask Dr. Van Houeweling how close it is to publication. I am uncertain about that.

Dr. VAN HOUEWELING. We have concluded in this collaborative study that the sensitivity of the method is two parts per billion.

We have another study underway to be concluded in about 2 weeks. If it turns out to be successful, we will be able to publish shortly thereafter. There is general agreement that it is capable of detecting DES at two parts per billion.

Mr. HUTT. I would like to return to the reason for the methodology.

The methodology does not establish whether we may prosecute for illegal residue. The methodology is required under section 512 of the act as a means of establishing the level at which no residue may be found in order to determine whether the drug should remain on the market or not.

If there is any residue by any legal method or unpublished method, then it is a violative article.

I might add that whenever we find a residue by any method whatever that is in our opinion a permissible method scientifically, all of the meat involved is immediately embargoed by the U.S. Department of Agriculture and will never reach the consumer.

Senator KENNEDY. Well, I will leave this, Mr. Counsel. I wish I could be more understanding of your position. I will let the record and the memorandums speak for itself.

Mr. HUTT. Very good, sir.

(The information referred to follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
ROCKVILLE, MD. 20852

OFFICE OF THE
GENERAL COUNSEL

OCT 3 1972

Hon~~orable~~ Edward M. Kennedy
Chairman, Subcommittee on Health
Committee on Labor and Public
Welfare
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

During the hearings on diethylstilbestrol on July 20, 1972, you were concerned that the fact that the new GLC method has not yet been published in the Federal Register as the official methodology for detecting DES might inhibit enforcement action against violators, As I testified at that time, it is our legal opinion that prosecution of violators is neither precluded nor inhibited by the fact that this method has not yet been published.

Section 512(d)(1)(H) of the Federal Food, Drug, and Cosmetic Act requires that methodology be published in regulations in order to determine whether residues of the drug will be found, for purposes of determining whether a new animal drug application for the drug may be approved. If, under the methodology contained in the published regulations, no residues are found, the drug may properly be approved.

The enforcement procedures, however, are entirely different, and are found in separate sections of the Act. Section 402(a)(2)(D) provides that a food is adulterated, and hence illegal, if it contains a new animal drug which is unsafe within the meaning of section 512. Section 512(a)(1)(B) in turn states that a new animal drug is unsafe unless its use conforms to an approved application. DES has been approved for use in animal feed and implants with a zero tolerance, that is, on the condition that it not be found in any edible portion of the animal. There is no requirement in these provisions of the statute that any particular methodology must be used in determining if an illegal residue is present. Accordingly, it is our opinion that the GLC method, and indeed any other scientifically valid method, may properly be used in determining residues, and residues so found may properly be the basis for enforcement action under the law.

The February 8 memorandum to which you referred during the hearing relied upon the failure to retain a duplicate liver sample as the controlling factor in determining that 18 cases could not be prosecuted. The fact that FDA was using new methodology was mentioned as a contributing factor, but was not regarded at the time as controlling. The February 8 memorandum was not intended as a full exposition of the subject, but rather simply as a means of summarizing our legal conclusion to the Bureau of Veterinary Medicine. This is corroborated by the fact that we have, since then, initiated enforcement action based upon the GLC method. We are confident that this enforcement action will be upheld in the courts.

Sincerely yours,

Peter Barton Hutt

Peter Barton Hutt
Assistant General Counsel
Food, Drugs, and Product
Safety Division

Senator KENNEDY. What about the two dairy cow violations? How does DES—why does DES appear in dairy cows?

Dr. VAN HOUWELING. I believe it is a common practice in many areas when a cow has been stopped being used for milk production, they are put in feed lots and fed for a period of time along with beef cattle being fed for slaughter. The Department of Agriculture is screening these dairy cattle along with the steers and the fed heifers.

Senator KENNEDY. Are you prepared to say the two cases were not milk-producing cattle?

Dr. VAN HOUWELING. I am confident they were not.

Senator KENNEDY. I mean, tell me now. You have investigated it. You know these cases.

Dr. VAN HOUWELING. We can supply the details for the record. I do not have them with me, sir.

Since January 1, 1972, the U.S. Department of Agriculture reported to FDA positive DES findings in two cows, the breed of which are normally used for milk-producing purposes. FDA's investigation, however, disclosed that neither instance involved dairy cows being used for such purposes.

In the first case, 2.85 parts per billion DES was found in a liver sample collected by USDA in April 1972. FDA's followup investigation revealed that the animal was an adult Holstein cow that had been raised in a feed lot. In this lot, cows were purchased from dairies as cull animals and fattened a short time prior to slaughter. Investigation disclosed that a withdrawal feed may have been cross-contaminated with DES.

The other case involved a liver sample collected in June 1972 by USDA in which was detected a residue of .9 part per billion DES. FDA's investigation divulged that the dairy cow was not a lactating animal but had been fattened for slaughter. A preliminary report of investigation disclosed a possibility that the mixing equipment was not being adequately cleaned to prevent DES contamination of the withdrawal feed.

Senator KENNEDY. It certainly seems to me to be inexcusable in a dairy cow. I am not an agriculture expert; but I know it was prohibited, as I understood, for dairy cows. You cannot give us assurance now that those were not milk producing, can you—can you or can you not?

Have you got anybody here? There must be somebody here with preparation that has reviewed these cases.

Dr. VAN HOUWELING. I do not have detailed records with me. I know there was one case that was alleged to have been fed to a dairy cow and the investigation was found to be a false report, and I do not have the detailed information. I will supply it with the other case.

Senator KENNEDY. We had some of the samples of field reports. There have been a number of samples, one from Mr. Graham, dated December 6. I will make this a part of the record; but here is the second paragraph, and I quote:

> Mr. Ringhausen's visit to Iroquois, South Dakota, was for the sole purpose of verifying these facts, prior to issuance of notice of hearing; and Mr. Ringhausen's visit did disclose the man's name was Mr. X and this individual had offered sheep for slaughter and not cattle.

It has Iroquois, S. Dak., as the middle of nowhere. We have no man in the State. Consequently, further followup would place undue burden on existing * * * and manpower. We do not believe the situation warrants any more work.

Dr. EDWARDS. I have no immediate explanation to that.

As you probably know, Senator, we have a tremendous manpower problem in the Food and Drug Administration. We have some 200 inspectors to monitor the food supply in this country, as a result of which we do have to establish priorities. Apparently the decision regarding investigation of the incident was based on the judgement of the Regional Director in accord with priorities he had established.

Senator KENNEDY. How can you give the assurances then, Mr. Commissioner, to the Congress, that that is just what you are going to do? Why are you not saying to the Congressman, throwing it right back up to Congress, telling us you cannot do the job we are charged to do because you have not got the manpower and resources?

Dr. EDWARDS. This is just exactly what we have done.

Senator KENNEDY. You did not do it through the Fountain Committee on this problem?

Dr. EDWARDS. We have told the Fountain Committee this on a number of occasions. Just because the Fountain Committee has not listened does not mean we have not said it.

Senator KENNEDY. You gave assurances?

Dr. EDWARDS. That is right.

Senator KENNEDY. How can you give assurances if you do not do the job?

Dr. EDWARDS. In considering the benefit-to-risk ratio, we believe the assurances we have given are justifiable.

Senator KENNEDY. Well, another report from the Minneapolis district, January:

> It appears that we have reached the end of the line here, so to speak, as is the usual result in this type of case. We therefore request your concurrence to place the subject number in permanent abeyance.

Dr. VAN HOUWELING. I think that is an investigation of one of these reports received last year.

As we indicated, we have greatly speeded up our reporting procedure and our request for investigations.

Last year there was quite a timelag in some instances from the time we got the report from Agriculture, before we were able to get out and make the investigation.

In some instances it was quite a timelag from the time the sample was collected until the report was given to us. Some of these were complicated last year by those time lags.

There was a considerable period of time from the time the samples were collected until the investigation was conducted.

Senator KENNEDY. We have other samples. We are running too late to go through them, but there are other examples that I would think certainly does not satisfy any reasonable investigating procedures that I have been aware of.

How do you, Mr. Commissioner, consider the benefit-risk ratio? Is this a proper function for the Food and Drug Administration?

Mr. EDWARDS. I think very definitely. In order to put this in proper perspective, Senator, I would like to ask Dr. Simmons if he would

speak to the risk-benefit ratio, particularly as it relates to some of the subjects being discussed by some of the scientific experts this morning namely, the therapeutic use of DES and compare that with the rather different problem that goes with the use of DES in feed.

Dr. SIMMONS. Mr. Chairman, there are really a number of facts which are vital in an objective public record on this issue; so I apologize for the length of what I have to say to answer your question; but we do consider them very important.

I will have to start by going back to some of the specific things we have talked about today, starting with the Herbst study on human carciongenesis.

We consider the Herbst study extremely important, and we hope for the benefit of all of science that it will be confirmed or rejected. It must be understood, certainly, by the Congress and the scientific community and the public that the Herbst study presented an association of diethylstilbestrol and vaginal cancer in offspring of mothers treated with that particular drug.

An editorial appearing with the article published in the New England Journal stated that it was an association which would have to be confirmed and certainly we would concur with that. That is one thing that it is important to consider.

Senator KENNEDY. I do not remember the doctor saying anything like you have said here.

Dr. SIMMONS. I am not talking about Dr. Herbst making that point. I am talking about others making an assumption that there is a causal effect. That is not so at present.

It is necessary to consider another control group that would substantiate that.

In the interest of science, we hope it will be followed up further. This is what Dr. Herbst is doing now and what we will be doing in some other studies.

Senator KENNEDY. Do you think it is bona fide carcinogen——

Dr. SIMMONS. Animal, not human.

Senator KENNEDY. How can you be so sure it is not human?

Dr. SIMMONS. I have no evidence.

Senator KENNEDY. Can you say it is not because——

Dr. SIMMONS. I have no evidence.

Senator KENNEDY. How can you give assurance?

Dr. SIMMONS. I am not giving you assurance. I am telling you I have no evidence that it is a human carcinogen.

Senator KENNEDY. There are researchers who believe that it is.

But continue.

Dr. SIMMONS. All right.

The other thing is, it is important to keep in mind that the dosage that was given in this association with females during pregnancy was thousands of times higher than may occasionally be found in an occasional liver and given at a crucial time in genesis. The risk even at that comparatively massive exposure was extremely small.

I think it is important for the public's benefit to remember that.

Now, to put things in further perspective.

Diethylstilbestrol is not a carcinogen, period. It is an estrogen. And it and other estrogens are carcinogens in certain instances.

Estrogens are also vital to life.

You, Senator, right now, are producing in your body 100 times more estrogenic substance every day than you are likely to eat in a piece of liver which you eat at any time or your family. That is the magnitude we are talking about.

Estrogen is vital to life, and with a very high dose it can be carcinogenic. It has not been demonstrated in humans to be carcinogenic at a normal dose.

In addition, as you know, in some instances, estrogens are actually treatment for carcinoma. There are carcinogens, Senator, all around us, every day, from the moment we are born; and they are now in the smoke in this room and they are in the atmosphere of Washington. We are exposed to them in the sun, in the soil, in our crops, and in a heavier concentration than we are likely to get in occasional liver. You know the figures on the environmental pollution, but every day in a city like Los Angeles, there are 1,000 to 2,000 tons of hydrocarbons thrown into the air, which contain carcinogens. Every time we burn an organic substance, we are likely to generate carcinogenic substances.

Everyone is aware of that in cigarette smoke and auto exhaust but few realize that carcinogens can be generated each time we burn food or fuel or cook our meats, especially charcoaling or grilling steaks.

And again, in higher exposure than we are speaking of here.

So, Senator, in answer to your original question, when we eat steak that is grilled, I think the honest answer is if there is an imminent hazard, it is more in charcoal grilled steaks and fires than DES residue in liver.

Senator KENNEDY. They have a choice as to whether they grill or broil. You are not offering them a choice when they pick up some meat at the market.

Dr. SIMMONS. Senator, any time we eat organic substances, we have the possibility of producing carcinogen. There is no way to prepare our meat supply without that possibility. In that respect, it is not a judgmental voluntary thing.

As I said, the other thing that we know about is that 5 to 41 percent less fat is produced in the meat on cattle fed diethylstilbestrol. There are people who would suggest that that also would produce less carcinogen, such as when heated.

In that respect, you might say it is beneficial. I am not going to make that judgment, but it should be considered.

And the other thing I think it is important to point out is that cholesterol is also shown to be a carcinogen in animals. This is another substance vital to human life.

Now, to go further to speak of the dose, the more important perspective that is important for all of us considering this issue is the dosage of diethylstilbestrol we are talking about.

In two parts per billion, in occasional liver samples, we are talking about a half microgram in a half-pound of liver.

As I said before, normal males and females produce every day about 100 to 200 times that estrogenic substance every day. Every day there are 8 million American women taking oral contraceptives which contain estrogens, again about 100 to 200 times the dose of diethylstilbestrol they may occasionally be exposed to.

The question I am really placing into the public record is what is the carcinogenic burden we are talking about? And that is what needs to be kept in perspective.

As far as the chance of exposure, when we testified before Congressman Fountain, we gave some interesting figures there.

You might be interested to know that your chance of eating liver that has two parts per billion diethylstilbestrol 4 days in a row are one in 706 million. That is the risk that we are talking about, about being exposed to this in the food supply as it currently exists.

Senator KENNEDY. You cannot give us these assurances now. The Commissioner just indicated the inadequacy of investigating manpower. We have just reviewed some of these investigations.

Before you give us assurances about what Americans can or cannot eat or what they can expect, I think you have to have a good deal more confidence in the kinds of investigating reports that say here that in Iroquois, S. Dak., is in the middle of nowhere, and you have no man in the State so consequently any further followup would place undue burden.

So before you start giving assurances to the American people, I think we ought to have a greater degree of confidence in what you can assure people about.

Dr. EDWARDS. I would like to correct the record on that one, Senator. We were talking earlier about our investigation. Once a positive is found it is on a responsibility to brake a follow-up investigation. The U.S. Department of Agriculture, on the other hand has the responsibility for testing the meat. I think the sampling that they are doing is statistically valid, and we can assure on the basis of this sampling. If we do not follow up adequately, that is a separate issue.

Senator KENNEDY. Why have 21 nations of the world banned DES to feed cattle? What do they know about it that we do not?

Dr. VAN HOUWELING. The use of DES in animal feed is particularly important when you are feeding cattle to fatten them for slaughter. This is done to a very limited extent in other countries.

Senator KENNEDY. Why do they ban it if it is done very limitedly?

Dr. VAN HOUWELING. There is no advantage to its use, so it is very easy to ban it.

Senator KENNEDY. Because they do not use much of it, it is easy to ban, and if they use a lot of it, it is more difficult to ban? Why is that?

Dr. VAN HOUWELING. They do not feed cattle for slaughter as we do in the United States.

Senator KENNEDY. Why did they ban it?

Dr. VAN HOUWELING. I started to finish by saying——

Senator KENNEDY. Do they know why they ban it? Do these 21 nations know why they ban it?

Dr. VAN HOUWELING. We have not been able to determine why they ban it.

The methods for feeding beef cattle and sheep in many countries are different than what is used in the United States and Canada. Cattle are range-fed in these countries and not fattened in a feedlot immediately prior to slaughter. DES is not considered to be effective in cattle that are exclusively range fed. FDA will contact each of the 21 countries that have reportedly banned DES and ask for more definitive information. This will be provided to the committee at a later date.

Senator KENNEDY. But they have been able to determine it.

Thank you very much.

We are going to recess briefly, because there is another vote; and then we will take up our other witnesses.

Thank you very much.

(Short recess.)

The subcommittee will come to order.

The next witness is Dr. Frank J. Rauscher, Director, National Cancer Institute, National Institutes of Health.

Dr. Rauscher, I welcome you and look forward to your testimony.

## STATEMENT OF DR. FRANK J. RAUSCHER, JR., DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

Dr. RAUSCHER. Thank you, Mr. Chairman.

My presentation, Mr. Chairman, is essentially a synopsis of scientific data, some of which was presented this morning and, in part, other data that NCI has provided to the FDA.

First of all, in terms of its carcinogenicity in animals, DES has been shown to be carcinogenic in mice of both sexes since the late 1930's. DES along with other estrogens has been widely used as an experimental carcinogen. All have been shown to produce a variety of tumor types in several species.

The structure of DES and its main tumor responses are tabulated in appendixes 1 and 2. They include tumors of several endocrine-related organs but also tumors of other tissues such as kidney tumors.

Dose-response studies have shown that the carcinogenic effect is retained at low levels of administration. In addition, a combined effect of X-irradiation and DES which results in the potentiation of mammary carcinogenesis in rats was recently reported by various workers.

Further work along these lines, using progressively lower doses of radiation combined with DES, is underway in Dr. Segaloff's laboratory under contract from the National Cancer Institute.

A point that needs to be made is that all the types of tumors induced by DES can also be similarly induced by natural estrogenic hormones. However, DES is chemically different from natural estrogens and we do not know its molecular mechanism of action.

### CARCINOGENICITY IN HUMANS

DES is used in therapy for its marked estrogenic activity in men and women. In this context, since estrogenic stimulation is well known as a causative factor of human cancers, DES, as an estrogen, must be considered a potential human carcinogen.

In addition, specific effects of DES have been recognized. Herbst et al., recently reported in New England Journal of Medicine, 284: 878–881, 1971, the development of adenocarcinoma of the vagina—an otherwise very rare type of cancer—in young women who had been exposed to DES during fetal life after their mothers were treated with DES during pregnancy.

This association has also been reported by Greenwald in previous testimony.

These tumors appeared at a very early age—late teens and early twenties—and they may therefore represent just the first manifesta-

tion of the carcinogenic effect which usually is manifested after a long latent period.

It is unfortunately quite possible that the population of women and men who have been exposed to DES during fetal life will represent a high-risk group for cancer, possibly at different sites—for example, breast, testes, pituitary, adrenals.

Therapeutic use of much higher doses of DES in male patients, in the therapy of prostatic cancer, also leads to the growth of mammary tissue in men and in some cases to the development of mammary cancers.

Finally, it has been known for many years that occupational exposure to estrogenic hormones—in laboratories and in manufacturing plants—can lead to growth of mammary tissue in men.

In conclusion, it can be stated that DES is definitely a carcinogenic substance for several animal species and apparently for the human.

Senator KENNEDY. You are satisfied it is also a carcinogenic substance for human beings?

Dr. RAUSCHER. The data we have right now, largely through the two studies reported this morning, are highly indicative that this is true. It is difficult to answer your question directly.

As a scientist, we know that the only real direct way of doing this is to inoculate test people and of course this would never be done. Rather than do that, we rely on epidemiologic information such as that presented this morning.

Senator KENNEDY. I suppose there is always more information that one could glean from additional research and testing. But as I understand, just from the available information, you believe that there is a reasonable presumption to assume that it is carcinogenic——

Dr. RAUSCHER. In my judgment; yes. Certainly with high doses, it is very reasonable to assume and——

Senator KENNEDY. You are not prepared at this time to give the degree or the quantites that would be necessary to induce cancer?

Dr. RAUSCHER. No; that is one of the problems. As the Commissioner mentioned this morning, we have to do far more at very low doses. But this is time consuming to the point of many years, frankly.

Senator KENNEDY. You cannot say at what levels, over what periods of time it will induce certain cancers. But then we cannot say that because there are some traces for a period of time that it will not mean that there is an increase in instances of cancer——

Dr. RAUSCHER. That is right; we cannot. I do not think we can say that about any compound. Of the thousand chemicals known to be cancer causing in animals, about 20 or 22 of these are known to be cancer causing in men.

I do not think that for one of these we can answer that question with any definitions. Part of the problem is that we are such a heterogeneous population. It depends on who is exposed at what time and what other factors he is exposed to. This is part of my concern about a presumed chemical carcinogen in man. It is not only that chemical, but it may be the chain reaction it contributes to which may eventually result in cancer. It is almost impossible, therefore, to pin down which chemical and at which dose.

Senator KENNEDY. Doctor, you are the chief, the distinguished head of the Institute. Just as a matter of conviction, if you felt there were some means of reducing any sort of exposure to DES, even if we do not know the precise amount which might cause cancer, it is still advisable to reduce that exposure to such——

Dr. RAUSCHER. Mr. Chairman, my job is to prevent people from getting cancer and to prevent the continuation of cancers. When I see any data that may be with reasonableness assigned to a potential carcinogenic role, I think the prudent course is to try to remove that possible carcinogenic stimulus from the environment.

Senator KENNEDY. As you point out, I suppose you have to balance that viewpoint against the other economic implications——

Dr. RAUSCHER. This must certainly be considered. For instance, in my own field, just to stay within cancer, we know that certain estrogens are potent chemotherapeutic agents for the treatment of men with prostatic cancers. So here clearly it is a balance, but our judgment is—and I think this is borne out by many studies now—that the use of that particular drug, although it may be carcinogenic, is far more valuable in warding off or controlling that particular tumor that the person has now. There is a risk-benefit ratio.

Senator KENNEDY. As I understand, the example you gave, Doctor, is a medical consideration and not an economic consideration.

Dr. RAUSCHER. That is right.

Senator KENNEDY. You are more sympathetic to considering the medical implications of it, I suppose, as a researcher.

Dr. RAUSCHER. Other economic or other kinds of considerations clearly must be considered. Additional studies may show or may not show that low doses of a particular chemical contribute to man's carcinogenic burden. In the case of DES, if this can be shown—and many more studies need to be done, admittedly—but if it is shown that way, I do not think the other economic benefits would outweigh removing a cancer causer from our environment, if in fact it is shown to be that.

Senator KENNEDY. As I understand further, you think that, although we cannot tell exactly the danger that is provided, at least we ought to determine that first before continuing even with the low distribution of DES.

Dr. RAUSCHER. I think these are testable hypotheses, and additional data will put us on more firm ground.

Senator KENNEDY. How long would that really take, do you think? I know it is always difficult to predict and project, but would your agency be willing to help in the research and cooperation with the Food and Drug——

Dr. RAUSCHER. Yes, indeed.

Senator KENNEDY (continuing). To try and make that determination, so if it really is not a danger, we could reinstitute it?

Dr. RAUSCHER. Absolutely. We are doing that now. Some of the studies you heard this morning were, in part at least, supported by the National Cancer Institute. The problem here, which I think is essential to much of the discussion that you heard this morning, is that with most drugs that you might consider toxic or hazardous to man, you know that it is toxic within 10 minutes to 10 days to 2 weeks; at least, very soon. With cancer causers—and we already have this information—it can take 20, 30, or more years.

There is evidence that tumors occur, for instance, in mammary cancer at a peak age in women between 25 to 45. Something happens in the first years of the life which eventually shows up as cancer. This may be the very thing we are talking about, with very low doses of a chemical like DES.

It could take another 10 or 20 years. The only way to determine that is to survey large numbers of the population, and this we are doing and continuing to do in collaboration with our colleagues in the FDA.

Senator KENNEDY. That is being done by research laboratory rather than experimenting with our own people?

Dr. RAUSCHER. The whole Nation is a research laboratory when it comes to this kind of population survey; yes.

Senator KENNEDY. Can you tell me whether in your own research or your own knowledge, why some of these other countries have banned DES? The Cancer Institute has tremendous contact with other nations and countries, and some research——

Dr. RAUSCHER. I do not know the specific answer to that question, but I have been told by some of my staff that these nations must be concerned about the knowledge that we have had for 30 years that DES is a carcinogen in animals. Certainly they are aware, as we are, of the literature—studies provided by my two colleagues this morning—that pregnant women put their female daughters at risk. I am concerned and I am impressed, frankly, with the fact that not only have other nations banned it, but two nations have banned the import of meat from our country. I can only presume they are concerned about DES as a potential health hazard.

As far as I know, neither they nor we have any direct evidence that DES causes cancer in people when they eat it at levels now being detected in the few samples of meat or liver in which it has been found. We have no direct evidence; and to that extent, my colleagues that appeared before me are absolutely correct.

Senator KENNEDY. But they do have good evidence that it does not?

Dr. RAUSCHER. That is right.

Senator KENNEDY. And that there has been research which would indicate that DES in other amounts has been at least to the satisfaction of these researchers, a primary cause for——

Dr. RAUSCHER. That is right. There is critical information that we do not have now, but which we are trying to get.

For instance, we know that DES is a chemical structure which is different from the naturally occurring hormones. Does this mean that it is a more potent carcinogen? We do not know yet, but we can find out. We do not know, for example, whether very young children exposed to this may have a higher response rate than you and I as adults. There are examples of this in cancer literature which show if you are young, you respond more quickly than if you are old. We do not have enough of this kind of information. Until we get it, I think the prudent course is the position I have taken before.

Senator KENNEDY. Which is to ban it?

Dr. RAUSCHER. Which is to insure, again in cooperation with the FDA, that man is not exposed to this material.

Would you like me to continue?

Senator KENNEDY. Yes.

Dr. RAUSCHER. Now, in terms of the extent of exposure in the population, far higher exposures of individual people to DES occur as a result of its drug use and of occupational exposure.

The administration of DES has recently been recognized by the FDA as contraindicated during pregnancy. The annual production as an animal feed additive is approximately 50,000 pounds per year.

The extent of occupational exposure is largely dependent on the large-scale production of DES for use in animal feed. A survey of occupational sources of exposures and an epidemiologic study of the exposed populations is highly recommended and is being done.

Finally, we come to the use of DES as a feed additive. Current use practice is reported to lead to the presence of detectable residues in over 1 percent of the samples of beef liver that have been analyzed. The doses that are present in such residues have been of two parts per billion or more. In a single 150-gram serving of beef liver, at two parts per billion, the intake would be about 0.3 micrograms. It should be noted that DES has not been detected, as far as I know, in any other edible portion of animals in which DES was detected in the liver.

The extent of use of liver in the diet varies, but liver is an item of large consumption.

The main reasons for concern over this environmental carcinogenic hazard are the following.

Individual doses of about one microgram of DES, ingested at long intervals, could add to the existing carcinogenic burden for the population. However, as long as the use of DES in feed is allowed to continue, there could occur instances of even higher contamination.

As mentioned above, another reason for concern about DES use is the occupational hazard to those people exposed to it continuously for long periods of time during the manufacture of the large amounts of DES required by the feed industry.

Finally, Mr. Chairman, and in order to put this testimony in objective perspective, I must say that at the present time, our data do not incriminate DES as a human carcinogen when ingested at levels currently being detected in beef liver.

This fact, however, will not allow us to forget our concern when you recall that DES has been used for only approximately 15 years as an additive to feed grain; even with the relatively high doses used in the treatment of pregnant women it has taken 14 to 20 years to determine that cancers were induced in young women whose mothers received this drug during pregnancy.

My point here, to deviate just a moment, is we simply do not have enough years under our belt to determine whether even low doses have any carcinogenic effect or not in man.

It is certainly true, as has been stated by some, that there is far more chemical substance capable of causing cancer in tobacco smoke or smoke which is generated during the process of charcoaling meat than there is in the occasional sample of liver found to be contaminated with DES.

Nonetheless, it is important also to point out that exposure to these sources of carcinogens are largely matters of personal choice and can therefore be avoided.

In conclusion, therefore, DES is (a) a potent carcinogen for animals, and (b) an apparent carcinogen for man under specific circumstances. These are the facts that we provided to the FDA.

Senator KENNEDY. Doctor, you have been enormously helpful today on this matter, as you are on some of the others.

The Cancer Institute, knows the full commitment of the Congress and the President on this whole area, and I think it is in excellent hands. You have been enormously valuable to us here this morning.

You have given us a very balanced and valuable comment. I understand from your conclusions that purely from a health consideration, given what you know about this, you would like to reduce even the limited exposure of American people to DES.

Dr. RAUSCHER. I think until we know more about it, this would be the prudent choice.

(The prepared statement of Dr. Rauscher follows:)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

STATEMENT

BY

FRANK J. RAUSCHER, JR., Ph.D.

DIRECTOR, NATIONAL CANCER INSTITUTE

NATIONAL INSTITUTES OF HEALTH

ON DIETHYLSTILBESTROL (DES)

BEFORE THE

SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE

JULY 20, 1972

Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to appear before you to present the scientific data on the carcinogenic hazards of diethylstilbestrol (DES).

A. Evidence of Carcinogenicity

1. Carcinogenicity in Animals. DES has been shown to be carcinogenic in mice of both sexes since the late 1930's. DES along with other estrogens has been widely used as an experimental carcinogen. All have been shown to induce a variety of tumor types in several species. The structure of DES and its main tumor responses are tabulated in Appendices 1 and 2. They include tumors of several endocrine-related organs but also tumors of other tissues such as kidney tumors. Dose-response studies have shown that the carcinogenic effect is retained at low levels of administration. In addition, a combined effect of X-irradiation and DES which results in the potentiation of mammary carcinogenesis in rats was recently reported at Segaloff et al (Cancer Research 31:166-168, 1971). Further work along these lines, using progressively lower doses of radiation combined with DES, is under way in Dr. Segaloff's laboratory under contract from the National Cancer Institute (NIH-NCI-E-71-2131).

A point that needs to be made is that all the types of tumors induced by DES can also be similarly induced by natural estrogenic hormones. However, DES is chemically different from natural estrogens and we do not know its molecular mechanism of action.

2. Carcinogenicity in Humans. DES is used in therapy for its marked estrogenic activity in men and women. In this context, since estrogenic stimulation is a well-known causative factor of human cancers, DES, as an estrogen, must be considered a potential human carcinogen. In addition,

specific effects of DES have been recognized. Herbst et al. recently reported in New England Journal of Medicine 284: 878-881, 1971, the development of adenocarcinoma of the vagina (an otherwise very rare type of cancer) in young women who had been exposed to DES during fetal life after their mothers were treated with DES during pregnancy. This association has also been reported by Greenwald (Hearings before the Subcommittee on Government Operations, House of Representatives, "Regulation of Diethylstilbestrol," November 11, 1971, pp. 9-20, and New England Journal of Medicine 285: 390-392, 1971). These tumors appeared at a very early age (late teens and early twenties), and they may therefore represent just the first manifestation of the carcinogenic effect which usually is manifested after a long latent period. It is unfortunately quite possible that the population of women and men who have been exposed to DES during fetal life will represent a high-risk group for cancer, possibly at different sites (e.g., breast, testes, pituitary, adrenals). Therapeutic use of much higher doses of DES in male patients, in the therapy of prostatic cancer, also leads to the growth of mammary tissue (gynecomastia) and in some cases to the development of mammary cancers. Finally, it has been known for many years that occupational exposure to estrogenic hormones (in laboratories and in manufacturing plants) can lead to growth of mammary tissue in men.

In conclusion, it can be stated that DES is definitely a carcinogenic substance for several animal species and apparently for the human.

B. Extent of Exposure in the Population

Far higher exposures of individual people to DES Occur as a result of its drug use and of occupational exposure. The administration of DES has

recently been recognized by the FDA as contraindicated during pregnancy. The annual production as an animal feed additive is approximately 50,000 pounds per year.

The extent of occupational exposure is largely dependent on the large-scale production of DES for use in animal feed. A survey of occupational sources of exposures and an epidemiologic study of the exposed populations is highly recommended. Such a suggestion has been forwarded to the National Institute of Occupational Safety and Health.

Finally, we come to the use of DES as a feed additive. Current use practice is reported to lead to the presence of detectable residues in over 1% of the samples of beef liver that have been analyzed. The doses that are present in such residues have been of 2 ppb or more. In a single 150 g serving of beef liver, at 2 ppb, the intake would be about 0.3 microgram. It should be noted that DES has not been detected in any other edible portion of animals in which DES was detected in the liver. The extent of use of liver in the diet varies, but liver is an item of large consumption.

The main reasons for concern over this environmental carcinogenic hazard are the following:

Individual doses of about 1 microgram of DES, ingested at long intervals, could add to the existing carcinogenic burden for the population. However, as long as the use of DES in feed is allowed to continue, there could occur instances of higher contamination.

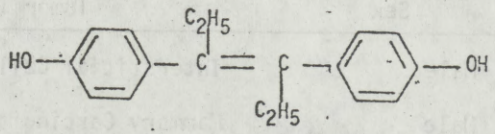
As mentioned above, another reason for concern about DES use is the occupational hazard to those people exposed to it continuously for long periods of time during the manufacture of the large amounts of DES required by the feed industry.

Finally, Mr. Chairman, and in order to put this testimony in objective perspective, I must say that at the present time our data do not incriminate DES as a human carcinogen when ingested at levels currently being detected in beef liver. This fact, however, will not allow us to forget our concern when you recall that DES has been used for only approximately 15 years as an additive to feed grain; even with the relatively high doses used in the treatment of pregnant women it has taken 14 to 20 years to determine that cancers were induced in young women whose mothers received this drug during pregnancy. It is certainly true as has been stated by some that there is far more chemical substance capable of causing cancer in tobacco smoke or which is generated during the process of charcoaling meat than there is in the occasional sample of liver found to be contaminated with DES. Nonetheless, it is also important to point out that exposure to these sources of carcinogens are largely matters of personal choice and can therefore be avoided.

In conclusions, therefore, DES is (a) a potent carcinogen for animals, and (b) an apparent carcinogen for man under specific circumstances. These are the scientific facts that are being weighed by the FDA in exercising its regulatory responsibilities.

APPENDIX I

1. Structural Formula for DES:




2. Accepted Chemical Abstract Registry Name and Number:

4,4'-Stilbenediol,α,α'-diethyl (#56,531)

3. Synonyms for DES:

alpha,alpha'-Diethyl-4,4'-stilbenediol
Bio-des
3,4-Bis(p-hydroxyphenyl)-3-hexene
Comestrol estrobene
Cyren A
DEB
Di-Estryl
trans-α,α-Diethyl-4,4'-stilbenediol
α,α'-Diethylstilbenediol
α,α'-Diethyl-4,4'-stilbenediol
Diethylstilbesterol
Diethylstilbestrol
trans-Diethylstilbestrol
4,4'-Dihydroxy-α,β-diethylstilbene
3,4'(4,4'-Dihydroxyphenyl)hex-3-ene
Domestrol
Estilbin "NCO"
Estrobene
Estrosyn
Fonatol
Grafestrol
3-Hexene,3,4-bis(p-hydroxyphenyl)-
HiBestrol
Microest
Milestrol
Neo-Oestranol 1
Oestrogenine
Oestromenin
Oestromensyl
Oestromienin
Palestrol
Perlestatrine Oestrogenique Iscovesco
Serral
Sexocretin
Sibol
Stil
4,4'-Stilbenediol,2,2'-diethyl-
Stilbestrol
Stilbestrol, diethyl-
Stilbetin
Stilboestroform
Stilboestrol
Stilkap
Stil-Rol
Synestrin
Synthoestrin
Syntofolin

APPENDIX 2

MOUSE

| Strain | Sex | Tumor Type |
|---|---|---|
| BALB/C3H | Male | Interstitial Cell Tumor |
| C3H | Male | Mammary Carcinoma |
| | Castrate Male | Mammary Carcinoma |
| Strain A | Castrate Male | Mammary Carcinoma |
| | Female | Mammary Carcinoma |
| -- | Male | Testicular Tumors |

RAT

| Strain | Sex | Tumor Type |
|---|---|---|
| -- | Female | Pituitary (Mammo-Lutcotrophic) |
| | Male | Pituitary (Mammo-Luteotrophic) |
| Sprague-Dawley | Female | Ovarian |
| | | Uterine |
| -- | Female & Male | Bladder |
| -- | Female & Male | Adrenal |

HAMSTER

| Strain | Sex | Tumor Type |
|---|---|---|
| -- | Male | Renal Tumor |
| | Male | Pituitary Chromophobe Adenomas |

MAIN TUMOR RESPONSES TO DES

Senator KENNEDY. Thank you very much.

Well, I have another vote on the floor of the Senate.

We have one more witness, and we will come back and hear the witness.

(Short recess.)

Senator KENNEDY. The subcommittee will come to order to hear Dr. Duane Flack, chairman, Task Force Committee on DES, American National Cattle Association.

## STATEMENT OF DUANE E. FLACK, D.V.M. CHAIRMAN, TASK FORCE COMMITTEE, DES, AMERICAN NATIONAL CATTLE ASSOCIATION

Dr. FLACK. Thank you, Senator.

On behalf of the American National Cattlemen's Association, thank you for this opportunity to present comments relative to the current interests and proposals concerning the use of diethylstilbestrol—DES—in animal feeds.

It is my understanding that the purpose of this hearing is to discuss the proposed banning of DES by the Food and Drug Administration—FDA—and pending hearings associated with that proposal.

I am sure there is concern in this committee in what would appear to be an increased incidence in the occurrence of DES residues in liver samples. The question is undoubtedly implied, if not stated, why not ban DES now? I am privileged and happy to speak to these points.

The use of this efficiency promoting additive has been a commonly accepted practice for nearly two decades. It has been estimated that 80 to 90 percent of the cattle on feed receive DES or similar hormonal products in one form or another.

Its advantages have been available to all segments of the industry. Simple calculations would indicate that DES is responsible for the production of literally billions of pounds of wholesome, pure beef per year.

If the efficiencies realized in just the finishing phase of cattle production were to be lost, sirloin steak would be 10 to 15 cents per pound higher than it is today.

That could be expanded against the number of pounds consumed today to equate $200 million to $400 million added food bill to this Nation's consumers.

Senator KENNEDY. As I understand, the Department of Agriculture studies estimate that the average cost would be 3 cents per pound, with a total of $3.65 per year per person eating 110 pounds of the meat—I am just wondering if you had a chance to examine those studies which they have done on this subject; and if you have had a chance to do so, what is your reaction to those studies?

Dr. FLACK. Yes, sir; I have.

I read through the report prepared for the USDA on this subject. The report was designed on three hypothetical circumstances that then led to conclusions that $3.85 per person would be the added cost.

The figure I am using, 10 to 15 cents per pound at retail level for cuts of sirloin steak, is based upon studies and investigations we have conducted ourselves, by taking groups of cattle, placing them on

feed, without use of any additive, following those cattle through the entire feeding period and calculating the measurable cost against those of comparable cattle using the drug.

You will come up with a cost of approximately 3 to 5 cents a pound, on a live cattle basis.

To convert that to 60-percent yield in the packing plant and apply the formula for various cuts of meat—all meat is not priced the same throughout the carcass—you come up with very legitimate estimate of 10- to 15-cent increase in cost for higher priced cuts of beef, such as sirloin steak.

In a marketplace that is today as concerned as it is about the high price of beef, I think this is pertinent. If for no other reason, doesn't this make it important not to ban the use of DES unless it is truly necessary? Is it?

DES has been used with unquestioned confidence in its safety and efficiency. It has only been in the last year, and more specifically in the past several months, that we have heard accusations, claims and counterclaims, reports of increased residue instances, and widespread publication of each.

These events have brought confusion and disagreement among the regulatory agencies, scientific and commercial representatives, the cattle industry itself, and most crucial of all, that ubiquitous group known as the consumer.

To the best of my knowledge, never has a residue of DES been detected in carcass beef even though samples are tested from the same animals from which other tissues are submitted. I have not heard of the first case to be identified of a human illness of any kind caused by the ingestion of DES in the form, the manner, or quantity represented in the residues identified in a few isolated liver samples.

I understand that chemicals of comparable estrogenic activity are present in many common natural foods at relatively much higher levels.

I also understand that DES specifically is commonly used for the therapeutic treatment of several conditions in men and women at tremendously high levels as compared to those we are discussing.

This is where it appears some problem has occurred. But surely some kind of dose to effect; and benefit-to-risk ratio should be applied. This is certainly the practice with any other therapeutic drug. The relation between therapeutic dose and tissue residue level are ridiculously far apart.

These facts being true, I find it alarming that there is being generated an impression that this Nation's meat supply is contaminated when, in fact, this simply is just not the case.

Right in this room today, we have heard references made to meat specifically, or steak. To date, all monitoring testing done by the USDA has not identified a residue of this chemical in carcass meat.

The beef cattle industry is concerned.

The ANCA has appointed the ad hoc committee which I represent today. Ours is a multi-billion-dollar industry. I think we rightfully have more sincere interest in the wholesomeness, purity, and quality of our product than all the scientists and legislators you could gather to discuss the subject.

Senator KENNEDY. On your committee, what is the makeup of that committee? How many members?

Dr. FLACK. It is a committee of four people, represented from throughout the Western part of the United States.

We have Dr. Jim Nofziger, consultant nutritionist from California; there is myself as cattle feeder and veterinarian; a man from Idaho, Mr. Tom Hovenden, executive secretary, and director of Idaho Cattle Feeders; Tom Herrick, president of the Texas Cattle Feeders Association.

Senator KENNEDY. You have got a researcher and yourself, a veterinarian, who would be evaluating the scientific information?

Dr. FLACK. Yes, sir; although the real purpose of the task force is not a research committee.

The committee was formed by ANCA for the specific purpose to act as liaison between regulatory agencies and the cattle feeding industry in the proper use and control of the product, not in the technical investigation or scientific aspects of the product itself.

We have heard comments concerning the use of DES in foreign countries.

I might just touch on that.

Specifically, there is some confusion as to what really constitutes a product that is being banned.

From one standpoint, you could refer to it as a specifically outlawed product where a legislative mandate has been passed, that this product will not be used.

On the other side of the picture, and I think much more commonly, the circumstances you have been referring to as far as the 21 countries, it just merely has not been approved for use.

In this, it is significant at least to point out that the husbandry and the cattle production practices of the rest of the world and the countries specifically that you are referring to are certainly much different than those in the United States today.

We probably have the only place in the world where cattle are under confinement, fed high concentrates for finishing of the beef to the condition that the American consumer desires and demands.

We can always take a great deal of pride in the amount of respect that our product has and the demand for our type of beef throughout the world.

Senator KENNEDY. Even though what you are really saying there is that they do not use it, still they banned it; why have they banned it?

Dr. FLACK. I think in many of the cases—I am not experienced or well versed in all phases of international law or regulatory services of the various countries—but I think in many of the countries it has not been banned. It has not been approved. This has really been a test of contention here in this country.

In some circumstances it has been legislatively banned, as I understand it. Many of these bannings go back many, many years before even the common use of the drug in animal feeds. I think there has probably—and I cannot speak for the legislative actions of other countries—has been a fear, so to speak, of just the classification "hormone"—there have been some other cases specifically, at least where the claim has been made that this has been used as a means of a nontax trade barrier for restriction of importation of American beef.

Senator KENNEDY. Argentina was in 1961; that is official bulletin; that is the list here. I am not going to take up your time by going through it.

I will make the list of the countries, what countries have undertaken the ban, included in the record at the appropriate place, so as not to interrupt the witness' testimony.

There are, of course, two countries which banned the importation of American beef because they used DES: Sweden and Italy. I am not sure they were great importers of beef, but they have taken that action.

Dr. FLACK. Here again, I cannot speak for this action or the reason why. It has been reported by industry people here that this has been done as a means of a trade barrier.

The apparent increased instances of residue identifications do not appear to be due to produce abuse. It does seem to be due to an accelerated monitoring program and simultaneous application of a much more highly sophisticated assay technique.

I am advised by competent authorities that the reliability of the gas liquid chromatographic—GLC—technique is questionable at levels less than one part per billion.

The availability of competent people and facilities to conduct GLC determinations are extremely limited. The industry needs a capability to monitor its own program. It takes time to develop these services.

I feel confident in saying that management practices and control of DES have improved significantly over the past year. This has been stimulated by an awareness that a problem does exist.

What happened, then, when residues have been identified? I feel that it would be erroneous to imply that some cases of failure to comply with the regulatory laws have not occurred. Where this is shown to be the case, the full weight of the law should be applied.

Intentional abuse or disregard of withdrawal regulation has not been a significant factor, however.

Inadvertent cross-contamination, for one reason or another, seems to have been the most common cause. Carelessness has happened, human error, poor management or manufacturing practices, have been identified. These are problems which are identifiable and manageable; they are not the exotic, profound, and mysterious.

Other questions of a more technical nature are also arising. The carcinogenicity of DES has been legitimately challenged.

Senator KENNEDY. Why do you think the incidence has been—you think the incidence has been increasing; you have given some of the ways and reasons; but you say they are controllable; yet, we find from those reports there has been some increase——

Dr. FLACK. There are two factors. No. 1, there have been a lot more tests run. We have larger total number tests.

No. 2, the tests or the specificity of the tests critical to two parts and below per billion really are levels that by prior methods would have been considered zero.

Senator KENNEDY. But the total numbers are higher, as I understand; the figures, the percentages, are higher than we were a year ago?

Dr. FLACK Yes, sir; and for that reason, because of the increased ability of the test, to detect very, very small levels, which was not the case a year ago, or previously.

Senator KENNEDY. Do you think as the tests get better that it is going to show other increases?

Dr. FLACK. That would be a matter of conjecture on my part. I cannot answer that. I think without a doubt the industry is responding to this. In other words, take the case of the individual user, the man on the farm who has been using this product, or others, in full confidence that his management practices were sufficient and now with the new test, which is pointing out that we do have a residue problem below levels previously detectable, we are finding a very extreme interest in the industry to improve management techniques and manufacturing practices.

I feel confident it will be done. The biological significance of these ultraminute traces, or the relationship to previously identified levels, has not been established.

I would quote—and this itself has actually been repeated by several different people this morning—one of the witnesses this morning, Dr. Greenwald, did state that, "It has been noted that as we have studied vaginal cancer patients in the State and mothers all treated therapeutically, there is no reason to suspect that DES in food caused any of the tumors." This is a point we feel needs a great deal more investigation and explanation.

What is the importance of the fact that residues have only been identified in a small percentage of liver and a few kidneys? What is the relationship of this to our total beef supply?

Are other means available to monitor and control potentially contaminated livers? Not all routes of original administration have been identified with residue problems?

The fact that DES is widely used, and yet well over 97 percent of the Government's objectively collected samples have shown no residue, bears undisputable evidence that the product is being safely used. We need to determine, then, what management and manufacturing practices need to be applied in those isolated instances to insure that no residues will occur in violation to regulation.

And, finally, what constitutes none? It has been stated on many occasions by competent scientific investigators that mankind, our environment, Mother Nature, herself, could not comply with an absolute zero attitude on anything.

These are not answers for me to determine. These are topics and discussions that need to be heard. For this reason, ANCA heartily endorses the efforts of FDA to bring this matter out in the open before taking further action.

We feel confident that these hearings will bring to light opportunities to solve problems and allow continued use of this tool. Take away a tool responsible for a 10-percent advantage in efficiency of production, and that cost will be reflected throughout the chain of production all the way to the consumer.

On the other hand, the unquestioned confidence of the consumer is the most valuable asset of the American agricultural producer. DES or any other product is of no value if it hinders product quality, wholesomeness, or safety. Such determination, however, must be based on fact, not emotion; true relevance, not speculative potentiality; and, above all, reason, not politically motivated and unfounded accusations.

Senator KENNEDY. Thank you very much, Dr. Flack, for your testimony. We have heard that there is a potential hazard to workers exposed to cattle using DES. Are you aware of this, concerned about it, or is your committee going to consider this as well?

Dr. FLACK. We have had no indications where any apparent problems have arisen. In my own schooling and experience as a veterinarian, prior to becoming directly involved in the feeding industry, I have heard reports of several problems of this nature, originating clear back with the original use of the product. Some of the investigators at laboratories that were under very close exposure over a period of time may have had some problem. I do not know of any reported problems of this nature since then, and it is not something we have considered as a problem in the feeding industry.

Senator KENNEDY. Do you plan to file an objection with the Food and Drug Administration?

Dr. FLACK. We are not a licensed manufacturer, so we are therefore not in a position to do so. We are a user, not a licensee.

Senator KENNEDY. You do not have the ability to do so under the regulations?

Dr. FLACK. No, sir. I understand it is merely the licensed manufacturer of the product who is in a position to file with the FDA.

Senator KENNEDY. Though I have some reservations about your position, I think you ought to be entitled to make those recommendations.

Dr. FLACK. I can assure you that we are confident these are being filed.

Senator KENNEDY. All right.

If this were to be banned, would it work an economic hardship on some cattle feeders more than others, or would the ban be served as an economic hardship equitably across the board, so to speak?

Dr. FLACK. The point was made earlier today in testimony, the comparison or the relative position of feeder against feeder, big and small.

This would, the banning of the product, totally taken completely out of use, put the feeding industry on an equal basis across the board; so there would be no advantage or disadvantage. I would like to extend on that a little bit.

The problem would come and it would be one that would be hard to identify who is going to pay the bill.

If we take a product which originates as calf on a ranch that has a value, and we end with a piece of meat on a consumer plate, and we reduce by a factor of approximately 10 percent, the efficiency of the production of that product, that cost has to be paid, whether it is less money for the original calf or whether it is more money for the eventual piece of meat, or if it is merely a decreased quantity which is to be consumed, a big concern of the cattlemen in this country.

(The prepared statement of Dr. Flack follows:)

STATEMENT

of the

AMERICAN NATIONAL CATTLEMEN'S ASSOCIATION

to the

SUBCOMMITTEE ON HEALTH

SENATE COMMITTEE ON LABOR AND PUBLIC WELFARE
ON THE SUBJECT OF DIETHYLSTILBESTROL

by

DUANE E. FLACK, D.V.M.

GREELEY, COLORADO

JULY 20, 1972

Gentlemen:

On behalf of the American National Cattlemen's Association, thank you for this opportunity to present comments relative to the current interests and proposals concerning the use of Diethylstilbestrol (DES) in animal feeds.

It is my understanding that the purpose of this hearing is to discuss the proposed banning of DES by the Food and Drug Administration (FDA), and pending hearings associated with that proposal. I am sure there is concern in this group in what would appear to be an increased incidence in the occurance of DES residues in liver samples. The question is undoubtedly implied, if not stated, why not ban DES now? I am privileged and happy to speak to these points.

The use of this efficiency promoting additive has been a commonly accepted practice for nearly two decades. It has been estimated that 80 to 90% of the cattle on feed receive DES or similar hormonal products in one form or another. It's advantages have been available to all segments of the industry. Simple calculations would indicate that DES is responsible for the production of literally billions of pounds of pure, wholesome beef per year.

If the efficiencies realized in just the finishing phase of cattle production were to be lost, Sirloin steak would be 10 - 15¢ per pound higher priced than it is today. In a market place so concerned about ..."the high price of beef"..., I think this is pertinent. If for no other reason, doesn't this make it important not to ban the use of DES unless it is truly necessary? Is it?

DES has been used with unquestioned confidence in its safety and efficacy. It has only been in the last year, and more specifically in the last several months, that we have heard accusations, claims and counter claims, reports of increased residue instances

and widespread publication of each. These events have brought confusion and disagreement among the regulatory agencies, scientific and commercial representatives, the cattle industry itself, and most crucial of all, that ubiquitous group known as the consumer.

To the best of my knowledge, never has a residue of DES been detected in carcass beef even though samples are tested from the same animals from which other tissues are submitted. I have not heard of the first case to be identified of a human illness of any kind caused by the ingestion of DES in the form, the manner, or quantity represented in the residues identified in a few isolated liver samples. I understand that chemicals of comparable estrogenic activity are present in many common natural foods at relatively much higher levels. I also understand that DES specifically is commonly used for the therapeutic treatment of several conditions in men and women at trememdously high levels as compared to those we are discussing. This is where it appears some problem has occured. But, surely some kind of a dose to effect; and benefit to risk ratio should be applied. This is certainly the practice with any other therapeutic drug. The relation between therapeutic dose and tissue residue level are ridiculously far apart.

These facts being true, I find it alarming that there is being generated an impression that this nations meat supply is contaminated, when in fact, this simply is just not the case.

The beef cattle industry is concerned. The ANCA has appointed the ad hoc committee which I represent today. Ours is a multi-billion dollar industry. I think we rightfully have more sincere interest in the wholesomeness, purity, and quality of our product than all the scientists and legislators you could gather to discuss the subject. There are yet unanswered questions, but some things are becoming clear.

The apparent increased instances of residue identifications do not appear to be due to product abuse. It does seem to be due to an excellerated monitoring program and simultaneous application of a much more highly sophisticated assay technique. I am advised by competent authorities that the reliability of the Gas Liquid Chromatographic (G.L.C.) technique is questionable at levels less than one part per billion. This level represents nearly a third of the current 50 some positives reported. The availability of competent people and facilities to conduct G.L.C. determinations are extremely limited. The industry needs a capability to monitor its own program. It takes time to develop these services.

I feel confident in saying that management practices and control of DES have improved significantly over the past year. This has been stimulated by an awareness that a problem does exist.

What happened, then, when residues have been identified? I feel that it would be erroneous to imply that some cases of failure to comply with regulatory laws have not occurred. Where this is shown to be the case, the full weight of the law should be applied. Intentional abuse or disregard of withdrawal regulation has not been a significant factor, however. Inadvertent cross contamination, for one reason or another, seems to have been the most common cause. Carelessness has happened, human error, poor management or manufacturing practices have been identified. These are problems which are identified and managable, they are not the exotic, profound and mysterious.

Other questions of a more technical nature are also arrising. The carcinogenicity of DES has been legitimately challenged. I have mentioned the reliability of the analytical technique at the levels being reported. The biological significance of these ultra

minute traces or their relationship to previously identified levels has not been established. What is the importance of the fact that residues have only been identified in a small percentage of liver and a few kidneys? What is the relationship of this to our total beef supply? Are other means available to monitor and control potentially contaminated livers. Not all routes of original administration have even been identified with residue problems.

The fact that DES is widely used and yet well over 97% of the government's objectively collected samples have shown no trace, bears undisputable evidence that the product is being safely used. We need to determine then, what management and manufacturing practices need to be applied in those isolated instances to insure that no residues will occur in violation to regulation.

And finally, what constitutes none? It has been stated on many occasions by competent scientific investigators that mankind, our environment, Mother Nature, herself, could not comply with an absolute zero attitude on anything. These are not answers for me to determine. These are topics and discussions that need to be heard. For this reason ANCA heartily endorses the efforts of FDA to bring this matter out in the open before taking further action. We feel confident that these hearings will bring to light opportunities to solve problems and allow continued use of this tool. Take away a tool responsible for a ten percent advantage in efficiency of production, and that cost will be reflected throughout the chain of production all the way to the consumer.

On the other hand, the unquestioned confidence of the consumer is the most valuable asset of the American agricultural producer. DES or any other product is of no value if it hinders product quality, wholesomeness, or safety. Such determination, however, must be based on fact, not emotion; true relevance, not speculative potentiality, and above all, reason must bear some influence on a logical conclusion.

- 0 -

Senator KENNEDY. Thank you very much. I appreciate your appearance here.

At this point I order printed all statements of those who could not attend and other pertinent material submitted for the record.

(The material referred to follows:)

CONSUMER ACTION NOW, INC., 815 PARK AVENUE, NEW YORK, N.Y. 10021

July 21, 1972

Honorable Edward M. Kennedy
House Sub-Committee of the Senate Labor and
Public Welfare Committee
The Senate Office Building
Washington, D.C.

Dear Senator Kennedy,

Unfortunately, we at Consumer Action Now were not informed of the hearing on S. 2818 in time to have one of our group testify. However, this letter is an effort to record the views of the membership and subscribership of C.A.N. on the use of diethylstilbestrol in the feed of U. S. meat animals.

Our feeling regarding the use of D.E.S. is one of concern and our reasons are as follows:

- D.E.S. at some dosage levels is a known carcinogen.
- The existence of D.E.S. residues in animal livers tested.
- the lack of more sensitive testing procedures for residues.
- The nature and infrequency of existing testing.
- The incidence of vaginal cancers in young women whose mothers were given D.E.S. to prevent miscarriage during pregnancy.

We receive many requests for information of an environmental nature by letter and phone at the C.A.N. office. It should be of interest to your committee that questions and concern about D.E.S. are second only to those involving the solid waste problem. The hundreds of letters questioning the safety of the use of diethylstilbestrol convince us that this concern is general and not confined to a small group of "food faddists".

The law says that additives shall be proven safe before entering our food supply. In our judgement, D.E.S. has not been proven safe. We find it particularly disturbing that even though the withdrawal period has been extended, residues continue to be found.


CONSUMER ACTION NOW, INC., 815 PARK AVENUE, NEW YORK, N.Y. 10021



We feel that the use of diethylstilbestrol in the feed of meat animals should be banned until such time as it is proven absolutely safe.

We sincerely hope that our views and those of the many concerned citizens whom we represent will be heard and given serious consideration.

Sincerely,

Carlin G. Masterson

Carlin G. Masterson
Consumer Action Now

BEFORE THE

HEALTH SUBCOMMITTEE

OF THE

SENATE LABOR AND PUBLIC WELFARE COMMITTEE

STATEMENT ON BEHALF OF VINELAND LABORATORIES, INC.
P. O. BOX 70, VINELAND, NEW JERSEY 08260

This statement is submitted in behalf of Vineland Laboratories, Inc. for inclusion in the record of the Subcommittee's hearing held July 20, 1972 to consider actions now pending with regard to the withdrawal of approval of new animal drug applications for diethylstilbestrol (DES), and to consider S. 2818 which would ban DES from use in animal feed.

Vineland Laboratories, Inc. holds a new animal drug application for the use of DES in implants. Its current authorization is NADA No. 10964.

The rigid safety standard imposed by the applicable law and regulations, i.e., that no detectable residue of DES may exist in edible portions of animal carcasses, is met fully when DES is administered by the use of implants in accordance with approved conditions specified in the applicable label instructions. Even with the recently increased testing and the use of the new chemical method of assay there has been no instance of detectable residues of DES from implanted animals. This was confirmed by Commissioner Edwards' statement before the Subcommittee

on July 20, 1972, which explained that the new controls over the use of DES in animal feed were instituted because of reports of misuse of DES resulting in illegal residues, but which emphatically distinguished the facts with respect to implants, saying:

> "No new restrictions were instituted for DES administered by implant because no violations were or have been found." (P. 3).

This assurance with respect to the safety of implants was reaffirmed specifically by FDA witnesses, and by an industry witness, before the FDA National Advisory Drug Committee in a public hearing at FDA on July 25, 1972. The FDA's own investigations thus prove that the factual basis stated by Commissioner Edwards for the withdrawal of approval of applications relating to DES (37 F.R. 12251, 12252) does not apply to implants.

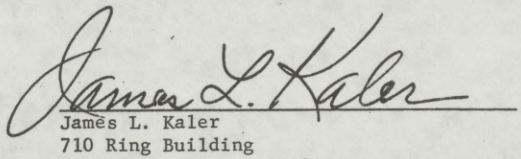
As the proven safety record of the implant method of administering DES shows, it inherently provides a positive and specific means of control. The conditions for the administration of implants specified in the label instructions for implants marketed by Vineland, for example, are simple and easy to follow. Clearly, there is no factual or legal basis for the withdrawal of approval of new animal drug applications which provide for the use of DES in implants.

Moreover, the alleged increase in the number of DES violations reported by the Department of Agriculture is based upon questionable data developed by the Department of Agriculture's use of a new chemical assay method to report purported detections of DES residues substantially below 2 parts per billion (ppb). According to the testimony to this Subcommittee

on July 20, this new assay method has not been officially published by the Food and Drug Administration because it has not yet been validated as a reliable means for detecting residues below 2 ppb. Whether the new method is more sensitive than the officially prescribed method, therefore, is seriously in question and the alleged increase in the number of violations reported may in fact be so-called "false positives" resulting from the new method.

Such questionable data cannot validly support the total withdrawal of DES from use. Even if it may have some genuine value as an alert to re-examine and improve control procedures and techniques for administration of DES, such efforts should be directed specifically to uses which have developed violations, not towards the use of DES in implants. Specifically, neither new legislation nor new regulatory actions with regard to DES should be permitted to involve or jeopardize in any way the administration of DES by the proven and safe implant method.

Respectfully submitted,



James L. Kaler
710 Ring Building
Washington, D. C. 20036
Counsel for Vineland Laboratories, Inc.

July 27, 1972

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
WASHINGTON, D. C. 20250

JUL 11 1972

Honorable L. H. Fountain
House of Representatives

Dear Mr. Fountain:

Enclosed is the DES report up to July 1, 1972, including a list of 1972 objective phase violations.

Sincerely,

Kenneth M. McEnroe

Kenneth M. McEnroe Acting
Associate Administrator
Meat and Poultry Inspection Program

Enclosures

REPORT ON DES SAMPLING
Meat and Poultry Inspection Program
For Week Ending July 1, 1972

| | | |
|---|---|---|
| Total Samples Analyzed | Selective | 818 |
| | Objective | 2310 |
| New Noncompliance Cases | Selective | 7 |
| | Objective | 0 |
| Total Noncompliance Cases | Selective | 28 |
| | Objective | 26 |
| Total Samples in Compliance | Selective | 790 |
| | Objective | 2284 |

DES Levels Reported Below the
Sensitivity (2.0 ppb) of the
Legal Assay Method

| | | |
|---|---|---|
| New Cases | Selective | 6 |
| | Objective | 4 |
| Total Cases | Selective | 39 |
| | Objective | 28 |

DES DETECTED ON OBJECTIVE PHASE SAMPLING - 1972

| Species | Date Collected | DES Level PPB (Liver) |
|---|---|---|
| Sheep | 1/27/72 | 3.3 |
| Cattle | 2/1/72 | 4.15 |
| Cattle | 2/14/72 | 1.5 |
| Cattle | 2/15/72 | 4.5 |
| Sheep | 3/3/72 | 1.80 |
| Cattle | 4/4/72 | 4.1 |
| Cattle | 3/15/72 | 0.60 |
| Cattle | 4/4/72 | 2.1 |
| Cattle | 4/3/72 | 5.9 |
| Cattle | 4/3/72 | 1.53 |
| Cattle | 4/3/72 | 1.30 |
| Sheep | 4/4/72 | 6.81 |
| Cattle | 4/4/72 | 2.0 |
| Cattle | 4/5/72 | 3.8 |
| Cattle | 4/11/72 | 2.0 |
| Cattle | 4/13/72 | 1.1 |
| Dairy Cow | 4/6/72 | 2.85 |

| Species | Date Collected | |
|---|---|---|
| Cattle | 4/8/72 | 1.10 |
| Cattle | 4/24/72 | 1.2 |
| Sheep | 4/20/72 | 2.4 |
| Cattle | 4/26/72 | 5.4 |
| Cattle | 4/26/72 | 3.0 |
| Cattle | 5/10/72 | 2.2 |
| Cattle | 5/10/72 | 1.9 |
| Cattle | 5/8/72 | 0.9 |
| Cattle | 5/12/72 | 1.6 |
| Cattle | 5/12/72 | 9.5 |
| Cattle | 5/11/72 | 3.6 |
| Cattle | 5/18/72 | 2.0 |
| Sheep | 5/23/72 | 2.1 |
| Cattle | 5/23/72 | 3.5 |
| Cattle | 5/26/72 | 1.4 |
| Cattle | 5/15/72 | 6.5 |
| Cattle | 5/24/72 | 0.7 |
| Cattle | 5/17/72 | 0.7 |
| Cattle | 5/23/72 | 0.5 |
| Sheep | 5/24/72 | 1.3 |

| Species | Date Collected | DES Level PPB (Liver) |
|---|---|---|
| Cattle | 6-2-72 | 0.7 |
| Cattle | 6-6-72 | 0.9 |
| Cattle | 5-31-72 | 1.3 |
| Cattle | 6-5-72 | 1.0 |
| Cattle | 6-6-72 | 0.7 |
| Cattle | 6-7-72 | 0.7 |
| Cattle | 6-6-72 | 0.5 |
| Cattle | 6-1-72 | 0.5 |
| Cattle | 6-1-72 | 1.2 |
| Cattle | 6-6-72 | 1.6 |
| Cattle | 6-6-72 | 2.7 |
| Cattle | 6-6-72 | 2.7 |
| Cattle | 6-8-72 | 2.9 |
| Dairy Cow | 6-8-72 | 0.9 |
| Cattle | 6-1-72 | 1.7 |
| Cattle | 6-12-72 | 1.6 |
| Cattle | 6-13-72 | 0.8 |

DATE : December 6, 1971

REPLY TO
ATTN OF : DEN-FO

James Aitchison
Iroquois, S.D.

SUBJECT : 076-524 E - Illegal Residues in Sheep Liver

TO : BUREAU OF VETERINARY MEDICINE (VM-220)
ATTENTION: JOHN C. EVANS, FOOD ~~AND~~ DRUG OFFICER

1. Inspector Dwight Ringhausen has reviewed your November 23, 1971 memo and attempted to answer the questions it raised to the best of his ability under these circumstances.

2. You must recall that this district was asked to issue a Notice of Hearing to a Mr. Jim Atcheson for offering cattle to a slaughter-house, the liver of which contained 6.5 ppb DES. Mr. Ringhausen's visit to Iroquois, S.D. was for the sole purpose of verifying these facts prior to the issuance of that Notice of Hearing. Mr. Ringhausen's visit did disclose that the man's name was James Aitchison and that this individual had offered sheep for ~~slaughter~~ and ~~not cattle~~.

Iroquois, S. D. is in the middle of nowhere; we have no man in the state; and, consequently, any further followup would place an undue burden upon existing DEN-FO inspectional manpower.

3. We do not believe the situation warrants any more work.

W.A. Graham
W. A. GRAHAM
Food and Drug Officer

---

DATE : December 6, 1971

FROM : Inspector Dwight Ringhausen, DEN-FO

SUBJECT: 076-524 E - Illegal Residues in Meats (BVM Memo 11/23/71)

TO : REGIONAL FOOD AND DRUG DIRECTOR, DEN-FO

In his memo dated November 23, 1971, John C. Evans, Food and Drug Officer, requested the following answers:

2. a. The sheep are not fed in same pens as cattle -- sheep would not have access to cattle feed unless wrong feeds were fed or sheep got out of pens into cattle feed. In such cases the feeder would have no records of such. Any such information would be recollections. I did not discuss the possibilities.

b. Mr. Aitchison had to be contacted at night. By the time preliminary information was obtained it was dark -- we did not examine any particular pens. In some cases the pens may have a driveway between them. Some pens may be side-by-side -- I don't know.

c. It was not discussed per se. I would assume that since feeds are picked up from different feed mills, the personnel would know what feed was to be delivered to what species of animal.

d. Storage conditions were not observed.

3. I would presume that there are records such as invoices showing where animals are purchased. I did not examine any. There are no records to show what animals go into what pens when they are received. There is no effort made to maintain identity of the animal after purchase. The animals are fed until fat, then placed into a fat pen pending shipment. A visit was not made to the slaughterhouse. Mr. Aitchison stated that all his sheep were under quarantine at the slaughterhouse for 48 hours until negative DES results were received from subsequent samples.

4. It was suggested to Mr. Aitchison that he inquire of the DES history of animals that he purchases so that he could hold animals prior to slaughter where indicated.

Dwight F. Ringhausen

DWIGHT F. RINGHAUSEN
Inspector, Denver Field Office

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WEL
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

TO : Dr. M. Adrian Gross
Bureau of Drugs
Food and Drug Administration

DATE: February 22, 1972

FROM : Nathan Mantel
Biometry Branch
National Cancer Institute

SUBJECT : Comments, as you requested, on Mitchell, Neumann, and Draper, "Metabolism of tritium-labelled diethylstilbestrol by steers", Agricultural and Food Chemistry, Vol. 7, No. 7, 509-512, July 1959.

In this article no results are presented which would allow one to judge how long it takes for tissue levels of diethylstilbestrol to become arbitrarily low once an animal has been taken off a regular feed containing diethylstilbestrol. What results are shown, however, are important in bringing out that some proportion of diethylstilbestrol will still be present in the animal for at least 10 days following ingestion.

The study made is subject to the limitations of being conducted on only 2 animals, one receiving a single oral dose of labeled diethylstilbestrol, the other receiving the stilbestrol in feed over an 11 day period. In the latter case, the animal was slaughtered only 27 hours after the last feeding and the resulting data could give no information on reductions in tissue levels that would occur with more prolonged periods following discontinuance of diethystilbestrol. Further, since the animal had not been on diethylstilbestrol for an extended period there could be no way of getting at the possibility that diethystilbestrol accumulation might occur in tissues from which it would not be readily released.

What the report does show is that for both animals some 50% of administered stilbestrol was recovered from feces and urine (and from rumen and intestine contents in the slaughtered animal ). In the case of the single-dose animal nearly all recovery was in the first 3 days, but there was continued recovery of small amounts in the next 3 days. For the daily stilbestrol-fed animal total recovery from feces and urine increased continually each day up till the tenth, although for urine alone the peak was achieved between days 4 and 5 (which the authors indicate may mean attainment of a threshold level in tissue retention.)

When the animal was slaughtered 27 hours after last feeding, only a small fraction of a percent of administered diethystilbestrol was recovered from the tissues. Lean meat and fat levels were 0.30 and 0.35 ppb, but there was accumulation in particular tissues, 9.12 ppb in liver, 4.15 ppb in kidney. Meat levels were so low that some 8960 pounds of meat would have to be consumed to provide 1 mg of stilbestrol — these levels were well below the 2 ppb level detectable by biological assay. About another 10%

of administered stilbestrol can be accounted for by incompleteness of the feces extraction procedure used, leaving still about 40% unaccounted for. Whether this could be due to respiratory losses is not discussed by the authors, but they do suggest the conversion of free phenols of stilbestrol to water-soluble forms as being a major pathway in stilbestrol metabolism.

The authors suggest that the time required for the elimination of stilbestrol from tissues of steers is about 72 hours. It is likely that this suggestion does not pertain to incorporated stilbestrol, but relates only to ingested stilbestrol. The authors had seen that nearly all fecal and urinary elimination had occurred within 72 hours; further, tissue levels only 27 hours after discontinued feeding (and possibly after threshold tissue levels had been attained) were trivially low (except in particular tissues like liver and kidney) by the standards at that time, 1959. These low tissue levels of 0.30 and 0.35 ppb would not be considered suitably low by today's standards, so more definitive work is needed to determine rates of disappearance of stilbestrol from animal tissues, particularly when the stilbestrol has been gradually incorporated over an extended feeding period.

The aspect of the data reported which is suggestive that a long stilbestrol-free period may be necessary was the continuing increase up till the tenth day in the amount of stilbestrol recoverable in feces and urine. If essentially all of a given day's administration of stilbestrol is lost within k days, then by the k'th day there should be near-stability of both retained and excreted levels of stilbestrol. The data do not indicate such stability to be occurring before the 10th day, and we must interpret this as meaning that even the first day's ingestion of stilbestrol is contributing to the tenth day's excretion.

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Virgil O. Wodicka
Director
Bureau of Foods (BF-1)

DATE: February 8, 1972

FROM : Leo Friedman, Ph.D., Director
Division of Toxicology (BF-150) Leo Friedman 2/8/72

SUBJECT: Diethylstilbestrol

We have recently reviewed the data, including recent publications, bearing on the use of diethylstilbestrol as a growth promotant in sheep and cattle. We believe that this review, including the new information presented, should be brought to the attention of the Commissioner.

The original decision in the 1950's to allow the use of this drug with a 48-hour withdrawal and an analytical sensitivity of 2 ppb by biological assay was sound, according to the data that were available at that time. Recently the findings of residues in cattle resulted in a change in regulations governing the use of DES in cattle and sheep which require a 7-day withdrawal interval before slaughter.

As you know, we recently reviewed a paper by Gass, et al, Journal of the National Cancer Institute, Vol. 33, No. 6, December 1964, in which the incidence of mammary carcinoma was increased in mice with levels of DES as low as 6.25 ppb.

Additionally, we call to your attention an article by Leslie G. Quinlivan, M.D., published May 15, 1968 in the American Journal of Obstetrics and Gynecology, in which he discussed treatment of senile vaginitis in post monopausal women. The study was 4 weeks in duration. Each woman served as her own control.

A group of 19 women received 0.1 mg DES orally for the 4-week period. All 19 responded with 16 being classified as "good." Two of these women showed withdrawal bleeding post treatment. Another group of 15 women were given 0.1 mg orally twice weekly. Again all responded, though only 7 were classified as "good." The number classified as "good" is less important than the fact that all of them made some response to this small dose of DES.

The dose of DES, 0.1 mg twice weekly, represents about 2 µg/kg at the time of administration and on a weekly basis averages about 0.5 to 0.6 µg/kg/day. Considered in terms of dietary intake, this is approximately 20 ppb of the total daily diet.

Comments have been made that we are continually exposed to naturally occurring exogenous and endogenous hormones in greater amounts than we would encounter from DES. The plant hormones which may be consumed by either man or animal vary widely in estrogenic effect but all are significantly lower in activity than DES. One of the most potent plant hormones, coumestrol, found in clover and alfalfa, has only 1/10,000th of the activity of DES. Genistein and genistin, estrogenic compounds derived from clover and soybeans, have about 1/300,000th the potency of DES.

The principal source of estradiol and its metabolites in our foods would be from meat. Data currently available (Hendricks et al., Endocrinology, Vol. 89, No. 6, December 1971), using a radioimmunoassay has, for the first time, really quantified this source. His data indicate that in the bovine female, total estrogens present in serum range from 0.5 to 10 parts per trillion in the diestrus state, and rises to between 20-30 parts per trillion about 24 to 48 hours prior to the onset of estrus, then falls rapidly (during the 6-8 hour period) following the onset of estrus. We have no reason to believe muscle levels would be above these amounts and would more likely be somewhat less than the serum levels. It is interesting to note that a 350 kg heifer needs only an increase of approximately 300 nanograms within the whole volume of her circulating blood to go into heat. A kilogram of liver with 1 ppb would contain 1000 nanograms. (Dr. Hafs, of Michigan State University, unpublished data, has checked the serum level of estradiol in steers and finds it in the same range as has been published by Hendricks for the diestrus female).

Estradiol is a natural hormone in man, and the metabolic pathways are already established so that in the event any is absorbed, it will be rapidly metabolized and excreted. DES, on the other hand, is a synthetic estrogen having ten times the potency of estradiol and is much more slowly metabolized and excreted, thus exerting its effect on target organs for a much longer period of time. Dr. Umberger has estimated the half-life of DES to be 12 hours, while Hendricks' (Clemson University) work would indicate the half-life of estradiol is much less, probably somewhere between 6 and 8 hours.

The level of circulating estradiol in serum of post-menopausal women is about 15 parts per trillion (Korenman et al, Journal of Clinical Endocrinology, 29:879, 1969). Assuming one of these women ate 4 oz. of liver containing 1 ppb DES, she would consume about 0.125 mcg or

0.0025 mcg/kg body weight, which is equivalent to 2.5 parts per trillion Since DES has ten times the activity of estradiol, this could be the equivalent of adding 25 ppt estradiol to that already normally present, almost tripling the physiological level on a whole body weight basis. If we assume that the DES and estradiol exist only in the circulating blood, the increase would be 22 times normal.

If violations of the 7-day withdrawal period should occur, the probability that muscle as well as kidney and liver, will be above what we now would consider an "acceptable" level, would be real. Furthermore, one must consider that such exposures would not be limited to an occasional piece of liver or that they would be equivalent to the natural exposure from the occasional slaughter of a pregnant cow, because:

1. Many people buy meat in quantity and store it in lockers or home freezers.

2. Liver is still considered a hematinic and, in some cases, consumed daily.

3. If violations of the withdrawal period do occur, it would not be limited to a random animal, but would more likely involve all the cattle marketed at that time by that producer.

4. Until sufficient time has elapsed to clear the animal's metabolic pool of DES, we are dealing with a population of hyperestrogenized animals that cannot be considered normal in this regard. We should like to have better evidence than we have now to conclude that 7 days are sufficient time to reduce the DES to the low physiological levels of estrogenic activity normally found.

The study by Mitchell et al in Agriculture and Food Chemistry, Vol. 7, No. 7, July 1959, is practically the only evidence to support the 7-day withdrawal period. By our current standards, this study is weak scientific justification for the conclusion:

1. Only one animal was used in this study.

2. Only a single dose of tritium labeled DES was given. The animal had not been equilibrated by feeding unlabeled drug.

3. Only 51% of the administered drug was recovered in urine and feces (29.3% in feces and 21.8% in urine), while 49% of the administered drug was not accounted for. Yet when untreated fecal material was spiked with radioactive material, from 73% to 83% could be recovered.

On the basis of all available evidence, Dr. Umberger, now retired, formerly of the Bureau of Drugs, indicates that a half-life for diethylstilbestrol is about 12 hours.

After a 48-hour withdrawal period, biological assay data indicate that livers are negative with respect to DES. Since the biological assay is sensitive at all times to 2 ppb, and occasionally, to a half a part per billion, we can assume that at 48 hours there may be as much as one and a half per billion, or on occasion, less than a half a part per billion. If 1.5 ppb is, in fact, present at 48 hours and if we accept a 12-hour half-life, then after the 7-day withdrawal period we would still have 1.5 ppt. This may, in fact, be higher, since for many drugs as the concentration in the body decreases, the excretion rate usually also decreases. If this is true with DES, there may be appreciably more than 1.5 ppt present after 7 days.

In view of the responsiveness of humans to low levels of DES, the carcinogenicity demonstrated in mice, and the low levels of estrogen found normally in steers and in certain parts of the human population, it would appear wise at the present time to: (1) obtain better data to more firmly establish the rate of disappearance of DES and to prove the adequacy of the 7-day withdrawal period; and (2) to initiate studies toward the development of an analytical method by the application of either protein binding or radioimmuno-assay techniques toward the development of a specific assay for diethylstilbestrol that would be capable of detecting DES in the part per trillion range.

We recommend that:

1. Studies being planned by BVM in collaboration with ARS/USDA to accurately determine the biological decay of DES in cattle and sheep be encouraged, and be performed promptly.

2. That Dr. Hafs and Dr. Wm. Hansel of Cornell University, Dr. G. W. Niswender, Colorado State University, and Dr. D. M. Hendricks, Clemson University, be invited to meet with Bureau of Foods personnel and representatives from BVM and BD, regarding the development of an assay procedure of the sensitivity desired in the ppt range.

Prepared by: A. J. Kowalk, D.V.M. and
R. L. Gillespie, D.V.M., BF-152

cc: Dr. A. C. Kolbye, Jr., BF-2
Dr. H. Fischbach, BF-100
Dr. H. Blumenthal, BF-151
Dr. C. J. Kokoski, BF-152
Dr. A. J. Kowalk, BF-152
Dr. R. L. Gillespie, BF-152

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : BUREAU OF VETERINARY MEDICINE VM-220
Attn: James O. Gesling

DATE: January 11, 1972

Shpr: Mr. Glenn Richards
Lodi, Wisconsin

FROM : Minneapolis District

SUBJECT: DOC 041-299 E, Beef Cattle (edible tissue)

PA WITH REVIEW REQUESTED

Response to citation of December 2, 1971, was answered by letter. We attach copy of the response as well as copies of investigation reports by Dr. Q. S. Paulson, State of Wisconsin, and our Inspector Eastwood.

It appears that we have reached the end of the line here, so to speak, as is the usual result in this type case. We therefore request your concurrence to place the subject number in PA.

Fermer W. Adair

Fermer W. Adair
Food and Drug Officer
Minneapolis District

Attachments

cc: MIN-DO

MIN-D40:FWAdair/sra 1/11/71

Atlanta District (ATL-D40)
Attn: Mr. J. R. Dupre

February 18, 1972

Suber Cattle Co., Inc.
Gretna, Fla.
and
John W. Suber
W. Harvey Suber

AF None

Bureau of Veterinary Medicine (VM-220)

22-654E, Illegal Residues in Meat

PROSECUTION DISAPPROVED

1. We are enclosing a copy of our memo of 10/29/71 forwarding your original prosecution recommendation on this number to the General Counsel with our approval.

2. By memo of 2/9/72, Mr. Hutt, the General Counsel, advised that the case could not be filed because of several legal insufficiencies. One infirmity involves the fact that the Hearing was held at the farm as a part of an unannounced inspection without forewarning the individuals of their rights. The second is the analytical methodology used to determine the DES residue in the meat, constituting a new chemical method rather than the old biologic method, whereas the regulations still retain the old biologic method. Finally, he advises, the case is infirm in that no reserve sample was retained with the result that we cannot corraborate the DES residue using the old biologic method and more importantly, we are unable to furnish a sample to the potential defendent as required by section 702(b).

3. In view of the foregoing, the case may not be forwarded for filing. Nor are we aware of any steps that can be taken at this late date to repair the deficiencies. Accordingly, we are most reluctantly returning the case.

4. For your information, so as to avoid future case failures in this regard, we are exploring at our Bureau level means to validate the chemical method with appropriate regulation promulgation in the FEDERAL REGISTER and to coordinate with the USDA to arrange for retention of sufficient reserve samples to permit assay to satisfy the 702(b) requirements.

Herbert Friedlander
Chief, Case Guidance Branch
Bureau of Veterinary Medicine

cc: VM-200(Gesling)
VM-8
CA-224
HFriedlander/pcm/2-18-72

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
Office of the General Counsel

TO : C. D. VanHouweling, D.V.M., VM-1 DATE: February 9, 1972

FROM : Peter Barton Hutt, GC-1 PBH

SUBJECT: Proposed Prosecution of Suber Cattle Company and Two Individuals

On October 29, 1971, Mr. Gesling forwarded to me a recommendation for prosecution of Suber Cattle Company, John Suber, and Henry Suber, as a result of a USDA finding of DES residue, for violation of the DES withdrawal requirements. Since we then had pending about 18 Section 305 citations involving similar circumstances, I requested that all such prosecution recommendations be forwarded to me for review at one time. In this way, our action would be consistent, based upon a total picture of DES feeding practices.

Last week you informed me that all of the pertinent hearings have now been held and that you were prepared to recommend prosecution only in this one case. Accordingly, we have reviewed this case to determine whether there is a legal basis for prosecution.

As you know, three potential legal infirmities exist in this case. First, the hearing was held at the farm as part of an unannounced inspection without forewarning the individuals of their rights. Second, the method used to determine the DES residue is the new chemical method, rather than the old biologic method, and the present DES regulations still retain the old biologic method. Third, no reserve sample was retained, with the result that we cannot corroborate the DES residue using the old biologic method, and we cannot furnish a sample to the potential defendants under Section 702(b).

In view of his long experience in this matter, I asked Al Gottlieb to review the question whether any or all of these three infirmities preclude criminal prosecution in this case. Al has concluded, and I concur, that prosecution cannot be recommended. Although the form of the Section 305 hearing is not in itself a legal impediment, the lack of Section 702(b) samples, especially in light of the fact that the residues were not determined by the method legally designated in the regulations, require the conclusion that the prosecution must be refused as legally defective. Al informs me that courts have dismissed a number of cases for failure to provide Section 702(b) samples since

without such samples a defendant cannot conduct tests to verify or disprove the residue allegation. And since the new (not yet legal) method was used, the need for confirmatory samples is even more acute.

This underscores the fact that the new chemical method must immediately be validated and promulgated in the Federal Register, and that USDA must immediately order retention of sufficient reserve samples to permit assay and to satisfy Section 702(b). (It is my understanding that FDA has a guideline for inspectors on collection of samples for assay, and this should be given to USDA.) Unless both are done, we have no choice but to withdraw approval of DES because we would otherwise be unable to enforce the regulations.

cc: OC-1
OC-2
CC-1
BF-1
VM-10

July 23, 1971

Mr. H. E. McGill
Livestock Commissioner
Department of Agriculture and Food
Parliament Building
Toronto 182, Ontario, Canada

Dear Mr. McGill:

With reference to your letter of July 5 to Dr. Edwards, we are sending you some speeches, reports, fact sheets, etc., concerning the use of Diethylstilbestrol, other drugs, and medicated feeds in livestock production. We are placing your name on our mailing list to receive future reports and statements involving these matters.

However, we wish to point out the testing programs for residues in meat is not in the responsibility of the Food and Drug Administration, but come under the jurisdication of the Consumer and Marketing Service, U. S. Department of Agriculture, C&MS is also responsible for making the information available through appropriate channels. We are referring your request to that agency so that you will receive these reports directly from them.

In your letter you also request the names of the 21 countries which have banned the use of hormones as growth promotants. The following list includes the names of those countries:

| | |
|---|---|
| Argentina | Jordan |
| Australia | Luxembourg |
| Austria | Madagascar |
| Belgium | Morocco |
| Brazil | Netherlands |
| Denmark | Peru |
| Eire (Republic of Ireland) | Poland |
| Federal Republic of Germany (West Germany) | S. Africa |
| France | Sweden |
| Greece | Switzerland |
| Italy | |

Sincerely yours,

K. F. Johnson, D.V.M.
Director, Division of
Veterinary Medical Review
Bureau of Veterinary Medicine

Enclosures

VM-220 (Friedlander)
JTLasila/ps/7-23-71

cc: LCS-40 OIA
C&MS, USDA (w/cy. incoming letter)
VM-600 (Dr. Johnson)
VM-400 (Dr. Cazier)
VM-400 (File)
VM-13
CA-224

Development and/or Refinement of Methodology for
Assaying Veterinary Drugs in Animal Tissues

PROGRESS REPORT

DES

Using the new Lilly procedure, we have successfully recovered both DES and DES monoglucuronide from beef liver. The quantitative accuracy of the results was compromised because the liver samples contained approximately 0.5 ppb endogenous DES monoglucuronide. This contaminated liver was obtained from two separate sources, and the identity of the interfering peaks was confirmed by their disappearance when the glucuronidase treatment was omitted. We intend to perform a final recovery experiment using "organically grown" liver. The supplier of this liver stated that the steers used had been on wholly "natural" feed for a minimum of 30 days prior to slaughter.

We have found that the dichloroacetyl derivatization method given by Dr. Donoho is inadequate in our hands. However, when we distill the dichloroacetyl chloride, wash the DES-ester solution with 1 N NaOH and water, and dry the solution with sodium sulfate satisfactory results are obtained. When these additional steps are omitted, the reagent blank background is two high to permit adequate quantitation.

Mr. Anthony Malinowski has described the formation of trifluoroacetyl esters of DES. He stated that he reacted DES in 1 ml benzene with 0.1 ml 1% pyridine in trifluoroacetic anhydride for 20 minutes at 75°. We have used this method and worked up the esters under anhydrous conditions by evaporating the reagents to dryness under a stream of dry nitrogen, adding 1 ml benzene and

repeating the evaporation, and bringing the residue to volume. To date we have had variable success with this method.

Results in our attempts to recover small amounts of DES from columns containing 10 ml 0.4 N NaOH have been inconclusive. Celite, cellulose powder, and glass beads were used as adsorbents of the caustic. We recovered about 600 ng of 1000 ng DES applied to a glass bead column with a 200 ml benzene elution. The ambiguous nature of this result warrant discussion with the sponsor before further work is undertaken. Perhaps collaboration with the project officer would be fruitful in this instance.

We will submit an interim technical report on DES giving our results in greater detail before the end of the year.

Submitted by: William F. Stephen Jr.
WILLIAM F. STEPHEN, Jr., Ph.D.
Biochemistry Department
Environmental Sciences Laboratory

Approved by: William A. Olson
WILLIAM A. OLSON, Ph.D.
Project Manager

THE DOOM COMMITTEE (ORGANIZED TO GET DRUGS OUT OF MEAT) INSTITUTED A MEATLESS WEEK ON JULY 4TH THROUGH JULY 11, 1971, IN ORDER TO ACQUAINT CONSUMERS WITH THE HAZARDS OF EATING MEAT THAT MAY POSSIBLY BE CONTAMINATED WITH A CARCINOGEN, THEREBY EXPOSING THEMSELVES TO ADDITIONAL CANCER HAZARDS. WE ARE AWARE 52 MILLION PEOPLE LIVING IN THE U.S. WILL DEVELOP CANCER, AND THAT IT WILL STRIKE 2-OUT-OF-3 FAMILIES...THAT THIS YEAR, ONE MILLION AMERICANS WILL BE UNDER MEDICAL CARE FOR CANCER...THAT DURING THE '70's THHERE WILL BE 3.5 MILLION DEATHS FROM CANCER, AND 6.5 MILLION NEW CANCER CASES, WITH 10.0 CANCER CASES UNDERGOING MEDICAL CARE, AND 650,000 NEW CANCER CASES DIAGNOSED FARR THE FIRST TIME IN 1972...THAT CANCER IS THE LEADING CAUSE OF DEATH AMONG CHILDREN UNDER THE AGE OF 15!!!

THERE MUST BE A REASON THAT IN 1900 64-OUT-OF 100,000 AMERICANS DIED OR CANCER, (OR WHAT WAS DIAGNOSED AS CANCER) IN 1940 THAT FIGURE REACHED 146-PER-100,000, BUT BY 1967 THERE WAS A DRAMATIC 600% INCREASE...THE FIGURE HAD RISEN TO 364.5-PER 100,000! CANCER CONTINUES TO STRIKE MORE OFTEN AND MUCH SOONER THAN EVER BEFORE.

THERE MUST BE A REASON THAT DEGENERATIVE KILLER-DISEASES ARE CLIMBING AMONG THE YOUNG AND THE OLD.....DEGENERATIVE DISEASES DO NOT AFFECT ONLY THE OLD. OUR YOUNGSTERS ARE FACED WITH DEGENERATIVE DISEASES THAT AFFECTED ONLY THEIR GRAND PARENTS IN DAYS GONE BY. CANCER IS AFFECTING THE YOUNG AS WELL AS THE OLD, AND WE FEEL THAT THE ANSWER LIES IN ALL OF THE FOOD WE ARE INGESTING THAT ARE LOADED WITH CARCINOGENS, WITH CHEMICALIZED FOODS, SOME OF THEM CANCER PRODUCING, WITH CHEMICAL CARCINOGENS THAT ARE ADDED TO OUR FOODS, IN THE GROWTH PROCESS (CATTLE AND SHEEP) TO FARM PRODUCTS, IN OUR AIR, OUR WATER, AND IN OUR SOIL, INGESTED BY US DAILY.

ONE OF THESE CHEMICALS, IS THE SYNTHETIC FEMALE SEX HORMONE, WHICH IS USED STRICTLY FOR ECONOMIC REASONS...BILLIONS OF DOLLARS TO THE PHARMACEUTICAL INDUSTRY, AND TO THE CATTLE AND SHEEP GROWERS, EXCESSIVE PRODUCTS, WHILE THE USE OF D.E.S. IS TRULY ILLEGAL, A VIOLATION OF THE DELANEY AMENDMENT OF THE FEDERAL FOOD DRUG AND COSMETIC ACT.

EVER SINCE 1954 OUR FEDERAL AGENCIES HAVE BEEN LYING TO US, AND THAT LIE WAS EXPOSED IN DECEMBER, 1971, AT WHICH TIME F.D.A. INFORMED US THAT THERE WAS NOW EVIDENCE THAT ALL FEED WAS ELIMINATED IN 7 BETWEEN 7 AND 10 DAYS, WHEREAS PRIOR WE HAD BEEN TOLD IT WOULD BE ELIMINATED WITHIN 48 HOURS.

-2- Testimony for DOOM Committee submitted to Sub-committee on Health 7-19-72, together with over 25,000 signatures on petitions.

EVER SINCE 1954 OUR CHILDREN HAVE BEEN DAILY EATING MEAT THAT WAS PROBABLY CONTAMINATED WITH THE CARCINOGEN, DIETHYLSTILBESTROL. I SUBMIT THE TESTIMONY OF THE 4 DOCTORS AT THE SYMPOSIUM ON MEDICATED FEED (MFW) HELD IN NEW YORK CITY, JANUARY, 1956. DRS: MARTIN, IGLESIAS, WILLIAM E. SMITH AND GRANVILLE KNIGHT: "..IT IS A CONTINUING EXPOSURE TO EXTREMELY MINUTE DOSES THAT IS TO BE FEARED FROM THE INTRODUCTION OF ESTROGENS INTO THE FOOD SUPPLY, EXPOSING HUMAN BEINGS FROM BIRTH ONWARD...1 POUND OF MEAT, CERTIFIED AS FREE OF DES COULD CONTAIN NEARLY 14 TIMES THE AMOUNT OF DES NECESSARY TO INDUCE CANCER BY A DAILY DOSE TO MICE..." ..."THAT THERE WAS NO WAY OF ELIMINATING DES RESIDUES FROM MEAT THAT HAD BEEN TREATED WITH DES."..AT ONE TIME FDA HAD RECOMMENDED"COOKING MEAT AT 428°F. FOR SEVERAL HOURS IN ORDER TO RESTROY RESIDUES OF DES." WHAT YOU'D END UP WITH IS DES CONTAMINATED SHOE LEATHER....THERE'S NO WAY OF ELIMINATING THIS CARCINOGEN ONCE IT GETS INTO THE STEER,COW OR SHEEP...JUST AS THE CHLORINATED HYDROCARBONS (DDT, 2,4-D, 2,4,5-T, 2,4-DP, PCB) REMAINS AND BUILDS UP WITHIN THE FATTY TISSUES, DES REMAINS WITHIN THE MEAT AND MUSCLE TISSUE OF THE ANIMAL, AND THERE'S NO WAY OF ELIMINATING THIS CARCINOGEN..... "A GREAT BODY OF EVIDENCE SHOWS THAT CANCER-INCITING CHEMICALS CAN EXERT THEIR EFFECTS IN CATALYTIC QUANTITIES, INDUCING CHANGES IN CELLS WHICH ARE MEDIATED BY UNKNOWN SUBSTANCES TRANSMITTED FROM CELL TO CELL LONG AFTER THE ORIGINAL CANCER-INCITING MATERIAL CEASES TO BE DEMONSTRABLE IN THE TISSUES."

WE HAVE ALL THE EVIDENCE NECESSARY TO BAN DIETHYLSTILBESTROL, AND AS OF MARCH 1971, THE REPORTS OF DR. ARTHUR L. HERBST OF HARVARD MEDICAL SCHOOL, ADENOCARCINOMA IN YOUNG GIRLS WHOSE MOTHERS WERE PRESCRIBED STILBESTROL TO CONTROL BLEEDING OR MISCARRIAGE...AUGUST,1971, DR. GREENWALD (N.Y.C.) ADDITIONAL CASES OF ADENOCARCINOMA....THEN ADD TO THIS, THE REPORTS OF DR. BRIAN HENDERSON AND MURRAY GARDNER, WITH U.S.C. SCHOOL OF MEDICINE, ~~XXXXXXX~~ CANCER OF THE TESTES IN YOUNG MEN, WHOSE MOTHERS HAD TAKEN DES, (Their findings are not complete as yet, having been given a $2½ million contract to investigate further)....BUT WE DO KNOW THAT MEN HAVE BEEN EFFECTED JUST AS WELL AS WOMEN...SYMPOSIUM (ABOVE) POINTS OUT 17 CASES OF BREAT CANCER (CARCINOMA OF THE MALE BREAST) IN MEN GIVEN DES, WITH AXILLARY METASTASIS FOLLOWING STILBESTROL THERAPY....A VETERAN ADMINISTRATION STUDY OF THE USE OF DES IN FIGHTING CANCER OF THE PROSTATE REVEALS 5 MG. OF DES APPARENTLY HASTENS THE ONSET OF ALL TYPES OF CARDIOVASCULAR PROBLEMS... THE BRITISH STUDY ...DES USED TO SUPPRESS LACTATION IN NURSING MOTHERS FINDS THAT ITS USE (DES) SIGNIFICANTLY INCREASES THE INCIDENCE OF THROMBOEMBOLISM, PARTICULARLY IN WOMEN AGED 25 YEARS OR MORE AND DELIVERED OF THEIR FIRST, SECOND OR THIRD CHILD"...

HOW MUCH ADDITIONAL EVIDENCE DO WE NEED....THE FACT THAT 21 NATIONS HAVE BANNED THE USE OF D.E.S., AND THERE IS ALSO THE POSSIBILITY THAT ENGLAND WILL JOIN THE LIST...AND SO WILL CANADA, NOW THAT THEY'VE JOINED THE COMMON MARKET...COUNT THEM.... ARGENTINA, AUSTRIA, BELGIUM, BRAZIL, DENMARK, REPUBLIC OF IRELAND, WEST GERMANY, FRANCE, GREECE, ITALY, JORDAN, LUXEMBOURG, MADAGASCAR, MOROCCO, NETHERLANDS, PERU, POLAND, SO. AFRICA, SWEDEN, SWITZERLAND, AND MANY OF THESE COUNTRIES WILL NOT ALLOW UNITED STATES BEEF TO ENTER THEIR COUNTRY, UNLESS IT HAS BEEN CERTIFIED FREE OF D.E.S. RESIDUES AND OUR GOVERNMENT CANNOT ASSURE THEM OF ANY SUCH THING.....IS LIFE THAT CHEAP IN THE UNITED STATES, COMPARED TO PROFITS OF INDIVIDUAL COMPANIES.... IR IS PATHETIC THAT THE IDENTICAL MEAT CONSUMED BY OUR PEOPLE IS UNSAFE FOR THE PEOPLE OF MANY FOREIGN COUNTRIES!!! HOW CAN WE CONTINUE TO BALANCE HUMAN LIFE AGAINST PROFIT....THE PRICE OF MEAT DOES NOT HAVE TO INCREASE, EVEN 3¢ PER POUND. USE THE SUBSIDY MONEY THAT IS SPEND TO NOT GROW GRAIN, AND THEREBY BRING THE GRAIN PRICES DOWN.... BEING THE RICHEST COUNTRY IN THE WORLD, WHY SHOULD WE BE ~~TAME~~ THE SICKLIEST...CANCER WILL NEVER BE ERADICATED, AS LONG AS WE CONTINUE TO INGEST CARCINOGENS...BAN D.E.S.

Consumer Advocate Ida Honorof.... Respectfully submitted Ida Honorof

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WEL
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : J. Richard Crout, MD,
Deputy Director, Bureau of Drugs, BD 2

DATE: January the 10th, 19

FROM : M. Adrian Gross, DVM
OPRT, Bureau of Drugs, BD 403

SUBJECT: Carcinogenicity of Diethylstilbestrol (DES)

I wish to express my sincere appreciation to you for having sent me a copy of your memorandum to Dr. Simmons of December the 21st last and for an invitation to discuss this subject with you later this week. I am preparing these notes in advance of that meeting so that I may be able to leave them with you (together with an additional copy which you may want to forward to Dr. Simmons) and I would thus hope that during our discussion we need focus only on some of the highlights of the issues relevant here.

It is perhaps worthy of note that this entire matter of residues of a food additive is not a primary concern of the Bureau of Drugs; yet, curiously, so far I have been involved in only one discussion on this subject outside of our immediate Office (OPRT) - the one called by Dr. Simmons on December the 6th, last in which you also participated - and now you have called a second meeting. It would appear, therefore, that our Bureau is the only organization in FDA willing to consider both sides of an argument; indeed it stands to its credit that its two top executives are expending time, thought and energy on a matter which, although not falling within the range of their immediate responsibilities, nevertheless is one where they feel they can help other Bureaus and the Commissioner reach a sound decision based on strictly scientific considerations. While you and I may not necessarily agree on all technical aspects of this problem at this time, at least there is some hope that we may do so in the future and the minimum I could say about you and Dr. Simmons is that you have both been eminently fair with me in the context of the DES issue.

Since our last meeting on this subject on December the 6th, I have received copies of certain other communications on DES and I shall have reference to them here; accordingly, I enclose copies of the following:-

a) a memorandum from Dr. Leo Friedman, Director of the Division of Toxicology, Bureau of Foods, to Dr. Virgil O. Wodicka, his Bureau Director, dated December the 17th, 1971;

b) a memorandum from Dr. Wodicka to the Commissioner dated December the 22nd, 1971;

c) a memorandum from Miss Anne Alderman, statistician in the Division of Mathematics, Bureau of Foods, addressed to Dr. R.L. Gillespie of the Division of Toxicology, Bureau of Foods, dated December the 21st, 1971.

Additionally, I would like to alert you on some future communications on DES which are currently being prepared; should I receive any copies of these, I shall forward them to you immediately:-

a) a memorandum on the toxicologic and regulatory aspects of DES as a food additive being prepared now for Dr. Friedman's signature by two of the reviewers in his own division who had primary responsibilities in this area for some years - Drs. Gillespie and Kowalk;

b) a memorandum being prepared by Dr. Simpson, the Bureau of Foods specialist in radiological matters where he reviews the studies concerned with the decay of DES in tissues ; these studies seem to constitute the cornerstone for our current regulatory program for this food additive;

c) a memorandum from the National Cancer Institute addressed to the Fountain Committee commenting on my own memorandum of December the 5th; I was informed today by the NCI that they have received this request from Mr. Goldhammer of the Committee's staff.

A. Comments on the Friedman memorandum of 12/17/71

Although this is being characterized by Dr. Wodicka as representing a reaction to my initial memorandum on DES of 12/5/71, it is interesting to note that DES is not mentioned even once either in the title (subject matter) or in the contents of this two-page memorandum. As such, a superficial judgment may indicate that it need not concern us here; on further thought, however, it becomes quite obvious that this is a truly pernicious document - one that is prejudicial to a sound handling not only of DES but also of all food additives in general since it deals with the very philosophy and policy of safety evaluation of all such products. In this context, it does merit some discussion.

To begin with, the memorandum has reference to an NAS/NRC report (the Food Protection Committee) which has been largely discredited by spokesmen and scientists from our own Department of HEW - see Recommendation No. 3 on page 1, paragraph 6 on page 7, Appendix II on page 10, etc. of the Report on Hearings before the Subcommittee on Agricultural Research and General Legislation of the Committee on Agriculture and Forestry, U.S. Senate, 92nd Congress, of March 1971; you may recall that this latter report was distributed by us to all participants at last month's joint FDA-NCI workshop on carcinogenesis. Furthermor Dr. Friedman's selection of "a definition of "hazard" as "... the probability that injury will result from the use of a substance in a proposed quantity and manner" can lead to a completely meaningless statement:- since probability invariably ranges from 0 to 1 (inclusive) it would follow, therefore, that by this definition, a completely innocuous agent with a probability at or near 0 to elicit injury could be viewed as being "hazardous".

We may turn next to the five items which Dr. Friedman apparently accepts as being "axiomatic", although I would doubt very much if this is the case for the "biologic scientist" in general, as he asserts.

Item (1). While one may readily agree that "there is always a threshold level", it is just as clear that there is not (nor can there ever be) any evidence that any true threshold level is not either zero or, at most, some finite, very small

positive quantity, i.e. one very close to zero. What Dr. Friedman seems to confuse is the true (parametric) threshold level - which, by definition, is unknown, will forever remain unknown, and is only estimable from experimental data - with the apparent threshold level suggested by such data. The two are never the same:- the first is a constant, the second a random variable; furthermore, in any experimental situation with a finite number of subjects, the apparent threshold level invariably exceeds the parametric one. To imply, as Dr. Friedman appears to do, that the parametric threshold level (which, presumably he considers as the "safe" level) can be estimated from the experimental threshold level by the use of a predetermined and seldom changing "safety factor" (meaning here the traditional 1/100 or 1/1,000) is to endorse a policy which has been conclusively demonstrated time and again to be scientifically bankrupt; this kind of policy makes no provision for using such pertinent information on the experiment as whether it was carried out with 1 subject, with 10, 1,000 or 10,000 subjects since it treats results from experiments as dissimilar as these in an identical manner; additionally, this kind of policy does not provide for using information on the slope of the dose-response relation (whether shallow or steep) and it certainly has no reference to the shape of such relation (whether linear, curvilinear, etc.) In brief, under the practice advocated by Dr. Friedman, most of the essential toxicologic information accrued during the experiment is being totally ignored when the estimation of the safe level is being made by his method. Furthermore, this characterization of a "safe" level (implying, of course, "absolutely safe" since there is neither a modifying clause nor any reference to any risks being incurred during the estimation procedure) is the real danger of this policy and outlook. All of this has been in the literature for at least ten years now. Dr. Friedman can hardly claim this comes to him as a surprise at this time since an advisory committee to FDA , of which he himself was an articulate member just before assuming his present position in FDA, has exhaustively and conclusively exposed the fallacy in this peculiar line of thinking some years ago. Since that time, at the urging of Dr. Friedman, among others, FDA scientists including such eminent toxicologists as O. Garth Fitzhugh have followed up on the work of this committee and extended these concepts to areas of toxicology quite apart from carcinogenesis. These efforts have been presented before toxicological meetings and published in the scientific literature (all with the blessings and encouragement of Dr. Friedman) thereby permanently laying to rest the overworked "safety factors" or "margins of safety" as they are alternatively referred to. Now, however, Dr. Friedman sees fit to have them resuscitated for yet another gasp of air. At least in attempting to do so, he can hardly be accused of manifesting undue consistency in his approach at safety evaluation.

Item (2). The relevancy of the number of molecules in the context of this discussion escapes me as does that of the example of botulinum toxin which I have difficulty in considering as a typical food additive.

Item (3). Here one may ask:- "so what ?" The problem confronting us in safety evaluation is not the necessity for "unequivocal evidence" to demonstrate the ability of some substance to elicit a (toxic) response; rather the difficulty here is the converse one - failure to elicit a toxic reaction at some concentration of an agent in a finite, relatively small number of experimental subjects cannot be taken as evidence that such concentration is unqualifiedly safe for a large population of such subjects.

Item (4). I agree with the first part of the first sentence (really, a trivial statement) but I must emphatically disagree with the second part. The issue is not whether bladders are examined if one is interested in detecting the presence of bladder tumors, since only an idiot would dispute this kind of proposition. However, to use Dr. Friedman's example here, if one finds no bladder tumors among 10,000 animals properly examined who have been exposed to some concentration of a test agent, this would give us considerably greater assurance on the safety of that concentration or some fraction of it, than would be the case if the same concentration had resulted in no tumors of merely 10 animals similarly exposed and examined. If Dr. Friedman is willing to subscribe to this, then we may both reject his implication that the number of animals used in an experiment is an unimportant consideration. I would furthermore challenge Dr. Friedman to demonstrate just how this particular aspect of number of experimental subjects is effectively handled in his preferred scheme of estimating safe levels of food additives from experimental data - his method of "judgment".

Item (5). I have no quarrel with the first paragraph here, in fact I could reinforce it by stating that lousy statistical techniques are very apt to result in lousy "no effect" levels. The same would be true for a line of thinking that could be aptly described as being "impacted".

The last two paragraphs amount to an attack on the Mantel-Bryan "model"; I find it extremely deplorable that for the sake of mere expediency - an answer to a question on the adequacy of the analytic sensitivity for DES - Dr. Friedman finds it convenient and necessary to throw out the baby with the bath-water. I can assure you, Dr. Crout, and you may easily verify this for yourself, that the Mantel-Bryan approach is not a "model" anymore than it is some kind of rigid formula or some intolerable straight-jacket that would suffocate us as Dr. Friedman would lead us to believe. It is merely a principle, a rational way of looking at experimental data, at all the data, when estimating a safe level. It is in itself not "an" estimate of a safe level but rather a method of estimation which can yield an infinity of different estimates depending on the actual results of any toxicologic trial and on the risks, explicitly stated (rather than swept out of sight under the carpet) that one is willing to incur. The best evidence perhaps of its lack of rigidity is that through its pioneering concept of "virtual safety" it has spawned other similar approaches:- the "exponential" method, the "logit" method, Schneiderman's concept of "acceptable risk dose" or ARD described at length in the hearings referred to here on page 2, the Gross-Fitzhugh-Mantel approach of "tolerable effects" and many others, each indicated for a particular toxicologic situation. Yet what all these have in common is that they are without exception, rational, objective attempts at estimating safe levels. I would not advocate the use of any particular approach over any of the others, but I would make a definite plea that at least here in FDA some such rational kind of thinking be applied to determining safe levels from experimental data, instead of continuing to plod along with a discredited system of "safety factors" about which no one (not excluding Dr. Friedman) has even the vaguest idea of how safe exactly they are themselves. As Mantel and Bryan point out in their original publication, the impetus for the development of these concepts was provided precisely by the shortcomings of the things Dr. Friedman seems to hold as precious:- "no-effect levels", "safety factors" and other similar eroded skeletons rattling in our closet. These are not just skeletons but actual monsters - by the very fact that one chooses to say nothing about the risks associated with estimates of unqualified "safe" levels, there is a considerable likelihood that such levels are markedly less "safe" than those which are estimated by some procedure that Dr. Friedman has chosen to attack here; they can be viewed therefore as actually "hazardous".

Although Dr. Friedman complains that the Mantel-Bryan principle may be a controversial one in that it is "not consistent with the judgments of experienced toxicologists", the fact is that it has never been successfully challenged by anyone who understands it; I wonder if Dr. Friedman is ready to claim, in all candor, that he really understands it and how it works despite the fact that he has had it explained to him countless times by many excellent statisticians including Mantel himself, Cornfield, Schneiderman, Winbush, Springer and others.

I wish Dr. Friedman would see fit to elaborate for us just once in some detail as to just exactly what he considers an "experienced toxicologist" to be; while he is at it, perhaps he can also shed some light on why it is (as he seems to assert, and which I would not dispute) that the "judgments" of such persons should so often be in conflict with a dispassionate scientific view. For that matter, are all such "judgments" essentially similar ? If so, perhaps we may dispense with the FDA program in the review and evaluation of food additive petitions - since all such petitions are prepared by industry toxicologists (all experienced people, no doubt) and since their judgment is invariably that the material and use level for which they petition is a safe one (or else they would not submit their petition for our approval) why should we have a different kind of judgment on the same set of known facts ? It may be interesting to note here that it seems to be precisely toxicologists of this particular background who seem to be the most vociferous at the slightest threat they see to have objective reason interfere with their "judgment" and who manage to find their way on such bodies as the NAS/NRC's "Food Protection Committee". I can only hope that some day it may be possible to have some committee concerned with our own protection rather than with that of food and of its additives.

Finally, Dr. Friedman's memorandum, featured, as mentioned, as a reaction to my memorandum on DES of 12/5/71, is perhaps most eloquent on the principal issue on which it chooses to be silent - is (or is not) the sensitivity of the analytic method for DES (2 parts per billion) adequate for the protection of the public against unsafe residues for this highly potent carcinogen ? Dr. Friedman has resorted to an attempt to discredit the Mantel-Bryan principle (fortunately, without much success), but the real irony of this situation is that one hardly needs Mantel-Bryan to arrive at a proper answer here. Would Dr. Friedman care to make a different estimate of a safe level for DES in food and enlighten us as to the properties of such estimate ? Even though one can dispense with the Mantel-Bryan principle to make such estimates, I felt it was necessary to to dispute most of Dr. Friedman's "axioms" since these, if allowed to go unchallenged, have a far greater potential for damage to our regulatory program in general than to the issue of DES in particular.

B. Comments on the Wodicka memorandum of 12/22/71

Although he states that he supports Dr. Friedman's comments, Dr. Wodicka deserves credit for at least attempting to come to grips with the data on DES; I am also grateful to him for having had the courtesy of at least sending me a copy of his communication together with the Friedman axioms.

Dr. Wodicka seems to be concerned with the shape of the dose-response function and he concludes in his last paragraph that we are dealing with a typical sigmoid curve, concave upwards initially and downwards terminally. As will be seen subsequently here there are reasons for this kind of consideration not being of any crucial significance, but a few comments of a different aspect are in order here. While I would not argue with Dr. Wodicka's conclusions on

curvilinearity, I would draw your attention to an enclosed copy of a memorandum prepared by Miss Alderman, one of the statisticians in Dr. Wodicka's own Bureau, who concludes that the relationship is consistent with linearity throughout its domain. It is quite obvious that what we have here is by no means a singular situation - the experimental dose-response function appears to be not inconsistent with either linearity or curvilinearity. Whenever this is the case, even a two-bit statistician will tell you that he prefers to handle the data as if they were linear rather than curvilinear and there is good reason for this - a curvilinear function may have up to many different constants to be estimated to describe it with any reasonable kind of precision while the linear function needs just two of these:- the slope (which is constant) and the intercept.

The reason that this issue is of secondary (if any) importance is similar to that given here at the top of page 3 - Dr. Wodicka is having reference to merely the experimental (apparent) dose-response function while the real target of our concern is the true (parametric) dose-response function. With respect to the latter, I can guarantee for Dr. Wodicka that if he only took the trouble to check the original publication by Mantel and Bryan to which I referred on 12/5/71 as well as our own FDA paper on food additives published in Biometrics (Vol. 26, pp 181-194, 1970) he could easily satisfy himself that what is being invariably postulated for the parametric relationship is precisely the kind of sigmoid curve that he seems to advocate. It would follow, therefore, that even if Miss Alderman's conclusion is ignored, Dr. Wodicka can have his way and draw his smooth curve to the points in his graph and this still would not change things in the slightest, in fact it would only reinforce them. In other words, it matters little whether the experimentally observed values mimic neither a straight line or a curve or both of these, since the true dose-response function is invariably assumed to be concave upwards in the vicinity of the zero dose. In fact, if it were not for this very reason, it would not have been necessary to have the Mantel-Bryan principle developed in the first place.

Although Dr. Wodicka appears upset overthe fact that we have used (as per Mantel-Bryan) a straight line for extrapolation, I shall not enter into a discussion of this aspect here since in their paper, Mantel and Bryan give more than ample justifications for this necessity. Suffice it to say, however, that the extrapolating slope is not (repeat, not) meant to represent an estimate of the true slope in the vicinity of the zero dose, but merely an upper limit on it. If this sort of thing is not clear to Dr. Wodicka, perhaps he can avail himself of the adequate talents in his Bureau of Foods' statistical force to elucidate this point.

As to Dr. Wodicka's contention that the mode of action of this compound is unknown, I could counter this with a number of questions:- is the mode of action of any carcinogen known to anyone ? for that matter, is the mode of action of any toxic agent completely known ? pending the availability of such detailed knowledge (at the cellular or subcellular level ?) on the action of carcinogens, should we be inhibited from regarding them as potentially and actually harmful ? should we restrain ourselves from regulating such agents in a manner consistent with such potential for harm, simply because we do not understand completely exactly how such agents elicit malignant neoplasms ? what would be Dr. Wodicka's estimate of the proportion of food additives on which we have made estimates of safe levels in the past without having a complete and detailed knowledge of their action ? should such knowledge be a necessary prerequisite before the FDA attempts to regulate any toxic agent ?

C. Comments on your own memorandum of 12/21/71

Under (1) - paragraph 2 - You are quite right that arguments can be advanced that either 12.5 or 25 ppb of DES is the lowest demonstrated concentration which can be associated with an increase in the incidence of malignant tumors in C3H mice; in fact we have both heard precisely this argument last December 6th from no less an expert than Dr. Leo Friedman. There appears to be only one small problem with such arguments - they just do not happen to be very good ones and, as such, they are not likely to generate much appeal among the disinterested scientific community. Miss Alderman, for one, would not subscribe to such a view, as her memorandum clearly indicates. I would therefore support you in your choice of the 6.25 ppb level as the lowest demonstrated carcinogenic level. It would be wise, however, if one were to qualify such a statement:- 6.25 ppb is the lowest level demonstrated not only to be carcinogenic, but "significantly" carcinogenic; moreover, it happens to be the lowest such level simply due to the fact that it was the lowest level tried in the experiment. In other words, when we say that 6.25 ppb is the lowest (significant) carcinogenic level of DES, this should not imply that still lower levels than this were used in the experiment and found not to be carcinogenic. Alternatively, what this says is that there is an excellent likelihood that levels markedly smaller than 6.25 ppb of DES are also carcinogenic if not outright "significantly" carcinogenic.

I trust that you have followed our analysis in the 12/5/71 memorandum and that it is clear to you that the estimate of a virtually safe level of DES in the diet of these mice is in no way dependent on what level anyone decides is a significant carcinogen. In fact the maximum estimate of a virtually safe level was provided by the data neither at 6.25 ppb, nor at 12.5 ppb, nor yet at 25 ppb, but rather at 1,000 ppb; in other words, the issue of significance plays no part whatsoever in the estimation of a safe level in food for any additive. We took some pains to develop this point in greater detail in my memorandum to Dr. Simmons of December the 6th, 1971. This same issue is also found to be of no relevance by the scientific community in the area of carcinogenesis - to paraphrase that consensus as expressed by Dr. Saffiotti of the NCI when he spoke here last month "a carcinogen is a carcinogen at any level" and this presumably includes the one-molecule level. Furthermore, federal law (specifically the so-called Delaney Clause) implies quite emphatically that there are no "safe" (noncarcinogenic levels for any carcinogen. It would appear therefore that there would be no further advantage in talking about which levels of DES are carcinogenic.

I applaud your valiant efforts under (2) to address yourself to the comparative exposure levels of mice and humans, a poorly charted territory at best. I would caution you though that your estimates may not be widely accepted by other scientists, perhaps not even those in FDA; for example, the one-half pound of meat per day, to which you refer - is this some kind of average consumption rate, rather than one near the upper tail of the distribution ? You know, of course, that at least in the food-additive area, it is the long-standing practice (for good reason, you will agree) to think of and use consumption rates near the maximum rather than those near the average. Also, if you think in terms of exposure rates in terms of micrograms/kg body weight, perhaps you may also wish to refer to doses per unit body surface area; Dr. Hall, whom you mention in the last paragraph of page 2, has been active in pushing this sort of concept for some years now. To convert units per weight to units per area, one may conveniently raise one's values to the two-thirds power e.g. 50 at the two-thirds power becomes approximately 13.6. Still, I am happy to see you state that we are not setting tolerances in food for DES, even though I do not understand what you mean when you write about increases in practical sensitivity.

Under (3), I shall obviously not dwell on the correctness of the "mantel-Bryan model" since we have discussed this issue quite extensively here. I would emphasize again only the fact that whatever one may think of it, one thing it is certain not to be is a "model". As to David Rall, a man whom I have known, admired and respected for many years both for his work and for the type of person that he is, I am quite convinced that he will be the first to disclaim that he might be in a position to evaluate the Mantel-Bryan approach; it is simply not his "bag". Also I would like to assure you that one thing the large-scale experiments at the National Centre for Toxicological Research will most definitely not do is shed light on the problem to which you refer - whether there is or there is not a threshold level for any agent. There are many other things these large-scale experiments will also not do (even though they are expected to) but they absolutely cannot under any circumstance accomplish what you seem to hope for. We may discuss this further, if you wish, at our forthcoming meeting.

The rest of this item (3) is somewhat murky to me - I cannot see at all, for instan how a change in the extrapolating slope is in any way related with the analytic sensitivity. I also am completely unclear as to what you mean when you talk of data which should indicate what extrapolating slope one should use. The whole point of extrapolation is precisely in the area where there are no data. Even if at some future time data are obtained in additional experiments at concentration closer to zero, this will not obviate the need for extrapolation nor tell us in any way that such extrapolating slopes should be different from the ones we are presently using. I believe, however, that this aspect can also be clarified during our forthcoming meeting.

M. Adrian Gross, DVM

UNITED STATES GOVERNMENT DEPARTMENT OF HEALTH, EDUCATION, AND W...
FOOD AND DRUG ADMINISTRATION

Memorandum

TO : Dr. Virgil O. Wodicka, Director
Bureau of Foods (BF-1)

DATE: December 17, 19...

FROM : Leo Friedman, Ph.D., Director
Division of Toxicology (BF-150) Leo Friedman 12/17/71

SUBJECT: Mathematical Models in Safety Evaluation

The evaluation of safety of a substance is based on studies designed to uncover the potential the substance may have to cause injury, and the development of sufficient data to warrant a conclusion that under conditions of proposed use the intake is so low in relation to the toxic dose that there is a practical certainty no harm will result. According to the NAS/NRC Report on Evaluating the Safety of Food Chemicals, safety is defined as " . . . the practical certainty that injury will not result from the substance when used in the quantity and in the manner proposed for its use." Furthermore, they define hazard as " . . . the probability that injury will result from the use of a substance in a proposed quantity and manner."

Studies in groups of animals or people have inherent limitations imposed by the limited number of experimental subjects and the fact that they are all not equally susceptible to every type of injury.

The biological scientist concerned with safety evaluation accepts as axiomatic the following premises:

1. For every biologically active substance there usually is a dose response relationship; there is always a threshold level below which the substance does not exert any physiologically significant effect and therefore, for every substance there is a "no effect" level. The design of a safety evaluation study is to determine a level at which there is no demonstrable effect. This level, when divided by a suitable safety factor, is then considered to be a safe level, in that there is a practical certainty that no harm will result from the use of the substance at that level.

2. Furthermore, we may accept as axiomatic that every animal has within itself one or more molecules of every stable substance in the environment. This is as logical an inference as any that can be derived from probability theory considering that 1 gram molecular weight contains $6 \times 10^{23}$ molecules; and that even the most exquisitely toxic substance e.g. botulinum toxin will, at a harmless dose, contain approximately $1 \times 10^{10}$ molecules.

3. It is taken as axiomatic that the ability of a substance to evoke a biological response must be demonstrated by unequivocal evidence. Inference alone is never sufficient to demonstrate such an ability.

4. The ability to detect a biological response depends primarily on the sensitivity of the assay procedure rather than the number of animals examined, e.g. if the bladders of experimental rats are not examined properly at autopsy, and if the tissues are not properly prepared for histological study, bladder tumors will not be seen even with groups of 10,000 animals.

5. The assessment of "no effect" level is dependent upon the adequacy of the methods used to obtain the toxicologic data, and on the statistical techniques applied in evaluating the data.

Mathematical models such as that of Bryan and Mantel, and others, based on similar principles, which have been designed to deal with the problem of effects in very low incidence, and which are at present beyond our ability to measure, are inconsistent with the premise of a threshold level and a no effect level. The estimates of "negligible" or "virtually safe" or "acceptable risk dose", which are developed by applications of such models, are not consistent with the judgments of experienced toxicologists; they are usually at least three or four orders of magnitude smaller and, for practical purposes, approach zero. They cannot be accepted as reasonable estimates of maximum safe levels. The model seems to break down on extrapolation to low levels in a manner similar to the departure of the ideal gas laws which depart from theory at extremes of temperature and pressure.

It has been evident for some time that there is a need to be able to quantify uncertainty of conclusions regarding safety which are based on limited data. We have been interested in and have studied the application of such models to accomplish this purpose. Any procedure which is less "arbitrary" and more rational than the current one of determining a "no effect" level and applying a safety factor, and which takes into account in a systematic manner the uncertainty inherent in experimental data, must be consistent with the accumulated experience of biological scientists. Estimates which are unreasonably small, as compared to the judgments based on generations of accumulated experience, must represent a paradox where "must be" according to the mathematical model simply cannot be according to practical experience. It is not always easy to determine where the fallacy in the logic of the model lies. It took 2000 years and the invention of the Calculus to explain the paradox of Xeno.

cc: Dr. C. C. Edwards
Dr. H. E. Simmons
Dr. C. D. Van Houweling
Dr. A. C. Kolbye, Jr.
Dr. Henry Fischbach
Dr. Herbert Blumenthal

Commissioner of Food and Drugs December 22, 1971

Director, Bureau of Foods, BF-1

Mathematical Models in Safety Evaluation

Attached is a memorandum from Dr. Friedman reacting to Dr. Gross' memo of December 5, 1971, on the carcinogenicity of diethylstilbesterol. I support the comments Dr. Friedman makes.

I would also like to supplement Dr. Friedman's comments. I have asked that the observations of Gass, Coates, and Graham, which furnish the basis for Dr. Gross' comments to be plotted as probit of response versus logarithm of dose, as is widely customary among toxicologists, and referred to by Dr. Gross. A copy of this plot is attached showing only the experimental points, with no lines drawn in to impute any relationships. I believe an examination of this graph will clarify the issues involved in this discussion.

First of all it should be pointed out that there is no theoretical basis for the relationship between dose and response in this study of the effect of diethylstilbesterol on mice. This is to say that the mode of action of the compound is unknown, and in discussion, Dr. Friedman has pointed out our general knowledge of biochemistry and physiology indicates strongly that at least two and possibly three mechanisms are at work here. In such a case, it would not be surprising to find that the relationship plotted would not be a straight line because one or another of the mechanisms would dominate the response in differing concentration ranges. This would cause inflections in the dose response curve. In any event, the mechanism of action is speculative and the relationship between dose and response is really only empirical.

It has long been well-accepted scientific tradition that when a relationship between two variables is empirical, inference regarding the relationship outside the observed range is not justified. In other words, when the reason for the relationship is unknown, there is no way to tell what direction the curve of relationship will take in regions not studied. Accordingly, any extrapolation of the dose-response relationship in a study such as this one, can serve only as a working hypothesis to be tested through further experimentation and not as a basis for drawing conclusions.

Now, finally looking at the actual results of this experiment as plotted, it is noteworthy that a smooth curve may be drawn connecting all the

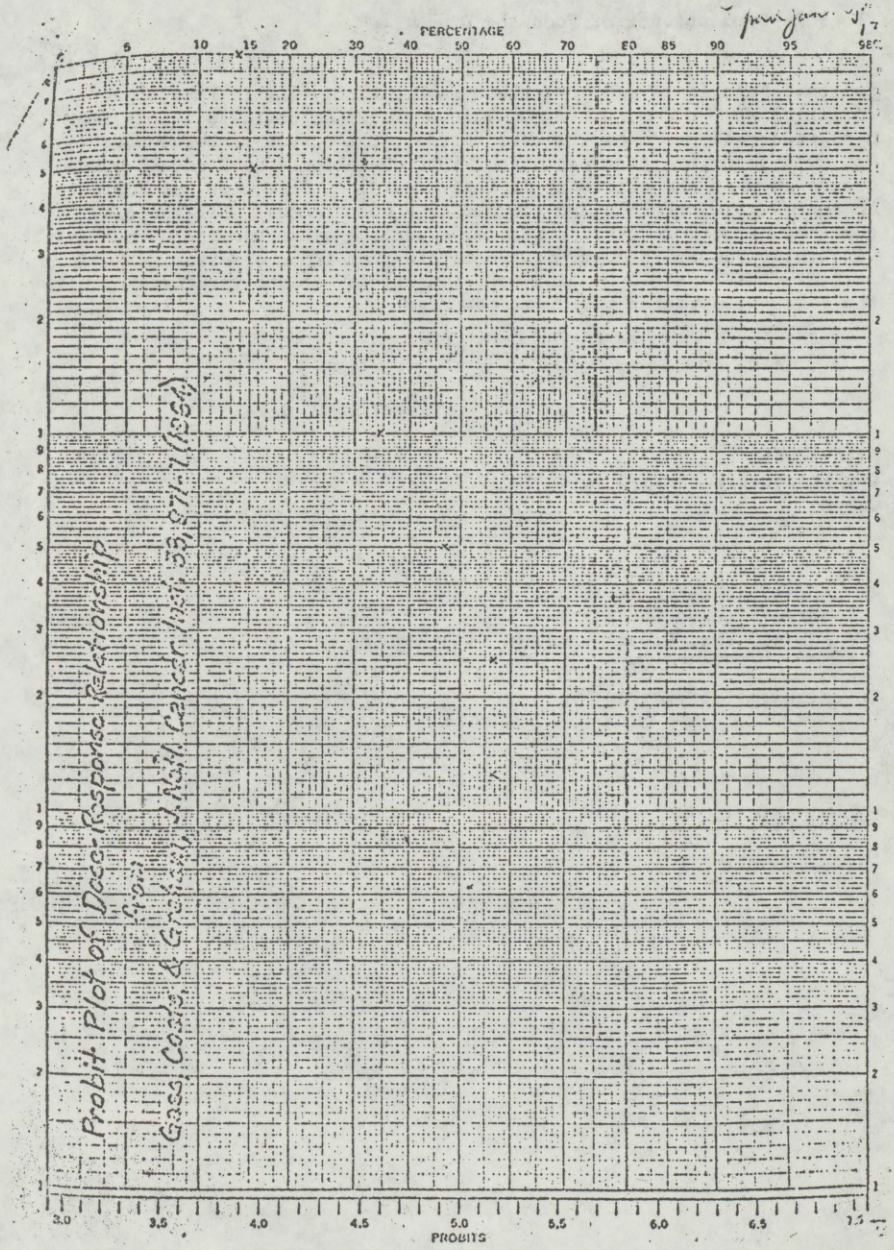
points. This is to say that there is remarkably little scatter or deviation from a smooth curve. This curve is essentially linear over a considerable range of the observations, but curves at both ends. One must therefore conclude either that deviation from a smooth curve occurs only at the extremes, or that a straight line does not represent an appropriate model in the low and high dose ranges. All the discussions of safe levels, therefore, depend on extrapolation of a straight line relationship to lower dosage levels than those observed, when in fact, that same straight line relationship is seriously questionable in the lower dose ranges that were observed.

Virgil O. Wodicka

Attachments
Cpy Friedman/Wodicka memo of 12/17/71
Graph

cc: BF-150 (Dr. Friedman)
BF-110 (Janet Springer)
BD-403 (Dr. Gross) w/cpy of attachments

VOWodicka:mlf 12/22/71


PERCENTAGE
5
10
15
20
30
40
50
60
70
80
85
90
95
PROBITS
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
Probit Plot of Dose-Response Relationship
Gass, Costa, & Greenwald, J. Nat. Cancer Inst. 35, 877-911 (1965)

December 21, 1971

Comments on a Paper by Gass, Coats and Graham on the Carcinogenic Dose Response Curve to DES

Dr. R. L. Gillespie
Division of Toxicology

The initial question concerned the fact that a significant ($P \leq .05$) difference from controls in tumor incidence for the female mice was found for the 6.25 ppb dose, but not for the 12.5 or 25 ppb groups.

The 6.25 ppb group does show a significant ($P \leq .05$) increase over the control. Although the other two groups do not differ significantly from the control at the .05 level of confidence, they also fail to differ significantly from the 6.25 group.

When the three lowest dosage groups (6.25, 12.5 and 25 ppb) are combined, they show a significantly ($P < .025$) higher incidence than the control group, indicating that there is evidence of an effect somewhere in this range. The usual conservative assumption in such cases is that there is an effect at the lowest level which differs from the control.

Although the authors only reported a linear log-dose response curve for the higher doses, this curve is linear for the whole range of doses used. That is, there is a significant ($P < .0005$) positive slope and no significant departure from linearity, whether probit analysis or simple regression of the proportions on the log dose are used. The respective slopes are 0.62 probits per log dose (with the treatment percentages uncorrected for the control effect) and 21.8 percentage points per log dose. The probit slope when percentages are corrected for the control effect was 1.04 probits per log dose. This is evidence that the dip observed in the curve at 12.5 and 25 ppb is simply due to random fluctuations.

Anne Alderman

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Date: February 11, 1972
Reply to Attn of: A. J. Kowalk, D.V.M. and R. L. Gillespie, D.V.M.

Subject: Diethylstilbestrol draft memo dated January 20, 1972, your memo dated Feb. 8, 1972.

To: Leo Friedman, Ph.D.
Director, Division of Toxicology BF-150

After further consideration of the draft memo we prepared for your signature on the above subject, we feel that the recommendations should be amplified to reflect adequately the full impact of the information contained in the body of the memo when we consider the following:

1. The extreme potency of the drug as a carcinogen and its very high hormonal activity compared with the activity of the few parts per trillion of physiologic estrogens normally found in fattening cattle.

2. The sensitivity of the available regulatory analytical method, 2000 parts per trillion, is such that only those producers who withdraw medicated feed less than 48 hours can be detected.

In addition to the recommendations in our January [illegible], 1972 draft, we wish the Commissioner to consider seriously the alternative of withdrawing DES from use in medicated feed until such time that an analytical method sensitive to 1 part per trillion is developed.

cc:
BF-1
BF-2
BF-100
BF-150
BF-151
BF-152

BF-152:RLGillespie/AJKowalk:bb 2/11/72

2/14/72 - Discussed with RLG + AJK to the effect that their recommendation as it stands is not sufficiently supported to warrant a change from present policy (that the presently available methods for enforcing the 7-day withdrawal period are adequate). If they can present a documented case to the effect that the 7-day withdrawal cannot be enforced by the "self-certification" approach [illegible]

MEMORANDUM OF MEETING
February 14, 1972

Between: Leo Friedman, Ph.D., Director, Division of Toxicology
and
A. J. Kowalk and R. L. Gillespie, D.V.M.

Subject: Diethylstilbestrol memo 2/11/72 by Drs. Kowalk and Gillespie

Discussed with Drs. Gillespie and Kowalk to the effect that their recommendation as it stands is not sufficiently supported to warrant a change from present policy (that the presently available methods for enforcing the 7-day withdrawal period are adequate). If they can present a documented case to the effect that the 7-day withdrawal cannot be enforced by the "self-certification" approach, together with present DES methodology, I would endorse it and send it forward.

Leo Friedman, Ph.D.
Director
Division of Toxicology
Office of Sciences
Bureau of Foods

cc: BF-1
BF-2
BF-100
BF-151
BF-152

LFriedman:amb--2/14/72

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : The Commissioner
Through: The Deputy Commissioner

DATE: December 21, 1971

FROM : Director
Bureau of Veterinary Medicine

SUBJECT: Comments in reference to the memo of December 5, 1971, from Dr. Adrian Gross to Drs. Leo Friedman and Daniel Banes.
INFORMATION MEMORANDUM

PURPOSE:

Attached you will find our comments concerning the above-described memo as well as a copy of the original memo. These comments were developed for me by Drs. Lehmann, Price and Condon.

C. D. Van Houweling, D.V.M.

Enclosures
Tab A - Comments in reference to subject memo
Tab B - Memo re Carcinogenicity of Diethylstilbestrol; Estimation of safe levels in diet.

Prepared by: VM-100, LEHMANN, 12/21/71, X34313

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. C. D. Van Houweling, VM-1

DATE: December 21, 1971

FROM : VM-100

SUBJECT: Comments in reference to the memo of December 5, 1971, from Dr. Adrian Gross to Drs. Leo Friedman and Daniel Barnes -- "Carcinogenicity of Diethylstilbestrol; Estimation of safe levels in diet"

The implications of Dr. Gross' analysis is that the FDA in effect is placing tolerances on a carcinogenic substance. Such is clearly not the case. Dr. Edwards has stated that he clearly recognizes that a zero-tolerance applies, and that the violative incidence of 0.5% is unacceptable. Therefore, the 7 day withdrawal period and mandatory withdrawal certification have been implemented to correct this apparent lack of compliance.

It should be pointed out that the only known biological activity of DES is its estrogenic effect. One should approach the problem of a synthetic hormone substance being a potential carcinogen, when given in excess of normal body level of the endogenous hormone either in test animals or humans, by understanding clearly that all mammals including humans produce estrogens naturally as a necessity of life. Studies have been conducted to show that DES is no different than other estrogenic substances with respect to the induction or exacerbation of cancer in sensitive strains of experimental animals.

Dr. Gross makes several statements in his conclusions which should be analyzed and commented on separately. Following the specific statements of Dr. Gross' memo are our comments.

1. "It appears from the work of Gass et al. reviewed here, that the ability of DES to elicit malignant tumors in female $C_3H$ mice is so marked that an estimated safe level of this agent in the feed of these animals is a minuscule fraction of 1 part per billion."

Dr. Gross has analyzed the Gass et al. data according to the model described by Mantel and Bryan in the J. Nat. Cancer Institute 27:455, 1961. He reaches the conclusion that, in order to measure a "virtually safe" level of DES in the diet of mice (i.e., a level which has a statistical probability of producing cancer in one out of 100,000,000 animals) we need an assay procedure for the mouse diet 20,000 times more sensitive than we now have. This assumes (a) that the Mantel-Bryan model is correct and (b) that the slope of the dose-response curve in the extrapolated low-range of dosage is 1 probit/log dose. The "virtually safe" level for any substance as determined by the Mantel-Bryan model is a function of the assumptions used in calculating

and extrapolating the "safe" level from laboratory animals to humans. The estimated "virtually safe" level is a negatively biased estimate of the true "safe" level (i.e., the "virtually safe" level as calculated by the procedure of Mantel and Bryan will, in the vast majority of determinations, be less than the true "safe" level).

The estimated "virtually safe" level is also an inconsistent estimator of the true "safe" level for two reasons: a) As the size of the sample used to determine the "virtually safe" level increases, the estimated "virtually safe" level does not tend to go to a specific value. In fact, Mantel and Bryan state that, "the use of extremely large studies to establish safety may well be selfdefeating. The almost certain occurrence of unusual syndromes in one or more of a large number of test animals, albeit these may have arisen spontaneously, will require admitting the possibility that they may be attributable to drug treatment." b) Small changes in the assumptions used result in large changes in the estimated "virtually safe" level.

The following calculations help to illustrate these points. If the actual values for the incidence of tumors in $C_3H$ female mice as reported by Gass et al. are used to calculate a "virtually safe" level of DES for $C_3H$ female mice (i.e., 33.0% for control and 86.2% for 1000 ppb DES), the virtually safe level would be 0.0007 ppb rather than 0.0001 ppb determined when the lower 95% confidence interval is used for the control and the upper 95% confidence interval is used for the 1000 ppb DES group. It can be argued that the actual values obtained in the experiment are the best available estimates and are the ones that should be used. Also, when several dose levels are involved, Mantel and Bryan indicate that the dose level which results in the largest calculated "safe" level should be used. Therefore, calculated "safe" values for any appropriate level would be equal to or smaller than the calculated safe value based on all the levels. This one change in the assumptions used changes the "virtually safe" level by a factor of 7. (These calculations and the following ones were made using a conservative slope of 1 probit/log dose).

The specific set of mice used in the Gass study makes a considerable difference in the "virtually safe" level determined. Using these data for the 1000 ppb level of DES in the diet the following "virtually safe" levels were determined:

| Type of mouse | "Virtually safe" level using 1000 ppb DES |
|---|---|
| $C_3H$ female | 0.0007 ppb |
| $C_3H$ male | 0.0040 ppb |
| Bittner Strain A castrate male | 0.0170 ppb |

Similarly variable estimates could be made using the different levels of DES. In this case, the type of mouse used makes an approximately 25 fold difference in the estimated "virtually safe" level.

In regard to the slope of the dose-response curve, Dr. Gross points out that the analytical sensitivity predicted by the model as necessary to insure a "virtually safe" level of DES in the diet is heavily dependent upon the slope one assumes in making the calculations. For example, if one assumes a slope of 1.5 probits/log dose (which is close to that obtained for the castrate strain A mice) instead of 1 probit/log dose, the analytical sensitivity needed for the diet fed to mice is only 100 times greater than we now have. The change in the slope from 1 to 1.5 probits/log dose changes the required sensitivity of the assay by a factor of 200 for the $C_3H$ female mice.

Because of the tremendous effect that these changes in assumptions have on the determined "virtually safe" level, one can specify almost anything by this method.

For example, using the upper 95% 2-tailed confidence limit on the tumor incidence for the $C_3H$ male mice, 54.0%, and a slope of 1.5 probits/log dose, the "virtually safe" level for the $C_3H$ male mouse is 0.16 ppb. This would extrapolate to "virtually safe" level in tissue of 8.4 ppb for humans. Similarly, $C_3H$ female data would indicate a "virtually safe" level of no less than 1.2 ppb and Bittner strain A data a level of 24.4 ppb for humans. Therefore, results from mathematical models like this one need to be interpreted with prudence.

2. "Even when the procedure for estimation uses assumptions whose safety can be questioned, the resulting estimates remain considerably below the official analytic sensitivity of 2 parts per billion."

The procedures for estimation which Gross says can be questioned are based on those discussed in the preceding paragraphs.

3. "It would follow that an analytic method such as this does not constitute sufficient protection that carcinogenic levels of DES may not be present in the material analyzed when in fact the result of such an analysis is that no DES whatsoever can be detected in such material."

Even though one grants that amounts less than 2 ppb in certain mice might be carcinogenic based on the Mantel-Bryan model, this cannot be translated into a human hazard. In his analysis, Dr. Gross documents the need for a more sensitive bioassay procedure for DES, and we would certainly concur in this judgment. However, it should be pointed out that the present method for DES is far more sensitive in estimating human exposure to DES than Dr. Gross' memo might suggest. It can be shown that a true concentration of 2 ppb in beef liver would expose an adult to a maximum DES intake of 0.5 µg/day if one-half pound of such liver were ingested. This would amount to a daily intake of 0.0071 µg/kg/day for a 70 kg man. By contrast, the sensitivity is much less when the assay is applied to the diet of the mouse, primarily because the mouse eats an extraordinary amount of food -- equal to about 20% of his body weight each day. A 15g mouse eating a diet containing 2 ppb DES therefore takes in about 0.006 µg of DES per day, which is a dose of 0.4 µg/kg/day. This dose is 56 times that taken in by the hypothetical man described above who eats liver on a daily basis even though in all cases the assay was sensitive to 2 ppb in the diet or tissue tested. Furthermore, the only human dose that has been considered to have a close association with human cancer was 5 mg per day decreasing to 5 mg per week for 35 weeks (Herbst et al).

4. "In this connection one may add that the USDA does not use the official biologic method for analysis set forth in the Code of Federal Regulations. The chemical method used by USDA is one which, to our knowledge, has never been evaluated as to sensitivity by a collaborative study and Dr. Banes informs us that it is his impression the chemical method may in fact have a sensitivity still lower than the biologic method, i.e., it is comparatively poorer than the biologic method and we have seen here that the latter is not nearly good enough."

The present GLC method is demonstrating a sensitivity of from 1-2 ppb and is performing satisfactorily for USDA in their regional labs as a regulatory tool. Apparently Dr. Gross is not aware of the present stage of development of the GLC method.

5. "It should be mentioned here that work is currently in progress in the Office of Pharmaceutical Research and Testing to increase the sensitivity of the biologic method by utilizing histopathologic procedures in the examination of test animals. The results should be available within a few

weight occurred before any histological changes appeared. It cannot be ruled out that changes may be detected using more sophisticated histopathological techniques. Certainly these techniques would render an already impractical method more impractical.

At this stage it seems appropriate to illustrate the above points by applying the model to situations for which we have adequate knowledge concerning the toxicity of the compound, its occurrence in natural feed stuffs and the nutritional requirements.

Example 1. Zinc in Beef Cattle.

It has been shown that 900 ppm zinc in the diet of cattle causes toxicity. Let us assume that 20% of the animals are adversely affected by this level of dietary zinc. Keep in mind that the nutritive requirement for zinc is 10 to 30 ppm and that normal feedstuffs contain 30 to 50 ppm of zinc.

Safe Levels - as determined by the model of Mantel and Bryan

Zinc* 900 ppm causes 20% toxicity in cattle

| Risk Factor | Probits/Log Dose 1 | 1.5 |
|---|---|---|
| 1/100,000,000 | 0.02** | 0.59 |
| 1/1,000,000 | 0.11 | 2.21 |
| 1/100,000 | 0.34 | 4.69 |
| 1/10,000 | 1.19 | 10.82 |
| 1/1,000 | 5.06 | 28.46 |

*Normal dietary level - 30-50 ppm
** ppm

Reference: L. A. Maynard and J. K. Loosli. Animal Nutrition. 6th ed. 1969. McGraw Hill, New York.

Example 2. Selenium in Beef Cattle.

It has been shown that 4 ppm of selenium in the diet of beef cattle cause toxicity. Assume that 10% of the cattle are adversely affected by 4 ppm of selenium in the diet. Keep in mind that the nutrient requirement for selenium is 0.05 to 0.10 ppm and that normal feedstuffs contain 0.10 to 1.0 ppm selenium.

Safe Levels - as determined by the model of Mantel and Bryan

**Selenium 4 ppm diet causes 10% toxicity in cattle

| Risk Factor | Probits/Log Dose 1 | 1.5 |
|---|---|---|
| 1/100,000,000 | 0.001* | 0.013 |
| 1/1,000,000 | 0.003 | 0.048 |
| 1/100,000 | 0.010 | 0.102 |
| 1/10,000 | 0.036 | 0.236 |
| 1/1,000 | 0.155 | 0.621 |

**Normal dietary level - 0.10-1.0 ppm diet.
*ppm

Reference: L. A. Maynard and J. K. Loosli. Animal Nutrition, 6th ed., 1969 McGraw-Hill, New York.

These tables illustrate that one would need to use very liberal and probably socially unacceptable assumptions to meet the requirements as being "safe" and still satisfy the known nutritive requirements of these essential elements.

CONCLUSIONS:

1. FDA is not in a position to set a tolerance on a carcinogen.

2. DES is apparently no different than other estrogenic substances, synthetic or natural, with respect to the induction of cancer in sensitive strains of experimental animals.

3. Dr. Gross states conclusions relative to the carcinogenic dose in mice based on an emperical, ultraconservative model which in turn is based on numerous assumptions. Since changes in the assumptions greatly affect the estimation of the "virtually safe" level of DES for the mouse, the analysis of the Gass, et al. data according to the Mantel-Bryan model, although interesting, does not unequivocally document the need for a more sensitive assay procedure. A stronger stimulus for improving the assay is the simple progmatic desire to have a rapid, sensitive method for monitoring the seven day withdrawal procedure.

4. Dr. Gross jumps from relationships in mice to relationships in humans without taking into account the difference in dose per unit of weight, exposure and the difference in reported carcinogenic dose for mice and man.

5. Dr. Gross comments on the tests in use, their sensitivity, and improvement without a full knowledge of this subject area as outlined above.

6. When utilizing the Mantel-Bryan model to analyze classical data on zinc and selenium, it is apparent that the calculated "virtually safe" levels are well below what is contained in normal feedstuffs and the animal's requirement. The same findings would result if the model were applied to similar compounds when considered for humans.

Richard P. Lehmann

Richard P. Lehmann, Ph.D.
Director,
Division of Nutritional Sciences

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

Food and Drug Administration,

Washington, DC, 20204

MEMORANDUM December 5, 1971

Banes 12-6-71

To :- Dr. Leo Friedman, Director, Division of Toxicology, Bureau of Foods, BF 150 and Dr. Daniel Banes, Director, Office of Pharmac. Research & Testi Bureau of Drugs, BD 400

From :- BF 152 and BD 403

Subject:- Carcinogenicity of Diethylstilbestrol; Estimation of safe levels in diet.

A letter was published recently in the Washington Post by a writer about whom it is said that he is part of a group presently suing the Food and Drug Administration and the United States Department of Agriculture on the continuing use of diethylstilbestrol (DES). The letter carried the information that a level as low as 6.25 parts per billion of DES is carcinogenic.

We believe we have come across the scientific source of this information:- an article by George H. Gass, Don Coats and Nora Graham from Southern Illinois University entitled " Carcinogenic Dose-Response Curve to Oral Diethylstilbestrol" which was published in the Journal of the National Cancer Institute, Vol. 33, No. 6, pp. 971-977 of December, 1964.

The purpose of this memorandum is to comment on that article and, based on the data presented there, to estimate what are safe levels of DES in the diet.

The article presents evidence that 6.25 ppb of DES is a significant carcinogenic concentration for female $C_3H$ mice:- the difference between 33.0% control animals with mammary adenocarcinoma and 48.2% of the mice at 6.25 ppb with this kind of malignant tumor is indeed statistically significant. There were also other findings:- the estimated dose-response slope was definitely linear between 25 and 500 ppb, the average latent period of these tumors generally decreased rather markedly with increasing dose and there was a significant increase of mammary carcinoma amongst the males of the same strain as well as amongst castrated males of Strain A mice. These increases were also associated with a reduction in the aver latent period of these tumors. In addition to these, there was a progressive reduction in weight of ovaries from mice at levels 25 ppb and above.

It would appear, therefore, that this work confirms the earlier established fact that DES is indeed a carcinogen. In this sense, the information presented there is not new; however, in light of the fact that cancer was elicited in a significantly increased incidence by levels of DES as low as 6.25 ppb, the question could be asked:- what are estimated levels of DES for which the increase in mammary carcinoma incidence among mice is no more than minimal? This question has relevancy if one considers that the official analytical method for this agent has a sensitivity limit as high as 2 ppb.

In order to answer the question posed above we turned to a paper published by Nathan Mantel and W. Ray Bryan:- "Safety Testing of Carcinogenic Agents" also published in the Journal of the National Cancer Institute, Vol. 27, No. 2, pp. 455-470 in August 1961.

In that paper the authors make the following main points:-

a) if the test has employed an animal other than man (i.e. the mouse) then it behooves us to ask what is a "safe" level of the agent tested for the mouse and only then extrapolate the results to man on the basis of known relative susceptibility of the two species.

b) since no estimate whatsoever can be made such that one is absolutely certain that this will not increase at all the tumor incidence in the entire population of animals to which we have reference, we are necessarily forced to consider the concept of "virtual safety". Under this concept one chooses a high level of assurance just short of 100% that the tumor incidence will be increased by a factor less than a given low proportion. Such a proportion suggested by the authors is 1/100,000,000 though, of course, one is free to select other such upper limits on the risk such as 1/1,000,000, 1/10,000, etc. Similarly, the confidence level used by the authors (99%) could be reduced to some other high level, say 97.5% or 95%.

c) from an examination of a variety of carcinogenic stimuli, the authors suggest that an extrapolating slope of 1 probit/log dose could be viewed as being conservative. We tend to agree with this conclusion, but again, if one chooses to be somewhat less conservative, one could extrapolate with other slopes:- 1.5 probits/ log dose or even 2 probits/log dose, although we would not view the last of these as being sufficiently safe.

We have applied the Mantel-Bryan principles in estimating safe levels of DES from the data presented by Gass et al. Our estimates are made at a confidence level of only 97.5% (i.e. our estimates are somewhat less conservative than those made by Mantel and Bryan) and we have made estimates for upper limits on the risk not only of 1/100,000,000 but also for risks markedly higher than this, up to 1/100. In addition to the extrapolating slope of 1 probit/ log dose we also give for purposes of information (though not necessarily as a recommendation) estimates based on slopes of 1.5 and 2 probits/ log dose.

We shall describe the estimation procedure in some detail so that it may be understood by all concerned.

From among the three systems tested by Gass et al., the female C3H mice appear to be the most sensitive and we shall limit our concern to the response of only these. Table 1 below would represent the essentials of the data in their paper:

Table 1

| Dose of DES (ppb) | Observed Proportion of mice with tumor | Combined Result | 2-sided 95% Confid. Interv. Lower Limit on Observed proportion | 2-sided 95% Confid. Interv. Higher Limit on Observed proportion |
|---|---|---|---|---|
| 0.00 | 40/121 or 33.0% | | 24.76% | |
| 6.25 | 27/ 56 or 48.2% | 79/176 or 44.9% | | 52.58% |
| 12.50 | 26/ 60 or 43.3% | | | - |
| 25.00 | 26/ 60 or 43.3% | | | - |
| 50.00 | 36/ 68 or 52.9% | | | 65.17% |
| 100.00 | 42/ 64 or 65.6% | | | 77.05% |
| 500.00 | 50/ 59 or 84.7% | | | 92.78% |
| 1,000.00 | 50/ 58 or 86.2% | | | 93.85% |

We note in the table above that the level of 12.5 ppb was associated with a lower incidence of tumors than the one immediately preceding it - 6.25 ppb - and the incidence at 25 ppb was identical with that at 12.5 ppb. In view of this we are justified in combining the response at these three levels for an overall rate of 79/176 positive mice and assign this response to the 6.25 ppb since all the 176 mice involved here have received at least this concentration of DES in their feed. Mantel and Bryan point out in their paper that this sort of combination of the response at several levels where there appears to be an "inversion" of the response is a proper procedure.

The last two columns in Table 1 have reference to the limits on the observed response. For the control level we use the lower limit and for the various treatment levels we use the upper limit. Note that in the selection of these limits we have used the 95% confidence interval rather than the more conservative 99% interval used by Mantel and Bryan which would have resulted in smaller concentrations of DES which can be viewed as being "virtually safe".

At this point we are interested in the increase in the incidence of tumors associated with each treatment level and, in order to obtain this, we make use of the Abbott formula. This formula estimates the increased incidence by reference to the proportion of unaffected control animals, which, again, is the proper procedure. For instance, the first treatment level, 6.25 ppb, can be

associated with a maximum increase in incidence over controls from 24.76% to 52.58% or 27.82%. This difference, however, when referred to the 75.24% of unaffected control mice becomes corrected by the Abbott formula to 36.98% since the increased incidence of the treated animals must be seen in the perspective of animals which, if untreated, would not have developed tumors. These increases in incidence of tumors associated with each treatment level have been detailed below in Table 2 together with the normal deviate which corresponds to each such increase.

Table 2

| Dose of DES (ppb) | Increase in Incidence calculated by Abbott's formula | Corresponding Normal deviate |
|---|---|---|
| 6.25 | 36.975% | - 0.3319 |
| 50.00 | 53.708% | 0.0929 |
| 100.00 | 69.498% | 0.5101 |
| 500.00 | 90.404% | 1.3047 |
| 1,000.00 | 91.826% | 1.3917 |

We are now ready to estimate "virtually safe" levels of DES in the diet of mice for various upper limits on the risk. For instance, an upper limit on the risk set at no more than 1/100,000,000 to develop mammary adenocarcinoma as a result of treatment with this agent corresponds to 5.612 probits. If we add the normal deviate corresponding to the first treatment level - 6.25 ppb - i.e. - 0.3319 to 5.612, we obtain 5.2801 and this is the number of logs we have to move to the left of 6.25 ppb to arrive at a "virtually safe" level if we extrapolate with a slope of 1 probit/log dose. The log of 6.25 is 0.79588 which results in an estimate of -5 plus 0.51578 logs or, taking the antilogarithm of this quantity, we obtain 0.000032793 ppb as the estimated virtually safe level of DES under the assumptions made. It is possible however that the 6.25 ppb concentration used underestimates the safe level and that the response observed at the other concentrations would provide higher estimates which would fulfill the same criteria. Repeating this process, therefore, for all concentrations used in this experiment, we obtain the following estimates given in Table 3:-

5

Table 3

| Dose of DES (ppb) | Estimated "virtually safe" level in diet based on an upper limit of the risk of 1/100,000,000 and an extrapolating slope of 1 probit/log dose | |
|---|---|---|
| | expressed in log (ppb) | expressed in ppb |
| 6.25 | $\bar{3}.51578$ | 0.000032793 |
| 50.00 | $\bar{3}.99407$ | 0.000098644 |
| 100.00 | $\bar{3}.87790$ | 0.000075492 |
| 500.00 | $\bar{3}.78227$ | 0.000060571 |
| 1,000.00 | $\bar{3}.99630$ | 0.000099152 |

We note from table 3 that all of the estimates, one provided by each of the concentrations used in the experiment, are essentially similar, the lowest differing from the highest by a factor of only three. The highest estimate was provided by the highest concentration used, 1,000 ppb, which is interesting even though it is a phenomenon which occurs in a majority of experiments of this sort that we have analyzed. This says that 1,000 ppb, although being associated with the maximum observed increase in the incidence of mammary adenocarcinoma, nevertheless provides the highest estimate of the safe level; the explanation for this lies in the fact that this concentration is so far distant from the control that this aspect more than offsets the high response observed. We shall select this estimate therefore from among the entire set of five such estimates and we may conveniently round it off to 0.0001 ppb or 0.1 part per trilion (ppt).

At this point we may enquire what would be the estimates for other selected upper limits on the risk in addition to the 1/100,000,000 considered above. Table 4 below presents this information which is obtained in a manner similar to the above:-

| Upper limit on risk | Estimated "virtually safe" level by using an extrapolating slope of 1 probit/log dose |
|---|---|
| 1/100,000,000 | 0.0001 ppb |
| 1/ 10,000,000 | 0.0003 ppb |
| 1/ 1,000,000 | 0.0007 ppb |
| 1/ 100,000 | 0.0022 ppb |
| 1/ 10,000 | 0.0078 ppb |
| 1/ 1,000 | 0.0332 ppb |
| 1/ 100 | 0.1929 ppb |

We would conclude, therefore, that even if we reduce the confidence level from 99% to a two-sided level of 95% (equivalent to a one-sided level of 97.5%) and even if we increase the upper limit on the risk 1,000,000 fold (i.e. from 1/100,000,000 to 1/100) our estimate of the safe level of DES is still less than one tenth of the sensitivity of the assay method. In fact it is much smaller than this since a risk such as 1/100 is unacceptably high as far as carcinogenesis is concerned.

As remarked in the introduction, one could be considerably less conservative and extrapolate with a steeper slope than the one advocated by Mantel and Bryan, namely 1 probit/log dose. Thus if one were to extrapolate with a slope of 1.5 probits/log dose, the estimate of a virtually safe level of DES for an upper limit of the risk set at 1/100,000,000 would be 0.02142 ppb; similarly, extrapolation with a slope as steep as 2 probits/log dose (which we would definitely not recommend as being sufficiently safe) and, again, for an upper limit of the risk set at 1/100,000,000 would be 0.3149 ppb. It is interesting to note, however, that even for these markedly less safe assumptions, the estimated safe level of DES remains below the analytic sensitivity of 2 ppb.

## Conclusions

It appears from the work of Glass et al. reviewed here, that the ability of DES to elicit malignant tumors in female $C_3H$ mice is so marked that an estimated safe level of this agent in the feed of these animals is a minuscule fraction of 1 part per billion. Even when the procedure for estimation uses assumptions whose safety can be questioned, the resulting estimates remain considerably below the official analytic sensitivity of 2 parts per billion. It would follow that an analytic method such as this does not constitute sufficient protection that carcinogenic levels of DES may not be present in the material analyzed when in fact the result of such an analysis is that no DES whatsoever can be

detected in such material. In this connection one may add that the USDA does not use the official biologic method for analysis set forth in the Code of Federal Regulations. The chemical method used by USDA is one which, to our knowledge, has never been evaluated as to sensitivity by a collaborative study and Dr. Banes informs us that it is his impression the chemical method may in fact have a sensitivity still lower than the biologic method, i.e. it is comparatively poorer than the biologic method and we have seen here that the latter is not nearly good enough.

It should be mentioned here that work is currently in progress in the Office of Pharmaceutical Research and Testing to increase the sensitivity of the biologic method by utilizing histopathologic procedures in the examination of test animals. The results should be available within a few weeks but we would offer a word of caution here:- it is extremely unlikely, if not well-nigh impossible, that under the best of circumstances and with the best of fortunes, the sensitivity of the analytic procedure would approach anything of what is needed here. It would seem, therefore, that neither the USDA nor the FDA are likely to have a strong case at the forthcoming trial.

M. Adrian Gross
Assistant Director for Scientific Coordination
Office of Pharmaceutical Research and Testing

January 10, 1972

Dr. Marvin A. Schneiderman
Associate Scientific Director
for Demography
National Cancer Institute
National Institutes of Health
Federal Building, Room 516
Bethesda, Maryland 20014

Dear Dr. Schneiderman:

This Subcommittee has held hearings on the use of Diethylstilbestrol in medicated animal feeds. At the last hearing on December 13, a memorandum prepared by Dr. M. Adrian Gross on the subject of "Carcinogenicity of Diethylstilbestrol; Estimation of safe levels in diet" was discussed. Since then, we have received from the Food and Drug Administration appraisals of Dr. Gross' memorandum by other scientists in the Food and Drug Administration.

It would be helpful to the Subcommittee in its evaluation of Dr. Gross' memorandum if it had the benefit of your or your staff's review of Dr. Gross' memorandum, particularly with respect to the validity of his presentation and his conclusions. Enclosed is a copy of his memorandum.

While I do not want to impede or interfere unduly with your regular activities, I would appreciate receiving your comments as soon as possible.

Thank you for your assistance.

Sincerely,

L. H. Fountain
Chairman

Enclosure

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Henry E. Simmons, M.D., M.P.H.
Director
Bureau of Drugs

DATE: December 21, 1971

FROM : Deputy Director
Bureau of Drugs

SUBJECT: Memos on DES from Dr. Gross dated
Dec. 5 & Dec 6, 1971 - INFORMATION MEMORANDUM

1. Dr. Gross has brought to our attention the paper by Gass et al. entitled "Carcinogenic Dose-Response Curve to Oral Diethylstilbestrol," J. Nat. Cancer Inst., 33:917-977, 1964. The paper contains very useful information on the carcinogenic effect of long-term oral administration of DES in the mouse. I have reviewed the paper in detail and agree that the work is well done from the technical standpoint and that the results should be believed. I also agree that we should accept 6.25 ppb as the lowest demonstrated dietary concentration of DES which produces an increase in the incidence of tumor in female C3H mice, according to this study.

Arguments can be advanced that a higher figure - either 12.5 ppb or 25 ppb - is more secure, but it is an accepted principle to err in the direction of being overly cautious on an issue such as this. The authors also interpret their own work as favoring the 6.25 ppb figure.

2. In his analysis Dr. Gross states there is a need for a more sensitive bioassay procedure for DES. I would not disagree with this judgment, but I am not impressed that the arguments in this memo offer strong new documentation of this need. The purpose of the 2 ppb assay is to aid in the detection of serious violation of the waiting period between DES administration and marketing. This assay is not used to generate the original research data on which the regulations are based. These research data are obtained from studies of radioactive - DES, in which the methodology is far more sensitive than the bioassay procedure. It should also be pointed out that the bioassay is more sensitive in estimating possible human exposure to DES than Dr. Gross' memo might suggest. This comes about because of the differing dietary habits of the mouse and man, and because there is (where it can be measured in violative DES-contaminated cattle) a substantial difference (10 fold or greater)

between the concentration of DES in the liver and that in muscle. A mouse eats an extraordinary amount of food - on the order of 20% of his body weight per day - all of which is contaminated with DES in the mouse bioassay procedure. On the other hand, a human adult who eats one-half pound of meat a/day takes in something on the order of 0.4% of his body weight - in the form of meat. Thus the dose (expressed as µg/kg of body weight) received by a human who might eat a contaminated sample of liver is roughly 50 times less than that received by a mouse who eats a total diet similarly contaminated, simply because the human eats roughly 50 times less contaminated food on a body weight basis. In the case of beef muscle rather than liver, this exposure would be again less by an additional factor of 10, or a total factor of 500, if one assumes that the concentration of DES in muscle is 1/10 or less that in liver. This is not to imply in any way that we are setting a tolerance for DES in the human diet with the 2 ppb bioassay or that we can in any way condone the entrance of violative samples of meat into the food supply. My purpose is simply to indicate that there are some factors relating to the sensitivity of the bioassay which have not been considered by Dr. Gross and which increase its practical sensitivity when applied as a compliance procedure in checking meat samples intended for human use.

3. Dr. Gross has analyzed the Gass et al. data according to the model described by Mantel and Bryan in the Journal of the National Cancer Institute, 27:455-470, 1961. He reaches the conclusion that, in order to measure a "virtually safe" level of DES in the diet of mice (i.e., a level which has a statistical probability of producing cancer in one out of 100,000,000 animals) we need an assay procedure for the mouse diet 20,000 times more sensitive than the one we now have. This estimate assumes (a) that the Mantel-Bryan model is correct and (b) that the slope of the dose-response curve in the extrapolated low range of dosage is 1 probit/log dose. In regard to the possible correctness of the Mantel-Bryan model, I have discussed this with Dr. David Rall, who tells us that there is no common agreement among experts in the cancer field that this model is correct. It assumes there is no completely safe dose for a carcinogen, i.e., there is no threshold dose below which a compound has no effect. The large-scale experiments currently being planned by the National Center for Toxicological Research will hopefully shed light on this problem. In the meantime, it should be pointed out that there is no example of any chemical or toxin which is known to fit the model. In regard to the slope of the dose-response curve, Dr. Gross points out that the analytical sensitivity predicted by the model as necessary to insure a "virtually safe" level of DES in the diet is heavily dependent upon the slope one assumes in making the calculation.

For example, if one assumes a slope of 1.5 probit/log dose instead of 1 probit/log dose, the analytical sensitivity needed for the diet fed to mice is only 100 times greater than we now have. Since the analytical procedure we now have is an estimated 50-500 times more sensitive when applied to monitoring the human diet, one might argue that the Mantel-Bryan model supports the view that our current bioassay procedure is sensitive enough to establish that beef contains levels of DES below the "virtually safe" levels as defined by Dr. Gross. I am not at all interested in supporting such an argument on these grounds. This is merely to emphasize that the assumption of a change in slope from 1.0 to 1.5 probits/log dose changes the required sensitivity of the assay by a factor of 200. With such a model and an absence of data bearing on what the slope ought to be, one can show almost anything he wants to.

4. I have talked with Dr. Banes about our DES assay. He believes the procedure for DES might be increased in sensitivity, perhaps as much as 10-fold, by combining it with an extraction procedure and by finding a more sensitive end point than uterine weight. He has offered the services of his laboratory in this regard if the Agency feels research should be devoted to this problem. Such a method would likely be more difficult technically than the current method.

Conclusions:

1. The Gass et al. paper contains important data showing 6.25 ppb in the diet as a demonstrated carcinogenic dose of DES in female $C_3H$ rats fed this concentration of DES over a lifetime.

2. Dr. Gross's analysis reinterprets the data of Gass et al. in light of the Mantel-Bryan model. His conclusion that the present bioassay procedure for DES "does not constitute sufficient protection that carcinogenic levels of DES may not be present in the material analyzed" is, in my opinion, not justified from the analysis offered. His argument presumes that we are willing to permit some tolerance level for DES which is "virtually safe" and that the method must have an analytical sensitivity down to that level. In fact, the data to support the regulations enforcing a zero tolerance are derived from research studies; the 2 ppb assay is for detecting violators, not for setting tolerances.

3. After thinking a good deal recently about the whole problem of analyzing DES in meat, I suspect that the greatest good would be done not by a more sensitive assay but by a more rapid assay which could be applied in the field for on-the-spot compliance purposes. I will discuss the technical feasibility of this with Dr. Banes and Dr. Gross in the near future.

J. Richard Crout, M.D.

HEW NEWS

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Rockville, Maryland 20852

Donald A. Berreth: 301 443-3285
Home Phone: [redacted]

72- 54

FOR IMMEDIATE RELEASE: May 31, 1972

DES

The Food and Drug Administration has instituted criminal action against a Utah cattle feeder who earlier this year marketed beef cattle with alleged residues of diethylstilbestrol (DES).

The FDA complaint was filed against Parnell Green, Green Livestock Company, 577 South Angel, Layton, Utah. It charges that meat from the animals was adulterated because it contained DES, and misbranded because a statement submitted with the cattle claimed that the food contained no DES.

The liver sample was collected by the U.S. Department of Agriculture, on February 1, 1972, from a shipment of 35 beef cattle made by Green Livestock Company. The liver was found to contain 4.2 parts per billion of DES.

DES is widely used in beef cattle and sheep to promote more rapid weight gain in a shorter feeding time. FDA regulations require that it be withdrawn from the feed of the animals seven days prior to slaughter to eliminate any residues from the meat.

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HEW NEWS

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Rockville, Maryland 20852

John T. Walden: 301 443-4177
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Diethylstilbestrol

72- 56

FOR IMMEDIATE RELEASE:
FRIDAY - June 16, 1972

The Food and Drug Administration today released the following statement by Charles C. Edwards, M.D., Commissioner of Food and Drugs, on the subject of diethylstilbestrol:

Diethylstilbestrol (DES) is widely used in beef cattle and sheep to stimulate more rapid weight gain with less feed.

A beef animal, for example, will reach market weight of 1,000 pounds 35 days sooner using 500 pounds less feed than a comparable animal not fed DES. Also, DES increases the ratio of protein to fat, resulting in more nutritious meat.

DES clearly is a useful and effective product. Furthermore, we are convinced that it is safe when used as directed. In spite of these advantages, studies have shown DES to be a carcinogen, and the law does not allow residues of a carcinogen in meat.

Six months ago, the U.S. Department of Agriculture and the Food and Drug Administration instituted new controls to assure elimination of DES residues. This was done after USDA's monitoring program disclosed illegal residues in approximately 1/2 of 1% of animal livers sampled. In response to those findings, FDA extended the withdrawal period for DES from 48 hours to 7 days before slaughter and USDA required producers to provide written certification of withdrawal.

-MORE-

In addition, a more sensitive method for detecting DES was put into use by USDA. Finally, in the most recent action, FDA initiated criminal prosecution against a producer for alleged misuse of the drug.

Nevertheless, in spite of these actions, the reports of illegal residues have not declined. They have, in fact, increased.

We have been informed by USDA that their monitoring program since January 8, 1972, has found illegal residues in 39 livers, or 1.9% of 2,081 samples analyzed.

This in our judgment does not indicate that the product cannot be used safely and effectively. It does suggest that, for whatever reasons, it is not being used in conformance with existing regulations.

It is apparent that additional action must be taken. It is equally apparent that any action with such major consumer impact must be taken only after the most careful consideration of all scientific information and regulatory alternatives. We recognize that competent scientists and concerned consumers have strong feelings on both side of this issue.

Before making further regulatory decisions affecting DES, the FDA must make absolutely certain it has all the facts. We have concluded that the most appropriate forum for accumulating additional facts is a public hearing. This will give everyone--scientists as well as consumers, industry as well as government--an opportunity to participate in the development, on the public record, of full information essential to balanced and reasonable judgment by the FDA.

Within the statutory framework of the Food, Drug, and Cosmetic Act, the only mechanism for proceeding to such a hearing is for FDA to propose a formal action to withdraw approval of the drug. Such a proposal automatically

provides an opportunity for an official hearing before an FDA appointed hearing examiner. Therefore, the necessary proposal for withdrawal will be published in the FEDERAL REGISTER next week. It will provide a procedure for us to carefully consider whether it is appropriate to withdraw approval of DES, to institute new and more effective restrictions to reduce the illegal residues, or to take other appropriate action.

Such a hearing would be open to the public. It is our intention to give everyone interested the opportunity to present evidence. We seek facts, and we are particularly interested in data on these subjects:

--Additional controls to eliminate the current rate of illegal residues;

--The consequences of withholding or discarding all livers, the only organ in which DES has been found by USDA;

--The feasibility of limiting use of the product to those producers who can demonstrate an adequate quality control program;

--The effect on the environment of withdrawing DES;

--The availability of alternative growth-promotant drugs;

--Differences or similarities in the potential for residues if DES is used in feed or as an implant;

--The likely result of the future availability of more sensitive detection methods.

We will continue, as we have in the past, to share information with authorities in Canada, where DES is also used. FDA and Canadian authorities agreed at a meeting this week that additional action is required.

-MORE-

Let me assure you that FDA is committed to eliminating DES residues from the meat supply in this country. At the same time, we have not yet concluded that withdrawal of approval for DES is the appropriate course of action. We believe that a full public hearing can help provide us with the information we need to make the correct decisions and take all appropriate action. The withdrawal proposal being announced today is designed to bring about such a hearing.

Persons interested in requesting a hearing or presenting data should inform the Hearing Clerk, DHEW, Room 6-88, 5600 Fishers Lane, Rockville, Maryland 20852.

# # # #

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[Docket No. FDC-D-494; NADA Nos. 9525, et. al.]

ELANCO PRODUCTS CO. et al.

DIETHYLSTILBESTROL; NOTICE OF OPPORTUNITY FOR HEARING ON PROPOSAL TO WITHDRAW APPROVAL OF NEW ANIMAL DRUG APPLICATIONS

Substantial public interest has been raised about the continued approval of diethylstilbestrol for use as a growth-promotant for cattle and sheep. A Subcommittee of the Committee on Government Operations of the House of Representatives held extensive hearings on this matter during 1971. The Natural Resources Defense Council has filed a lawsuit to compel the Food and Drug Administration to withdraw approval of diethylstilbestrol. In December 1971 the Food and Drug Administration and the United States Department of Agriculture instituted a joint program to extend the withdrawal period for diethylstilbestrol containing feeds from 2 days to 7 days and to require written certification of withdrawal (36 F.R. 23292, 24928). At the same time, a new and more sensitive method of detecting diethylstilbestrol was put into widespread use. Using this more sensitive method, the number of reported illegal residues of diethylstilbestrol in animal livers has increased rather than decreased.

(Page 1a follows)

-1a-

In light of this increase in reported diethylstilbestrol residues the Commissioner of Food and Drugs is considering whether it is appropriate to withdraw approval of diethylstilbestrol, to institute new more effective restrictions to reduce illegal residues, or to take other action. The Commissioner has concluded that,

prior to making a final decision as to the appropriate course of action to be taken, additional information is needed from all segments of the public, including consumer organizations, the animal husbandry industry, the pharmaceutical industry, the academic community, members of Congress, and other governmental agencies and departments.

The Commissioner has concluded that the most appropriate forum for public consideration of this matter is a public hearing, to develop on the public record the information necessary for a conclusion as to the proper handling of this matter. Under section 512 of the Federal Food, Drug, and Cosmetic Act, an opportunity for a hearing on a proposal to withdraw approval of a new animal drug application is provided to the holder of the application. The Commissioner has discretion in permitting other interested individuals and organizations to participate in any subsequent hearing. Accordingly, the Commissioner has concluded that it would be appropriate to propose withdrawal of the approval of the new animal drug applications for diethylstilbestrol in order to utilize the hearing mechanism provided in the statute for this purpose.

The Commissioner has not yet concluded that withdrawal of approval for diethylstilbestrol is the appropriate course of action. Requests for a public hearing may be accompanied by proposals for additional and more effective restrictions on diethylstilbestrol that would obviate such withdrawal of approval. Alternative restrictions that could be considered include prohibition of use for human food of livers from animals receiving diethylstilbestrol, or requiring such livers to be

tested prior to marketing, or requirements limiting the persons who may use the drug.

In the event that a hearing is held, the Commissioner will wish to obtain data and information from all interested persons with respect to such relevant matters as the current rate of illegal residues and ways in which this might be reduced, the potential effect upon the public health and safety of a low rate of illegal diethylstilbestrol residues, the likely effect on the environment of withdrawing approval of diethylstilbestrol, the availability of alternative growth-promotant drugs and their safety and effectiveness as compared with diethylstilbestrol, the need for growth-promotant drugs in the animal husbandry industry, differences or similarities between administration of diethylstilbestrol by feed or by implant with respect to the potential for residues, the accuracy and reliability of present detection methods for diethylstilbestrol, the potential availability of more sensitive detection methods for diethylstilbestrol and the likely result of their use, and any other relevant information.

Accordingly, notice is hereby given to the following listed holders of new animal drug applications that the Commissioner of Food and Drugs proposes to issue an order under section 512(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(e)) withdrawing approval of the following listed new animal drug applications which

provide for use of diethylstilbestrol as a growth promotant for cattle and sheep:

Elanco Products Company, P. O. Box 750, Indianapolis, Indiana 46206.

NADA Nos. 9525

11090

42162

Pfizer, Inc., New York, N.Y. 10017.

NADA Nos. 9757

9783

11356

9770

Walnut Grove Products, Division of W. R. Grace Co., Atlantic, Iowa. 50022.

NADA No. 10132

Dawes Laboratories, Chicago, Illinois 60632.

NADA Nos. 10421

11485

34916

Simonsen Manufacturing Company, Quimby, Iowa 51049.

NADA No. 10566

Vineland Laboratories, Inc., Subsidary of Damon, Vineland, N. J. 08360.

NADA No. 10964

Hess & Clark, Division of Rhodia, Inc., Ashland, Ohio 44805.

NADA Nos. 11295

12553

44344

45982

45981

Peter Hand Foundation, Inc., Waukegan, Illinois 60085.

NADA No. 14773

O. M. Franklin Serum Company, Denver, Colorado 80216.

NADA No. 15274

Fort Dodge Laboratories, Fort Dodge, Iowa 50501.

NADA No. 31446

Thompson-Hayward Chemical Company, Kansas City, Kansas 66106.

NADA Nos. 35019

35017

Feed Additives, Inc., Fremont, Nebraska 68025.

NADA Nos. 36313

37869

Dale Alley Company, St. Joseph, Missouri 64501.

NADA Nos. 36671

36554

Standard Chemical Manufacturing Company, Omaha, Nebraska 68103.

NADA Nos. 36976

34735

National Oats Company, East St. Louis, Illinois 62205.

NADA Nos. 37148

37541

Texas Nutrition & Service Company, Ft. Worth, Texas 76108.

NADA Nos. 38507

38510

39509

Bresley-Koelling, Inc., Ord, Nebraska 68862.

NADA No. 39491

Feed Products, Inc., Denver, Colorado 80211

NADA Nos. 39716

39718

39717

39715

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc. Rahway, New Jersey 07065.

NADA Nos. 39772

42840

10261

Chemetron Corporation, Chicago, Illinois 60611.

NADA Nos. 42355

Farmland Industries, Kansas City, Missouri 64116.

NADA No. 42702

Western Farmers Association, Seattle, Washington 98111.

NADA No. 44526

E. R. Squibb & Sons, New Brunswick, New Jersey 08902.

NADA No. 11365

Western Feed Supplements, Ellensburg, Washington 98926.

NADA No. 40014

Ultra Life Labs., Inc., East St. Louis, Illinois 62201.

NADA No. 38682

Square Deal Fortification Company, Kouts, Indiana 46347.

NADA No. 39161

Falstaff Brewing Corporation, St. Louis, Missouri 63166.

NADA No. 44795

Feed Products, Inc., Denver, Colorado 80211.

NADA No. 39715

American Cyanamid Company, Princeton, New Jersey 08540.

NADA No. 10258

S. B. Penick Company, New York, N.Y. 10008

NADA No. 36479

The Commissioner, based on an evaluation of new information before him with respect to such drugs together with the evidence available to him when the applications were approved, concludes that there is a question as to whether the drugs are shown to be safe under the conditions of use upon the basis of which the applications were approved.

Information available to the Commissioner establishes that use of such drugs has resulted in illegal residues of diethylstilbestrol in animal livers.

In accordance with the provisions of section 512 of the act (21 U.S.C. 360b), the Commissioner hereby gives the applicants an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of the above listed new animal drug applications should not be withdrawn. Promulgation of the proposed order would cause any such drug containing diethylstilbestrol to be a new animal drug for which no approved new animal drug application is in effect. Any such drug or any animal feed bearing or containing such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Product Safety Division, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or

2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner, without further notice, will enter a final order withdrawing approval of said applications.

Failure of such persons to file a written appearance of election within 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing concerning a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance. Interested persons who are not parties may intervene to present evidence and file pleadings, and may cross-examine witnesses when in the judgment of the hearing examiner their interests are not adequately protected otherwise or it is required for a full and true disclosure of the facts.

If such persons elect to avail themselves of the opportunity for a hearing, they must file a written appearance requesting the hearing and giving the reasons why the approval of the new animal drug applications should not be withdrawn together with a well-organized and full-factual analysis of the data they are prepared to prove in support of their opposition to the Commissioner's

proposal. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the applications, the Commissioner will enter an order stating his findings and conclusions on such data. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

Responses to this notice may be seen in the Office of the Hearing Clerk (address given above) during regular business hours, Monday through Friday.

Pending consideration of responses to this notice, no action will be taken on the notice of opportunity for hearing pertaining to diethylstilbestrol liquid premixes, published in the FEDERAL REGISTER for March 11, 1972 (37 F.R. 5264). Both notices will be acted upon at the same time.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343-51; 21 U.S.C. 360b) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: JUN 16 1972

Charles C. Edwards

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

FDA Position On
DIETHYLSTILBESTROL (DES)
Synthetic Hormone For Beef and Sheep

FDA has approved several synthetic hormones for stimulating growth of animals and improving feed efficiency. One of these, diethylstilbestrol (DES), is widely used as a feed additive for beef cattle, and also is administered to sheep. There will be no detectable residues of the hormone in meat derived from the animals, if the required 48-hour withdrawal period is observed.

Diethylstilbestrol, a synthetic compound with properties of the female sex hormone, is "capable of producing and has produced cancer in animals and this drug may be expected to produce, excite or stimulate the growth of certain cancers in human beings" (Quotes are from Code of Federal Regulations 130.201).

The Delaney clause of the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act provided, in effect, that no food additive could be approved by FDA for any human food use if the additive has been shown to induce cancer when ingested by man or animal.

The Kefauver-Harris Drug Amendments of 1962 exempted from the Delaney clause drugs or chemicals added to animal feeds, provided it is shown that no harm to the animal results and that there are no residues of the additive in the meat or other products reaching the consumer.

The Department of Agriculture's Consumer & Marketing Service samples 600 cattle each year for residues of DES.

In June 1970, The Associated Press reported that government inspectors had found residues in 0.7 percent of the beef they checked in 1965, 1.1 percent in 1966, 2.6 percent in 1967 in 1968 and 0.6 percent last year.

On August 21, 1970, Dr. C.D. Van Houweling, director of the FDA's Bureau of Veterinary Medicine, told the Association of American Feed Control Officials that although the hormone is beneficial to growers, the government cannot tolerate any residues.

"If residues persist because feeders are not following the specified restrictions and withdrawal period, there will be no alternative left but to withdraw approval of its use," Van Houweling said.

On September 19, 1970, FDA issued a new regulation allowing beef growers to use up to twice the amount of DES in cattle feed. Where they formerly were allowed to feed up to 10 milligrams, the new regulation permits daily use of up to 20 milligrams of the hormone for each animal weighing more than 750 lbs. This order means that most of the cattle going to market may have received twice as much DES as formerly but also takes into account the dose/weight relationship since calves weighing only 350 pounds may receive up to 10 mg. per day.

84-843 O - 72 - 11

FDA allowed the DES increase in response to a request from Elanco Products Co., the agricultural division of Eli Lilly & Co., and the FDA order affects only the product made by this company. The firm provided FDA with studies showing the increased doses produced faster weight gain while leaving no residues after the 48-hour withdrawal period. Lilly has submitted data indicating that dosage of 50 mgs daily per animal would leave no residues providing the proper withdrawal period of 48 hours is observed.

On October 8, 1970, the American National Cattlemen's Association announced a new self-certification program asking "every cattle feeder in the country to certify in writing that their cattle have not been fed DES for at least 48 hours prior to slaughter."

Commenting on the ANCA program, Dr. Charles C. Edwards, Commissioner of the Food and Drug Administration said, "Your indication of willingness to embark on this program will go a long way in assuring the consuming public that red meat products are wholesome and free of residues."

Commissioner Edwards continued, "I feel it is important to emphasize that whenever we document the fact that residues are present in edible parts of a slaughtered animal we will take appropriate action. I feel also that vigorous enforcement on the part of FDA will enhance the possibility of success of your proposed program."

In 1969, an estimated 18 million beef cattle were fed DES which possibly resulted in a saving of more than 6 billion pounds of feed worth 157 million dollars. It is estimated that withdrawal of DES might increase the price of beef by 20 percent.

DES implants in ears of cattle and sheep is also allowed. Simultaneous use of DES implants and DES in feed is not approved by FDA.

Firms that wish to make feed containing diethylstilbestrol or market diethylstilbestrol used as an implant in the ear of beef cattle and sheep must have approval through a New Drug Application (NDA). The NDA requires proof that no residue of the drug will be left in any human food derived from the animal.

# # # # # #

Prepared by the Office of Public Information, FDA, January 20, 1971.

BUREAU OF VETERINARY MEDICINE
CASE GUIDANCE BRANCH - (VM-220)

Chicago District
October 27, 1971

RECORD OF HEARING

SAMPLE NO. AND PRODUCT: DOC 007-925 E
Beef Livers

INDIVIDUAL CITED: James Malcomson
Frederick, Illinois

DATE OF HEARING: Response received
October 27, 1971

Mr. Malcomson responded to the Notice of Hearing issued on October 8, 1971 by letters of October 14, 1971 and October 27, 1971. The Notice of Hearing was issued charging Mr. Malcomson with delivering beef steers with contaminated livers to a federally inspected meat packing plant. The livers were found, by USDA, to contain 15.4 ppb diethylstilbestrol.

Mr. Malcomson denied any knowledge of a violation of the law. He claimed that he had not been advised of the necessary withdrawal period. Copies of Mr. Malcomson's letters are attached.

Roger C. Burrows
Hearing Officer
Chicago District

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PERMANENT ABEYANCE AFTER RESPONSE TO NOTICE OF HEARING:

As instructed by H. Friedlander on October 27, 1971 we are placing this number in P.A.

FOLLOW-UP: Reinspect in 90 days to determine if withdrawal periods are being observed. Samples are to be collected if suspicion of violation exists. Note Field Management directive #6, dated 1-12-71.

R.C.B.

VM-220 O+1 w cy Malcomson/FDA 10/27/71 ltr.
C-DI 2
CHI-RO CHI-DO

ct

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

*Date:* February 4, 1972

*Reply to Attn of:* WILLIAM L. SCHWEMER, FOOD & DRUG OFFICER - DET-DO - D-40

*Subject:* Doc. 093-292 E - DES Residue in Cattle

*To:* VM-220

Sam Washburn
East Street
Fowler, Indiana

PERMANENT ABEYANCE

Mr. Washburn was cited on subject sample on 11/30/71 following a report from USDA that DES residues were found in animals marketed by Mr. Washburn at Emgee Packing Co. in Anderson, Indiana.

Mr. Washburn stated at the hearing that he was at a loss to explain the findings because his records clearly showed that DES feeds were properly withdrawn.

Mr Washburn's records were reviewed during a farm inspection on 1/7/72 and they indicated a 7 day withdrawal period prior to shipment of the lot in question. An inspection of Mr. Washburn's feed supplier, Farmers Cooperative, Remington, Indiana, was conducted by the Indiana State Chemists office on 12/9/71. The mill was found to meet the requirements of GMP and to have exceptionally good housekeeping conditions.

On 12/6/71, Inspector Hangartner visited the Emgee Packing Co. in an attempt to document the authenticity of the Washburn cattle sample taken by USDA. The identity of the person or persons who identified the lot and or collected the sample is not known.

It is evident that further investigation at this time would be unrevealing. Accordingly we are placing the subject number in Permanent Abeyance.

W. L. Schwemer
Food & Drug Officer
Detroit District

cc: this memo
cc: CHI-F2
cc: Indpls R/P
cc: S/B - R/P
cc: EF/file

WLS/mmj

HORMONES

List of Hormones which may be added to feed

1. DIETHYLSTILBESTROL (Fattening cattle, sheep and poultry)

*C.N. 3,4-bis(p-hydroxyphenyl)-3-hexene

**E.F. $C_{18}H_{20}O_2$

2. HEXOESTROL (Fattening cattle, sheep and poultry)

C.N. (±)-3,4-di(p-hydroxyphenyl) hexane

E.F. $C_{18}H_{22}O_2$

3. PROGESTERONE (Growth promotion)

C.N. -4-prenene 3,20 dione

E.F. $C_{21}H_{30}O_2$

4. TESTOSTERONE PROPIONATE (Growth promotion)

C.N. 17 -hydroxy-4-androsten-3-one propionate

E.F. $C_{22}H_{32}O_3$

5. ESTRADIOL BENZOATE (Growth promotion)

C.N. 1,3,5,(10) estratriene-3,17 -diol 3 benzoate

E.F. $C_{25}H_{28}O_3$

6. ESTRADIOL MONOPALMITATE (Produce more uniform fat distribution)

C.N. 1,3,5(10)-estratriene-3,17, -diol 17-palmitate

E.F. $C_{34}H_{54}O_3$

7. DIENESTROL DIACETATE (Promotion of fat distribution for tenderness)

C.N. 3,4-bis(p-acetoxyphenyl)2,4-hexadiene

E.F.

*C.N. Chemical name

**E.F. Empirical formula

8. MEDROXY PROGESTERONE ACETATE (Synchronization of Oestrus and ovulation)

C.N. 17-dihydroxy-6 α-methyl pregn-4-ene-3,20-dione 17 acetate

E.F.

9. SODIUM THYROXINE (To induce mild hyperthyroidism in farm animals)

C.N. Sodium L- amino- β-(4-(4-hydroxy-3-5-di-iodo-phenoxy)-3,5-di-iodophenyl) propionate pentahydrate

E.F. $C_{15}H_{10}I_4NNaO_4.5H_2O$

10. PREDNISOLONE (Corticosteroid)

C.N. 11 β,17 α,21-trihydroxypregna-1,4-diene-3,20-dione

E.F. $C_{21}H_{28}O_6$

11. PREDNISONE ACETATE (Corticosteroid)

C.N. 21-acetoxy-17 α-hydroxypregna-1,4-diene-3,11,20-trione

E.F. $C_{23}H_{28}O_6$

ADMINISTRATION OF HORMONES

These substances are administered to cattle or sheep either by implantation of a pellet in the ear or in feeds. In cases where poultry are treated the hormones are normally implanted in the subcutaneous tissues of the neck at the base of the skull or added to the feed.

CONDITIONS OF USE OF HORMONES IN COUNTRIES WHERE ALLOWED

U.K.

Beef Cattle Hexoestrol- 36-45 mg. by implantation

or Hexoestrol- 10 mg. daily intake in feed

Lambs: Hexoestrol - 10-15 mg. by implantation

or Hexoestrol - 2 mg. daily intake in feed

Poultry: Hexoestrol - 10-15 mg. by implantation.

Diethylstilbestrol is not widely used in the U.K. but its use is not forbidden.

9663

U.S.A.

Beef Cattle

DIETHYLSTILBESTROL

- 10 mg. per head per day
- in not less than 1 lb. of feed
- withdraw 48 hours before slaughter
- do not feed to breeding or dairy animals
- may be used in mixtures with chlortetracycline, oxytetracycline and bacitracin

.....

PROGESTERONE (for steers weighing 400-1000 lbs.)

- 200 mg. per dose by subcutaneous ear implantation
- in mixtures with Estradiol benzoate 20 mg. per dose
- one dose per animal
- not to be used within 60 days of slaughter

.....

TESTOSTERONE PROPIONATE (for heifers weighing 400-1000 lbs.)

- 200 mg. per dose by subcutaneous ear implantation
- in mixtures with Estradiol benzoate 20 mg. per dose

- one dose per animal
- not to be used within 60 days of slaughter
- not for dairy animals

BREEDING CATTLE:

HYDROXYPROGESTERONE ACETATE

- 180-250 mg. per head per day
- fed daily to achieve recommended dose
- daily for 18 - 30 days

SHEEP:

DIETHYLSTILBESTEROL

- 2 mg. per head per day
- withdraw 48 hours before slaughter
- do not feed to breeding animals

.....

PROGESTERONE (lambs 60-85 lbs.)

- 25 mg. dose ....in mixture with Estradiol benzoate 2.5 mg.
- subcutaneous ear implantation
- one dose per animal
- not to be used within 60 days of slaughter

EWES:

HYDROXYPROGESTERONE ACETATE

- dose 50-100 mg. per head per day
- dosage daily 14-21 days

ROASTING CHICKENS:

ESTRADIOL BENZOATE

- dose 10 mg.

- one dose per bird by injection under skin at base of skull
- at less than 5 weeks of age
- not to be used within 5 weeks of slaughter
- polyethylene glycol used in preparation must be according to specifications

.....

DIENESTROL DIACETATE

- dose 20.9 gm. per ton (0.0023%)
- withdraw 48 hours before slaughter
- start treatment at 5-6 weeks
- treat for 6-10 weeks

.....

DIENESTROL DIACETATE

- dose 31.8 gm. per ton (0.0035%)
- withdraw 48 hours before slaughter
- start treatment at 8-9 weeks
- treat 5-7 weeks

BROILER CHICKENS:

DIENESTROL DIACETATE

- dose: 20.9 gm. per ton feed (0.0023%)
- withdraw 48 hours before slaughter
- start treatment at 5-6 weeks of age
- treat 4-6 weeks

.....

DIENESTROL DIACETATE

- dose: 63.6 gm. per ton (0.007%)
- withdraw 48 hours before slaughter
- start treatment at 3 weeks
- treat for 3 weeks

TURKEY BROILERS:

DIENESTROL DIACETATE

- dose: 63.6 gm. per ton (0.007%)
- withdraw 48 hours before slaughter
- start treatment at 8-10 weeks
- treat 3 weeks

ISRAEL

BEEF CATTLE:

DIETHYLSTILBESTEROL

- dose: 36. mg. per steer
- 3 months between treatment and slaughter

RESIDUES IN THE FLESH OF ANIMALS TREATED WITH HORMONES

U.S.A.

DIETHYLSTILBESTEROL a tolerance of 0 is established for residues in the edible portions of beef cattle and sheep after slaughter (as determined by the method prescribed).

PROGESTERONE: a tolerance of 0 is established for residues in the uncooked edible tissues and by products of lambs and steers (method described in regulations).

ESTRADIOL BENZOATE: a tolerance of 0 is established for residues in the uncooked edible tissues and by products of heifers, lambs and steers (reference to method).

ESTRADIOL PROPIONATE: a tolerance of 0 is established for residues in the uncooked edible tissues and by products of heifers (reference to method).

FLUMESOLONE a tolerance of 0 is established for residues in milk from dairy animals.

DIENESTROL [illegible] a tolerance of 0 is established in the uncooked edible tissues and by products of chickens (reference to method).

[illegible] a tolerance of 0 is established for residues in milk from dairy animals.

DIENOESTROL DIACETATE: a tolerance of 0 is established for residues in the uncooked edible tissues and by products of chickens and turkeys (reference to method).

METHOXYCHLOR IRON ACTION: a tolerance of 0 is established in edible tissues and by products of sheep and cattle, 0 in milk (method described).

Residues (cont'd). Extract from U.K. note.

Cattle. Residual levels of oestrogens in edible tissues from treated cattle and sheep have not been detected by bio-assay techniques and would therefore appear to be not significantly greater than those probably present in untreated animals.

American studies have shown oestrogen residues in tissues of poultry implanted with 15 mg. diethylstilbestrol.

Residues: muscle..... 3.3 - 7.7 mg. per kg.

liver..... 2.5 - 36.9 mg. per kg.

skin..... 3.1 - 9.5 mg. per kg.

abdominal fat.. 0 - 11.7 mg. per kg.

Similar British studies with birds implanted with hexoestrol have shown residues in muscle from 3.0 - 12.0 mg. per kg. (i.e. less than 1.12 ppm).

UNABSORBED RESIDUES

There is a potential danger to the human consumer

of meat from animals and poultry which contains unabsorbed oestrogen pellets either because the bird or animal was killed too soon after implantation before the pellet had dissolved and dispersed, or because the pellet had failed to dissolve because of the formation of scar tissue around the pellet at the time of implantation thereby sealing it off. The sites of implantation, i.e. the ears of cattle and the base of the skull in poultry, are, however, not normally used for human consumption. No case is known of unabsorbed pellets being accidentally consumed by humans in this country (U.K.) but there have been reports from abroad of trouble due to this cause, usually leading to a loss of virility in men. Such cases, however, are believed to have been due to repeated consumption of poultry offal containing (presumably) unabsorbed pellets. The Department has been advised that the accidental ingestion of a single pellet would have no effect whatsoever on a human being.

COUNTRIES WHERE THE USE OF HORMONES HAS BEEN BANNED OR WHERE HORMONES ARE NOT USED

(1) ARGENTINA - Ban on oestrogenic hormones as growth stimulants (Boletin Official - No. 19,545,2/VI/1961). The use for therapeutic purposes on livestock for export will be governed by special regulations.

2 AUSTRALIA - All hormones not permitted as feed additives, not only oestrogens, therapeutic uses governed by other rules.

(3) AUSTRIA.: The addition of hormones to feeds is prohibited without exception.

(4) BELGIUM: Animal feeds banned if they contain any substances having hormonal activity. Therapeutic use under veterinary supervision for protecting animals' health, and not for growth improvement.

(5) BRAZIL: The use of synthetic oestrogens is banned.

CANADA: Permitted in feed for cattle or by implantation in ear in cattle - permitted in feed for sheep - banned for poultry.

(6) DENMARK: The use of hormones is prohibited - oestrogens banned in 1963, thyreostatics banned in 1965.

(7) EIRE: Prohibited for use except therapeutic purposes (Regulations 1962).

(8) FEDERAL REPUBLIC OF GERMANY: Addition prohibited to feed.

(9) FRANCE: The decree of 20 March 1959 explicitly forbids feeds to which oestrogens have been added and also animals or foodstuffs derived from animals to which oestrogens have been fed unless they are intended for therapeutic purposes.

(10) GREECE: The use of synthetic oestrogens prohibited since October 1960.

(11) ITALY: Ban on use of oestrogens as growth stimulants or sex inhibitors in animals whose meat or products is intended for human consumption (Gazzeta Ufficiale No. 43, 18/II/1961). The prohibition covers poultry and other farm animals marketed live or imports.

ISRAEL: Hormonization of poultry by means of synthetic or natural oestrogens banned (Regulations 1960).

JORDAN: Prohibits hormones, also synthetic, intended to promote growth or sterilize animals whose flesh is intended for human consumption. Bans sale of meat, milk products from treated animals, including domestic animals, sold live (Official Gazette No. 1572, 19/IX/1961).

LUX MBOURG: Not allowed in feedstuffs (Memorial du Grand Duche A-No. 23. 30/VI/1961).

MADAGASCAR: Ban on oestrogenic substances in feed of animals whose flesh or products are for human consumption - does not apply to therapeutic uses (Journal Official de la Republique Malagache No. 339, 22/II/1964).

MOROCCO: Ban on feeds and other uses of oestrogenic substances in animals whose flesh or products are for human consumption - does not apply to therapeutic uses (Bulletin Official No. 2649, 22/VII/1963).

NETHERLANDS: Prohibited except under veterinary prescription.

NEW ZEALAND: Oestrogens banned for poultry 1964.

PERU: Prohibits import and sale of oestrogenic hormones (El-Peruano, No. 5822, 16/IX/1960).

POLAND: Forbidden to add hormones to feed.

SOUTH AFRICA: Hormones banned.

SPAIN: Ban on "prepared poultry feed" includes eggs and poultry from countries where allowed (Boletin Oficial do Estado - No. 69 20/III/1964).

SWEDEN: Juni 1961 - hormones banned for poultry except pharmaceutical purposes - banned as feed additives.

SWITZERLAND: Ban on use of oestrogens and import of oestrogen treated poultry and cattle - March 1960.

U.S.A.: Diethylstilbesterol banned for use on poultry.

## OTHER SUBSTANCES AFFECTING THE GROWTH OF ANIMALS

1. ARSANILIC ACID

C.N. p-aminobenzenearsonic acid

E.F. $C_6H_8AsNO_3$

2. 3-NITRO-4-HYDROXYPHENYLARSONIC ACID

C.N. 4-hydroxy-3-nitrobenzene arsonic acid

E.F. $C_6H_6AsNO_6$

3. SODIUM ARSANILATE

C.N. sodium p-aminobenzene arsonate

E.F. $C_6H_7AsNaO_3$

4. METHYL THIOURACIL

C.N. 4-hydroxy-2-mercapto-6-methyl pyrimidine

E.F. $C_5H_6N_2OS$

5. PROPYL THIOURACIL

C.N. 4-hydroxy-2-mercapto-6-propyl pyrimidine

E.F. $C_6H_{10}N_2OS$

Others Arsenobenzene

Arsenosobenzene

Thiouracil

NATIONAL LEGISLATION REGARDING THE USE OF GROWTH SUBSTANCES OTHER THAN OESTROGENIC HORMONES

AUSTRALIA: Arsanilic acid, Arsenoso benzene, 3-nitro-4-hydroxy phenyl arsonic acid permitted. Thiouracil is not permitted.

DENMARK: The use of thyreostatics is prohibited (23/IX/1965).

FRANCE: Arsenicals prohibited under decree of 20 March 1959.

ISRAEL: Arsenicals prohibited.

MADAGASCAR: " "

MOROCCO " "

SPAIN: " "

U.K.: Iodinated casein, thyroxine, thyroprotein, propyl thiouracil methyl thiouracil.

U.S.A.: Arsanilic acid, Sodium arsanilate, 3-nitro-4-hydroxy phenyl arsonic acid.

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CHEMOTHERAPEUTIC SUBSTANCES

COCCIDIOSTATS

1. ACETYL -(p-nitrophenyl) SULPHANILIDE

C.N. acetyl-(p-nitrophenyl) sulphanilimido

E.F. $C_{14}H_{13}N_3O_5S$

2. AMPROLIUM HYDROCHLORIDE

C.N. 1-(4-amino-2-n-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride

E.F. $C_{14}H_{20}Cl_2N_4$

3. AKLORIDE

C.N. 2 chloro-4-nitrobenzamide

E.F. $C_7H_5O_3N_2Cl$

4. BITHIONOL

C.N. 2,2'-thiobis(4,6-dichlorophenol)

E.F. $C_{12}H_6Cl_4O_2S$

5. DIAVERIDINE

C.N. 2,4-diamino-5-(3,4-dimethoxybenzyl)pyrimidine

E.F. $C_{13}H_{16}N_4O_2$

6. 3,5-DINITROBENZAMIDE

C.N. 3,5-dinitrobenzamide

E.F. $C_7H_5N_3O_5$

7. METHIOTRIAZAHINE

C.N. 4,6-diamino-1-(4-methylmercaptophenyl)-1,2-dihydro-2,2-dimethyl-1,3,5, triazine hydrochloride

C.F. $C_{12}H_{19}N_5SHCl$

8. NITROFURAZONE

C.N. 5-nitro-2-furaldehyde semicarbazone

E.F. $C_6H_6N_4O_4$

9. NITROPHENIDE

C.N. bis(m-nitrophenyl) disulphide

E.F. $C_{12}H_8N_2O_4S_2$

10. NICARBAZIN

C.N. 4,4-dinitrocarbanilide 2-hydroxy-4,6-dimethyl pyrimidine complex

E.F. $C_{19}H_{18}N_6O_6$

11. PYRIMETHAMINE

C.N. 2,4-diamino-5-(p-chlorophenyl)-6-ethyl pyrimidine

E.F. $C_{12}H_{13}ClN_4$

12. SULPHADIMIDINE SODIUM

C.N. sulphadimidine

E.F. $C_{12}H_{13}N_4NaO_2S$

13. SULPHAGUANIDINE

C.N. N-p-aminobenzenesulphonyl guanidine monohydrate

E.F. $C_7H_{10}N_4O_2SH_2O$

14. SULPHAQUINOXALINE

C.N. 2-p-aminobenzene-sulphonamido quinoxaline

E.F. $C_{14}H_{12}N_4O_2S$

15. ZOALENE (METHYLDINITROBENZAMIDE)

C.N. 3,5-dinitro-o-toluamide

E.F. $C_8H_7N_3O_5$

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OTHER COCCIDIOSTATS

16. ALINITROZOLE

17. ETHOPABATE

18. GLYCARBYLAMIDE

19. NITROXYNIL

20. TRITHIADOL

THE USE OF COCCIDIOSTATS (material gathered from various sources).

AUSTRALIA: amprolium, zoalene, nitrofurazone, nicarbazin, sulphoquinoxaline, phenosulphazole, diaveridine, nihydrazone.

AUSTRIA zoalenes (on experimental basis).

BELGIUM: sulphaquinoxaline, amprolium, zoalene, nicarbazin, and N-5(5 nitro-2-furfurylidine)-3-amino-2-oxazolidine.

DENMARK: amprolium, zoalene.

EIRE: coccidiostats may be used.

FEDERAL REPUBLIC OF GERMANY: amprolium, zoalenes, ethopabate (in mixtures with amprolium).

FRANCE: nitrofurazone, nicarbazin.

LUXEMBOURG: use by special permission.

NETHERLANDS: nicarbazin, nitrofurazon, nitrophenid, sulphachinoxalin, amprolium, zoalene, amino-5-nitrothiazol.

NORWAY: coccidiostats forbidden.

POLAND: nitrofurazone.

SWEDEN: amprolium, nicarbazin, nitrofenid, zoalene, amprolium.

SWITZERLAND: formocibazol, furzolidine, nicarbazine, nitrofurazone, nitrophenide, zoalene, amprolium.

U.K.: nitrofurazone, nitrophenide, nicarbazine, pyrimethanine, zoalene, amprolium, trithiadol, sulphadimidine, sulphaguanidine, sulphaquinoxaline.

U.S.A.: zoalene, amprolium, nihydrazone, bithionol, methiotriazamine, 3,5-dinitrobenzamide, sulphanitran, 2 chloro-4 nitro benzamide, acetyl-p-nitrophenyl, sulphanilimide, aklomide.

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OTHER THERAPEUTIC AGENTS

In addition to coccidiostats many therapeutic substances may be added to animal feeds and drinking water. Veterinary therapeutic substances may give rise to residues but the following is a list of substances added directly to the feed. This material is mainly from U.K. and U.S.A. sources.

1. ACINITRAZOLE (antiblackhead)

C.N. 2-acetamido-5-nitrothiazole

E.F. $C_5H_5N_3O_3S$

2. AMINONITROTHIAZOLE (antiblackhead)

C.N. 2-amino-5-nitrothiazole

E.F. $C_3H_3N_3O_2S$

3. DIMETRIDAZOLE (antiblackhead)

C.N. 1,2-dimethyl-5-nitroimidazole

E.F. $C_5H_7O_2N_3$

4. FURAZOLIDONE (antiblackhead-treatment of bacterial scours)

C.N. 3-(5-nitrofurfurylideamino)-2-oxazolidinone

E.F. $C_8H_7N_3O_5$

5. HALOXON (an organophosphorous antihelmintic)

C.N. o,o,di-(2-chloroethyl)o-(3-chloro-4-methylcoumarin-7-yl) phosphate

E.F.

6. HEXACHLOROPHENE (control of worms, liver flukes etc.)

C.N. 2,2'-methylenebis(3,4,6-trichlorophenol)

E.F. $C_{13}H_6Cl_6O_2$

7. NIHYDRAZONE (prevention of respiratory disease)

C.N. 5-nitro-2-furaldehyde acetyl hydrazone

E.F. $C_7H_7N_2O_4$

8. NIROFURAZONE (treatment of diarrhea)

C.N. 5-nitro-2-furaldehyde semicarbazone

E.F. $C_6H_6N_4O_4$

9. NITHIAZINE (antiblackhead)

C.N. 1-ethyl-3-(5-nitro-2-thiazolyl)urea

E.F. $C_6H_8N_4O_3S$

10. PHENOTHIAZINE (antihelmintic)

C.N. thiodiphenyl amine

E.F. $C_{12}H_9NS$

11. PHENZIDOLE (antihelmintic)

C.N.

E.F.

12. PROMAZINE HYDRACHLORIDE (tranquilizer)

C.N. 10-(3-Dimethylaminopropyl) phenothiazine

E.F. $C_{17}H_{20}N_2S$

13. THIABENDAZOLE (antihelmintic)

C.N. 2-(4'-thiazolyl)benzimidazole

E.F. $C_{10}H_7N_2S$

14. SULPHAETHOXYPYRIDAZINE (treatment of bacterial scours)

C.N. N'(6-ethoxy-3-pyridazinyl) sulphanilimide

E.F. $C_{12}H_{14}N_4O_3S$

15. RONNEL (control of grubs and hornflies)

C.N. o,o-dimethyl-o-(2,4,5,-trichlorophenyl) phosphorothioate

E.F.

16. RUELENE (systemic insecticide and antihelmintic)

C.N. 4-tertiary butyl-2-chlorophenyl methyl methyl phosphoroamidate

E.F.

NUTRITIONAL ADJUNCTS

The problems connected with the use of these substances are mainly economic, the residues produced being of minor importance.

The following is a list of substances added in various countries.

MINERALS

Cobalt, Copper, Iron, Manganese, Zinc, Molybdenum, Potassium, Boron, Calcium, Phosphorous, Iodine, Sulphur, Magnesium.

VITAMINS

A,B (Riboflavin, Nicotinic acid, Calcium pantothenate, Pyridoxine, Cyanocobalamin, Folic acid, Biotin, Choline chloride) Ascorbic acid, $D_3$, $D_2$, Vitamin E acetate, Vitamin K analogue (menadian)

AMINO ACIDS

Methionine, lysine, Crotic acid, Orotic acid, Glycine, Glutamic acid.

OTHER SUBSTANCES

Urea, Methyl esters of higher fatty acids, p-amino benzoic acid.

Banned

Selenium

CHEMICAL PRESERVATIVES IN ANIMAL FEEDSTUFFS

The addition of antioxidants is regulated in some countries. The following is a general list of antioxidants used.

B.H.A., B.H.T.

ETHOXYQUIN (1,2-dihydro-6-ethoxy 2,2,4-trimethyl quinoline)

HYDROQUINONE

PROPYL GALLATE, OCTYL GALLATE, DODECYL GALLATE

DITERT BUTYL PARACRESOL

RESIDUES

Residues for Ethoxyquin are set in U.S.A. regulations.

5 p.p.m. - uncooked fat of meat

3 p.p.m. - uncooked liver or fat of poultry

0.5 p.p.m. - uncooked muscle meat

0.5 p.p.m. - eggs

STABILIZERS AND EMULSIFIERS

U.S.A. regulations allow the following stabilizers:

POLYOXYETHYLENE GLYCOL (400) mono and dioleates

" " (200)

POLYSORBATE (60)

" (80)

SORBITAN MONOSTEARATE

These substances are used mainly in calf milk replacer formulations.

Other National regulations include the following stabilizers:

GELATIN, NATURAL GUMS, AGAR-AGAR, CARRAGEEN, ALGINATES, PECTINS CELLULOSIC ALKYLESTERS (up to 1% Belgian regulations)

EMULSIFIERS - mono and diglycerides of higher fatty acids

- alkylates of mannitol

PIGMENTS

The main use of pigments in animal feeds is to enhance the colour of egg yolks.

The following substances are used:

CAROTENOIDS - Beta apo-8-Carotinoic acid (ethyl ester)

- carotenic acid ester

- p-apocarotenol

Eosine

Xanthophylls

Swiss regulations - prohibit the colouring of eggs

- by injecting colouring solutions into yolk

- by feeding hens artificially coloured feeds

* carotenes added to feeds are not considered artificial colouring agents.

CAKING AGENTS, FILLERS, PELLETING AIDS, LUBRICANTS etc.

The following are allowed in the U.S.A.

1. CALCIUM SILICATE

- anti caking agent

2. DISODIUM EDTA

- to solubilize trace minerals

3. ETHYL CELLULOSE

Cellulose ether containing ethoxy groups attached by an ether linkage and containing on an anhydrous basis not more than 2.60 ethoxy groups per anhydroglucose unit.

- binder or filler for vitamin preparations

4. LIGNIN SULPHONATES

Either one or a combination of the ammonium, calcium, magnesium or sodium salts of the extract of spent sulphite liquor derived from the sulphite digestion of wood

- pelleting aid

5. MINERAL OIL

- Lubricant for preparation of pellets
- reduces dustiness
- prevents segregation of minerals

6. PETROLATUM

- same uses as mineral oil.

7. PYROPHYLLITE

ALUMINUM SILICATE MONOHYDRATE

- anti caking agent etc.

8. VERXITE (exfoliated hydrobiotite)

Thermally expanded magnesium aluminum iron silicate

- non nutritive bulking agent
- anti caking agent, blending agent, pelleting aid.

9. YELLOW PRUSSIATE OF SODA

SODIUM FERROCYANIDE DECAHYDRATE

$Na_4Fe(CN)_6$

- anti caking agent

ENZYMES

AUSTRALIA - the list includes the following enzymes. There are no recommendations regarding use.
PANCREATIN, PEPSIN, PAPAIN, PROTEASE, AMYLASE AND GUMASE.
The following is an extract from the U.K. note regarding the use of PAPAIN:

14. Papain is used in the pre-slaughter injection of animals to tenderize the meat and anlthough not an animal feed adjunct it would seem proper to regard it, since it results in residues in human food, as falling within the scope of this paper.
15. It is an enzyme extracted from the paw-paw fruit. When applied to meat, it acts on the protein molecules during cooking and makes the meat more tender than it would otherwise have been. It has been used in this way widely and for a long time but is only effective near the surface. A process introduced a few years ago consists of injecting a concentrated preparation of papain into the animal's blood system via the jugular vein about half an hour before slaughter. The blood distributes the enzyme throughout the body tissues so that if the animal is slaughtered soon after treatment, all the meat contains small quantities of the enzyme which tenderizes all the tissues when the meat is cooked.
16. The treatment can only make the meat more tender; it does not alter its appearance or flavour.
17. The liver, kidneys and tongue of a treated animal tend to disintegrate on cooking because of their high enzyme content and are therefore usually sold for

manufacturing purposes where special cooking processes can be used or where they can be included in products which do not require the meat to retain the original shape. The enzyme does not survive normal cooking.

18. The size of the injection is between 200 and 500 cc. according to the weight and age of the animal and it consists of 1 part papain and 9 parts saline solution.

19. The residues of papain in the raw meat (other than the kidneys and the liver) are not more than 5 ppm.

20. Papain is used therapeutically in humans as an aid to digestion, the dosage being 0.12 to 0.6 gm. It is also used in beer to prevent turbidity.

21. The Food Standards Committee, which is an advisory committee of independent food experts and representatives of the general public, advised the Minister of Agriculture, Fisheries and Food in February 1964, that they saw no hazard to health from the consumption of meat tenderized by the pre-slaughter injection of papain.

22. The pre-slaughter injection of papain is permitted in the United Kingdom, Australia, Canada, the United States and several other countries.

Cincinnati District (CIN-D1)

January 12, 1972

L. A. Pretz
Weston, Ohio

Bureau of Veterinary Medicine (VM-220)

DOC 11-260E, Illegal Residue in Meats
(yr memo 12/27/71)

1. On the basis of the information provided in your EIR of 12/6/71, concerning follow-up investigation, we concur with your recommendation of PA for the subject number.

2. You may wish to schedule follow-up in accordance with Compliance Program 7326.01 - Misuse of Animal Drugs: Residue in Meats and Poultry.

John C. Evans
Food and Drug Officer
Bureau of Veterinary Medicine

cc: CHI-DO
RO-10
VM-200n(Gesling)
CA-224
JCEvans/pcm/mj/1/12/72

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : VM-220

DATE: December 27, 1971

FROM : CIN-D40

SUBJECT: Doc. 011-260 E
Cattle Tissue

L. A. Pretz
Route 1
Weston, Ohio

Permanent Abeyance

Attached is a copy of an EIR of December 6, 1971, and the December 15, 1971, memorandum concerning investigation at Sandusky Dressed Beef Company. As expected, investigation after the fact has produced no facts on which to pursue any further action.

We are, therefore, placing this number in permanent abeyance and marking the file, by copy of this memorandum, for follow-up inspection in 90 days to determine what, if any, irregularities may attend any future feeding of cattle by this individual.

Robert E. Keating
Food and Drug Officer
Cincinnati District

Enclosures:
EIR 12/6/71
Insp. Mramor's Memo 12/15/71

cc:
CHI FI
R.P. Toledo

Senator KENNEDY. The subcommittee stands in recess.
(Whereupon, at 1:35 p.m., the subcommittee was recessed.)

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