REPORT OF THE
COMPTROLLER GENERAL
OF THE UNITED STATES

Use of Cancer-Causing Drugs in Food-Producing Animals May Pose Public Health Hazard: The Case of Nitrofurans

Food and Drug Administration
Department of Health, Education, and Welfare

Residues of nitrofurans--a class of animal drugs shown to cause cancer--may be present in food taken from treated animals. Some nitrofuran metabolites may also cause cancer, but the Food and Drug Administration has not obtained data on the extent of metabolite residues in food.

Continued use of nitrofurans without data showing the absence of residues of the drugs and of any cancer-causing nitrofuran metabolites in food may pose an imminent hazard to the health of man.

MWD-76-85

FEB. 25, 1976

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

The Honorable John E. Moss, Chairman
Subcommittee on Oversight and Investigations
Committee on Interstate and Foreign Commerce
House of Representatives

Dear Mr. Chairman:

In response to your May 16, 1975, request, this is our report on the Food and Drug Administration's regulation of nitrofurans, a class of animal drugs.

The Food and Drug Administration is part of the Department of Health, Education, and Welfare. As directed by your office, we obtained formal written comments on the report from the Department, but have not obtained written comments on or discussed the matters in the report with the sponsors of the drugs.

We invite your attention to the fact that this report contains a recommendation to the Secretary of Health, Education, and Welfare. As you know, section 236 of the Legislative Reorganization Act of 1970 requires the head of a Federal agency to submit a written statement on actions he has taken on recommendations to the House and Senate Committees on Government Operations not later than 60 days after the date of the report, and the House and Senate Committees on Appropriations with the agency's first request for appropriations made more than 60 days after the date of the report.

We will be in touch with your office in the near future to arrange for copies of this report to be sent to the Secretary of Health, Education, and Welfare and to the four Committees to set in motion the requirements of section 236.

Sincerely yours,

Comptroller General
of the United States

C O N T E N T S

ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
HEW	Department of Health, Education, and Welfare
NADA	new animal drug application
ppb	parts per billion

COMPTROLLER GENERAL'S REPORT

USE OF CANCER-CAUSING DRUGS IN FOOD-PRODUCING ANIMALS MAY POSE PUBLIC HEALTH HAZARD: THE CASE OF NITROFURANS

Food and Drug Administration
Department of Health, Education, and Welfare

D I G E S T

Nitrofurans are a class of animal drugs used at low levels in feed for chickens, turkeys, swine, and other animals. Their purpose is to increase resistance of the animals to disease, thereby assisting the animals' growth. These drugs also are used to fight breast or mammary gland infections in dairy cattle.

Four nitrofurans are used in food-producing animals--nitrofurazone, nihydrazone, furazolidone, and furaltadone. The Food and Drug Administration has concluded that furazolidone causes cancer--in other words, it is a carcinogen. Nitrofurazone, nihydrazone, and furaltadone are highly suspect, also as carcinogens. In addition, Food and Drug Administration officials have said that some nitrofuran metabolites are suspect carcinogens.

Accurate assessment of the health risk created by these animal drugs is particularly important. There is the possibility of long-term, low-level public exposure to residues of these drugs, and/or their metabolites, through consumption of meat, milk, or eggs from treated animals.

Continued use of nitrofurans, therefore, may pose a public health hazard where information is not available to demonstrate the absence in foods of residues of the drugs and of their metabolites.

The Secretary, Department of Health, Education, and Welfare, should consider suspending use of these four drugs where it has not been demonstrated that no residues of the drugs or of their active metabolites remain in food.

(See p. 47.)

The Federal Food, Drug, and Cosmetic Act requires that before an animal drug is introduced into interstate commerce it must be approved as safe and effective by the Food and Drug Administration.

The agency is required to prohibit use of an animal drug shown to induce cancer in humans or animals unless it can be shown that no drug residues will be found in food.

If the Secretary of Health, Education, and Welfare determines that use of an animal drug poses an imminent hazard to public health he may immediately suspend approval to market the drug and provide for an expedited hearing on the withdrawal.

When experience or new scientific data shows that use of a drug is unsafe, but its use is not determined to pose an imminent hazard to human health, the Commissioner, Food and Drug Administration, before removing the drug from the market, must provide interested parties an opportunity for a hearing.

Since 1965, the Food and Drug Administration has been aware that nitrofurans might cause cancer. On the basis of study reports submitted to the Food and Drug Administration between 1965 and 1967, the agency concluded that the drugs were tumorigenic and possibly carcinogenic. As a result, the Food and Drug Administration publicly proposed, in 1971, to withdraw its approval to market nitrofurans. (See ch. 2.)

On the basis of additional studies (in November 1973 and March 1974), the Food and Drug Administration concluded that furazolidone was a carcinogen and that nihydrazone, nitrofurazone, and furaltadone were highly suspect carcinogens. (See ch. 3.)

Other studies have demonstrated that nitrofuran residues may remain in food when the drugs are used in accordance with label directions. However, no tests have been performed to determine the extent of such residues in marketed food since there are no approved methods for detecting nitrofuran residues. (See ch. 4.)

Data indicates that nitrofurans metabolize rapidly and that some of the metabolites may be carcinogenic. The Food and Drug Administration has not obtained data on the extent of metabolite residues in food. (See ch. 4.)

As of February 1, 1976, the Food and Drug Administration had neither held nor denied a hearing on the 1971 proposal to remove the nitrofurans from the market. (See p. 17.)

The Department of Health, Education, and Welfare advised that the Commissioner, Food and Drug Administration, believes that publication in the near future of a revised Notice of Opportunity for Hearing--rather than immediate suspension--is the best course of action to resolve the nitrofuran safety question.

Under the strict interpretation of imminent hazard used by the Food and Drug Administration, the Department said that continued use of nitrofurans during the time required for administrative resolution does not pose an imminent hazard to human health.

Although the decision to suspend a product as an imminent hazard rests with the Secretary of Health, Education, and Welfare, GAO believes that the Federal Food, Drug, and Cosmetic Act and recent court decisions support the use of an interpretation of imminent hazard that is more liberal than that stated by the Department. (See pp. 47 to 49.)

CHAPTER 1

INTRODUCTION

By letter dated May 16, 1975, the Chairman, House Subcommittee on Oversight and Investigations, Committee on Interstate and Foreign Commerce, requested that we review the Food and Drug Administration's (FDA's) regulation of nitrofurans. ACC 148

WHAT ARE NITROFURANS?

Nitrofurans 1/ are a class of drugs used at low levels in animal feed as antibacterial and antiprotozoan agents to increase resistance to disease, thereby assisting growth. They are also used in dairy cattle to treat mastitis (an infection of the mammary glands).

Four nitrofurans are used in food-producing animals--nitrofurazone (NF-7), nihydrazone (NF-64), furazolidone (NF-180), and furaltadone (NF-260). Several other nitrofurans are used in non-food-producing animals.

In addition to being used in animal drugs, some nitrofurans are also used in human drugs, including drugs for treatment of vaginal infections and prevention of infection in burn patients. Regulatory actions relating to nitrofurans in human drugs have been considered in this review only to the extent that they effect regulation of nitrofurans in animal drugs.

1/ For the purposes of this report, nitrofurans will refer specifically to the 5-nitrofuran derivatives used in animal drugs. They are derived from furan, a colorless organic liquid obtained from wood tar or other organic substances. Furan's chemical structure is represented as a closed cycle, or ring, composed of four carbon atoms and one oxygen atom bonded together. Positions on the ring are numbered counterclockwise beginning with the oxygen atom. A hydrogen atom is attached to each carbon atom in the furan ring. Presently used nitrofuran animal drugs are formed when a nitro group (a chemical radical, NO2, composed of two oxygen atoms and one nitrogen atom) replaces the hydrogen atom in the fifth position of the furan ring, and a more complex chemical radical replaces the hydrogen atom in the second position.

Only one U.S. company--Norwich Pharmacal Company, Division of Morton-Norwich Products, Inc.--manufactures and markets the four nitrofurans used in food-producing animals. Hess and Clark, Division of Rhodia, Inc. 1/ markets nitrofurans.

REGULATION OF ANIMAL DRUGS

FDA, of the Department of Health, Education, and Welfare (HEW), administers the Federal Food, Drug, and Cosmetic Act, as amended (FD&C Act) (21 U.S.C. 301 et seq.). The FD&C Act requires that a person (a manufacturer or other individual or group seeking to ship a new animal drug in interstate commerce) file a new animal drug application (NADA) with FDA and obtain its approval before introducing such products into interstate commerce. FDA must approve the drug for both safety and effectiveness. If the new animal drug is to be used in food-producing animals, FDA must also approve the safety of any drug-related residues in food.

The FD&C Act (21 U.S.C. 321(w)) defines a new animal drug, in pertinent part, as any drug intended for use in animals other than man:

> "(1) the composition of which is such that such drug is not generally recognized * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * * or
>
> (2) the composition of which is such that such drug, as result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which had not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions; * * *"

1/ Hess and Clark was formerly a division of Richardson-Merrill, Inc.

FDA's regulatory authority over new animal drugs was broadened by the 1958 Food Additive Amendments (Public Law 85-929) to the FD&C Act, which authorized FDA to issue regulations prescribing the conditions under which an animal drug may be safely used in food-producing animals. This authority was clarified by the 1968 Animal Drug Amendments to the FD&C Act (Public Law 90-399).

FDA regulations (21 C.F.R. 514.1 et seq.) require that any animal drug residue in meat, milk, or eggs be proven safe and that FDA set a limit, or tolerance, on the amount of the drug allowable in food. FDA is also authorized to establish a withdrawal period before slaughtering an animal or taking any food yielded by or derived from the animal during which time the animal drug may not be administered (21 U.S.C. 360(i)).

In addition, the FD&C Act provides that no regulation be issued permitting an animal drug to be used if it is found to induce cancer when ingested by man or animal unless it can be shown that no drug residues will be found in food. This prohibition is known as the Delaney Clause (21 U.S.C. 360b (d)(1)(H)).

FDA's Bureau of Veterinary Medicine has primary responsibility for reviewing NADAs which are submitted to demonstrate the safety and effectiveness of new animal drugs. FDA's Bureau of Foods assists the Bureau of Veterinary Medicine by reviewing data submitted to demonstrate the safety of any drug-related residues in food. 1/

1/ The Bureau of Veterinary Medicine was established on Jan. 1, 1966. Before then, the Bureau of Medicine had responsibility for regulating both human and animal drugs.

The Bureaus of Foods and Drugs were established Feb. 1, 1970. Before then, the functions of the Bureaus of Foods and Drugs were divided among the former Bureaus of Medicine, Science, and Compliance.

FDA regulations (21 C.F.R. 514.1) specify that the NADA must include

--copies of all labeling to be used for the new animal drug;

--a complete list of all articles used in producing the drug, including a list of each article's composition;

--a full description of the methods used in, and the facilities and controls used for, manufacturing, processing, and packaging the drug;

--a description of practicable methods for determining the quantity, if any, of the drug in or on food, any substance formed in or on food through its use, and any tolerance or other use restrictions required to assure that, when used as proposed, the drug will be safe; and

--full reports of investigations made regarding the drug's safety and effectiveness.

After an NADA has been approved, additional uses for the drug or changes in the directions for its use must be approved through a supplemental NADA. FDA has not been willing to approve a supplemental NADA unless the drug's safety and effectiveness could be established under the conditions of use contained in the supplemental NADA.

A holder of an approved NADA is required to submit periodically a "Drug Experience Report," including information on (1) any new studies relating to the drug, (2) any adverse reactions to the drug that have been reported to the holder, and (3) the amount of the drug distributed during the preceding year (21 U.S.C. 360b (1) (1); 21 C.F.R. 510.300).

The FD&C Act (21 U.S.C. 360b(e)(1)) and FDA regulations (21 C.F.R. 514.115) permit the Secretary, HEW, to suspend approval of an NADA if the Secretary determines that use of the animal drug as intended creates an imminent hazard to the health of man. The holder of the NADA is to receive prompt notification of this action and an opportunity for an expedited hearing on the suspension.

According to FDA regulations (21 C.F.R. 3.73) an imminent hazard to the public health exists when:

> " * * * the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is held."

The FDA regulations further state that:

> "The 'imminent hazard' may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurance of the final anticipated injury is not essential to establish that an 'imminent hazard' of such occurance exists."

If an animal drug does not pose an imminent hazard to public health, but experience or new scientific data shows the drug to be unsafe under its approved conditions of use, the Commissioner, FDA, is required, after notifying the NADA holder of the findings and affording him an opportunity for a hearing, to issue an order withdrawing approval of the NADA (21 U.S.C. 360b(e)(1)).

A Notice of Opportunity for Hearing, which is published in the "Federal Register," affords the NADA holder and other interested parties 30 days to file objections to FDA's proposed actions and to request a hearing to discuss their objections. FDA can either grant a hearing if it determines that the request raises issues of fact or deny a hearing if it finds that the request raises no valid issues (21 C.F.R. 514.200).

Approval of nitrofuran NADAs

Between 1948 and 1963, FDA approved NADAs for the use of the four nitrofurans--nitrofurazone, nihydrazone, furazolidone, and furaltadone--in food-producing animals.

In 1948 FDA approved an NADA for nitrofurazone, the first nitrofuran approved for use in food-producing animals. Nitrofurazone is approved for use in (1) mastitis products for dairy cattle (dry cow treatment only), (2) suppositories for vaginal infections in large animals, and (3) medicated swine, chicken, turkey, and mink feed for prevention and control of bacterial enteritis (a disease

causing diarrhea and inflammation of the intestines).

The initial NADA for furazolidone was approved in 1953. Furazolidone is approved for use in medicated feeds for chickens, turkeys, swine, and rabbits for the treatment of bacterial enteritis and CRD (a protozoan disease).

Furaltadone was approved in 1962 for treatment of mastitis in dairy cattle through injections into the mammary glands.

Nihydrazone was approved in 1963 for use in medicated chicken feeds for prevention of a number of diseases.

CHAPTER 2

SAFETY OF NITROFURANS NOT ESTABLISHED

The FD&C Act requires FDA to withdraw its approval to market an animal drug if scientific data shows the drug to be unsafe under the conditions of use approved in the NADA. A decision regarding the safety of an animal drug depends not only on the drug's toxicological properties, but also on the extent of the drug-related residues in food.

In April 1965 FDA was notified of the nitrofurans' possible tumorigenicity. When subsequent studies confirmed their tumorigenicity, FDA, in March and August 1971, issued Notices of Opportunity for Hearing proposing to withdraw approval of the NADAs for nitrofurazone, nihydrazone, furazolidone, and furaltadone for use in food-producing animals (36 F.R. 5926-5927, Mar. 31, 1971; 36 F.R. 14343, Aug. 4, 1971).

As of February 1, 1976--about 4 years after FDA proposed withdrawing approval of the nitrofuran NADAs and about 10 years after the question of their possible tumorigenicity was raised--FDA had not published a final order concerning the safety of nitrofuran use in food-producing animals.

INITIAL NOTIFICATION OF POSSIBLE CARCINOGENICITY

In April 1965 a University of Wisconsin scientist notified FDA that results of studies at the university (see p. 22) indicated that nitrofurazone might be tumorigenic. In June 1965 FDA, HEW's National Cancer Institute, Norwich, and the university scientists met to discuss the findings of the university scientists.

Following these discussions, Norwich began studying the effects of long-term feeding of furazolidone, furaltadone, nitrofurazone, and nihydrazone to rats. Norwich submitted to the Bureau of Veterinary Medicine, as part of a June 2, 1967, "Drug Experience Report," a report on the results of those studies. (See p. 23.) A Bureau employee who reviewed the "Drug Experience Report" notified the Director, Division of Veterinary Medical Review, by memorandum dated June 27, 1967, that according to the Norwich report, a significantly higher incidence of mammary tumors occurred in rats fed furazolidone than

in the control rats fed a furazolidone-free diet. The memorandum did not discuss the results of tests using the three other nitrofurans.

Norwich also furnished the Bureau of Drugs a copy of its report. By letter dated August 30, 1968, the Bureau of Drugs advised Norwich that its review of the report indicated that all four nitrofurans were possibly tumorigenic. The Bureau of Drugs recommended that Norwich perform additional testing on the nitrofurans using a protocol furnished by the Bureau.

The Bureau of Veterinary Medicine received a copy of the Bureau of Drugs letter to Norwich. The Bureau of Veterinary Medicine subsequently obtained a copy of the Bureau of Drugs file on nitrofuran tumorigenicity and forwarded it to the Bureau of Foods for review on October 7, 1968.

On November 6, 1968, Hess and Clark, during a meeting with the Bureaus of Foods and Veterinary Medicine, indicated that on February 17, 1967, it had submitted, as part of a "Drug Experience Report" to the Bureau of Veterinary Medicine, a report on a 2-year study of furazolidone fed to rats. (See p. 24.) According to a Bureau of Veterinary Medicine official, the Bureau was not aware of the study report before the meeting with Hess and Clark because it lacked the staff to review "Drug Experience Reports." Following the Hess and Clark meeting, the Bureau of Veterinary Medicine forwarded the report to the Bureau of Foods for review.

On December 18, 1968, a Bureau of Foods veterinarian notified the Bureau of Veterinary Medicine that data in the Hess and Clark study showed that furazolidone was carcinogenic. He further stated that there was sufficient data to implicate nitrofurans as carcinogens or having carcinogenic potential.

In a May 7, 1969, memorandum to the FDA Commissioner, the Director, Bureau of Veterinary Medicine, stated that the Bureau did not consider nitrofurans to be an imminent health hazard, but noted that the Delaney Clause would have to be recognized if any of the drugs were determined to be carcinogenic. He recommended that FDA initially focus its attention on the mastitis products because of the importance of milk in the diet. He further recommended that:

"For other products concluded to be carcinogenic but for which data are inadequate to satisfy the provisions of section 409(c)(3)(A) [Delaney Clause] of the Act, furnish industry an opportunity to submit adequate data before removing such products from the market."

On June 4, 1969, a Bureau of Foods official notified FDA's Associate Commissioner for Science that the Bureau could not definitely conclude that three of the nitrofurans (nitrofurazone, nihydrazone, and furaltadone) were carcinogenic. He recommended additional long-term studies on their carcinogenicity.

ADVISORY COMMITTEES REVIEW
NITROFURAN CARCINOGENICITY

On June 24, 1969, the FDA Commissioner directed FDA's Associate Commissioner for Science to submit the question of nitrofuran carcinogenicity to the Interdepartmental Technical Panel on Carcinogens for review. The panel included representatives from FDA, the National Cancer Institute, and the U.S. Department of Agriculture.

After reviewing studies by Norwich, Hess and Clark, and the University of Wisconsin, the Interdepartmental Technical Panel notified the FDA Commissioner on August 14, 1969, that evidence was inadequate to make a definitive ruling on the nitrofurans' carcinogenicity. However, the panel concluded that these drugs generally induced mammary tumors, and recommended that chronic toxicity studies of at least 18 months duration be performed. It also recommended that studies be performed on rats and mice to determine whether the drug or its metabolites build up in certain organs or tissues and that regulations be issued requiring that nitrofurans be withdrawn from animal feed 21 days before slaughter of the animal to prevent transmission of metabolites to humans.

On October 21, 1969, the Bureau of Veterinary Medicine briefed FDA's Associate and Deputy Associate Commissioners for Science on the status of nitrofurans. Both officials had assumed their positions since issuance of the Interdepartmental Technical Panel's report on nitrofurans.

Because most of the Interdepartmental Technical Panel's members had retired and there was disagreement among FDA scientists on the carcinogenicity of the nitrofuran drugs, FDA's Associate Commissioner for Science on November 25, 1969, asked the Director, Bureau of

Veterinary Medicine, to consider establishing another ad hoc committee to review the nitrofurans. The Director, in a December 5 memorandum to the Associate Commissioner, agreed to establish an ad hoc committee because he felt that these drugs were extremely important to certain companies.

The ad hoc committee, established on December 11, was composed of two members from the National Cancer Institute and a member from the University of Nebraska's Eppley Institute for Research in Cancer. The three members were nominated by the Director, Bureau of Veterinary Medicine, with the concurrence of the Bureau of Foods. One committee member from the National Cancer Institute had also been a member of the Interdepartmental Technical Panel.

The ad hoc committee did not issue a formal report on its evaluation of the nitrofurans.

By letter dated January 19, 1970, the two National Cancer Institute committee members advised the Bureau of Veterinary Medicine that they had completed reviewing reports on studies concerning nitrofuran tumorigenicity. They stated that the drugs should not go into man by any route for any extended period of time until additional chronic testing was completed. However, they agreed with the use of the drugs in animals with a 5-day withdrawal period providing data was available showing that residues from such use were negligible.

The member from the Eppley Institute reviewed mammary tissue slides from the Norwich and Hess Clark studies as well as the study reports and in a June 5, 1970, telephone conversation, he advised the Bureau of Veterinary Medicine that his review of the slides showed all four nitrofurans to be carcinogenic.

Consequently, on June 19, 1970, the Director, Bureau of Veterinary Medicine, forwarded to FDA's Acting Associate Commissioner for Compliance a proposed order withdrawing approval to market the four nitrofurans. However, on June 22, the Director, Bureau of Veterinary Medicine, asked the Acting Associate Commissioner to delay any action regarding withdrawal of the nitrofuran NADAs for about 10 days to allow one of the National Cancer Institute committee members to review the findings of the Eppley Institute committee member. The other committee member from the National Cancer Institute was out of the country and did not participate in the additional review.

After the National Cancer Institute committee member completed his review, he recommended to the Bureau of Veterinary Medicine, by letter dated July 29, that FDA (1) withdraw the animal drug uses of nitrofurans where significant amounts of the nitrofurans or their active metabolites were likely to remain in food and (2) permit continued use of nitrofurans while chronic toxicity studies were being performed where there was no demonstrable residue of the nitrofuran or its active metabolites in food.

On August 31, 1970, the Director, Bureau of Veterinary Medicine, sent the ad hoc committee members a draft memorandum he proposed to send to the FDA Commissioner. The draft memorandum cited the inability of the two advisory committees to decisively conclude that the nitrofurans were carcinogenic and proposed that (1) no action be taken to withdraw the drugs from the market, (2) Norwich be required to complete or initiate additional carcinogenicity studies, and (3) FDA's final decision on carcinogenicity be withheld until the additional studies were completed. The Director indicated that the above actions were justified because available data showed that significant residues of nitrofurans did not remain in food.

The committee members from the National Cancer Institute, in a September 3 memorandum to the Director, agreed with the proposal that no withdrawal action be taken provided the four nitrofurans were used only under such conditions that no residue, measurable by available procedures, be present in products for human consumption.

The ad hoc committee member from the Eppley Institute in a September 10 letter to the Director, Bureau of Veterinary Medicine, strongly disagreed with the proposed course of action. In his letter he stated:

> "I have no question or doubt from the material presented so far that these compounds are carcinogenic and cannot understand your conclusion."

In a September 15 memorandum, a Bureau of Drugs veterinarian provided the Bureau of Foods' Division of Toxicology estimates on safe levels of nitrofurans. He stated that the Hess and Clark study submitted to FDA in 1967 demonstrated that furazolidone was carcinogenic. The safe levels, computed from both the Hess and Clark and the Norwich studies submitted to FDA in 1967, were less than 2 parts per billion (ppb) for all four nitrofurans, assuming the drugs were only tumorigenic and not carcinogenic. The veterinarian stated:

" * * * I find it very difficult to understand the Bureau of Veterinary Medicine's reluctance to act on the recommendation of the Division of Toxicology made more than a year ago that these agents should be considered as hazardous from a tumorigenesis point of view * * * they have no place in the treatment of food-producing animals."

The Director, Bureau of Foods, notified the Director, Bureau of Veterinary Medicine, by memorandum dated October 13, 1970, that he objected to the Bureau of Veterinary Medicine's August 31 draft memorandum to the FDA Commissioner. He stated that the Bureau of Foods considered all four nitrofurans tumorigenic and probably carcinogenic and that they should be removed from the market until it was either proven that they were non-carcinogenic or that there were no harmful residues present in food.

In a November 12 memorandum to FDA's Associate Commissioner for Medical Affairs, the Director, Bureau of Veterinary Medicine, recommended that furazolidone and nitrofurazone be withdrawn from the market. The memorandum also contained data on nihydrazone residues in chicken tissues and furaltadone residues in milk, but made no recommendation concerning their disposition.

In a November 17 memorandum to FDA's Associate Commissioner for Medical Affairs, the Deputy Director, Bureau of Foods, recommended that all four nitrofurans be withdrawn from the market.

After reviewing the above recommendations, FDA's Associate Commissioner for Medical Affairs recommended to the FDA Commissioner, in a November 27 memorandum that immediate action be taken to withdraw the use of all four nitrofurans in food-producing animals. The Director, Bureau of Veterinary Medicine, notified Norwich and Hess and Clark of the proposed action on December 14.

On the same day, a Norwich representative telephoned the Associate Commissioner for Medical Affairs to request a meeting to discuss the status of the nitrofurans. According to an FDA memorandum of the telephone conversation, the Norwich representative maintained that the action being planned by the Bureau of Veterinary Medicine " * * * was contrary to the spirit of discussions that he had had with the Commissioner * * * ." A meeting was later scheduled between Norwich and the Bureaus of Foods and Veterinary Medicine.

In a January 4, 1971, meeting between Norwich, Hess and Clark, and the Bureaus of Foods and Veterinary Medicine, Norwich proposed as an alternative to removing the nitrofurans from the market that their labeling be revised to delete certain uses and add or extend withdrawal periods for other uses. (See pp. 37 and 40.) Norwich also proposed to develop improved methods for detecting nitrofuran residues. By letters dated January 7 and 8, 1971, Hess and Clark and Norwich, respectively, submitted supplemental NADAs to the Bureau of Veterinary Medicine proposing more restrictive uses for their nitrofuran products. Norwich also made a commitment to develop a method for detecting nitrofuran residues that is sensitive to 2 ppb.

NOTICES OF OPPORTUNITY FOR HEARING

At a February 1, 1971, meeting between Norwich, Hess and Clark, and the Bureaus of Foods, Drugs, and Veterinary Medicine, the Bureau of Foods agreed that withdrawal action would be withheld on furazolidone and furaltadone if (1) residue depletion data was adequate to substantiate the withdrawal periods proposed by Norwich and Hess and Clark, (2) the methods for detecting residues were found to be practical for regulatory purposes, and (3) the companies extended the withdrawal periods as proposed in January 1971. The Bureau of Foods, however, recommended that nitrofurazone and nihydrazone be removed from the market because no new methods for detecting their residues had been submitted to FDA.

On March 31, 1971, FDA issued Notices of Opportunity for Hearing proposing to withdraw approval of NADAs for nitrofurazone and nihydrazone. Joint requests for a hearing on both nitrofurazone and nihydrazone were filed by Norwich and Hess and Clark on April 29, 1971.

In a June 7, 1971, memorandum to the Director, Bureau of Veterinary Medicine, the Director, Bureau of Foods, recommended that furazolidone and furaltadone be withdrawn from the market because adequate methods for detecting their residues in food had not been developed. Subsequently, on July 1, 1971, the Director, Bureau of Veterinar Medicine, forwarded a memorandum to the FDA Commissioner recommending that furazolidone and furaltadone be withdrawn from the market.

Accordingly, on August 4, 1971, FDA issued Notices of Opportunity for Hearing proposing to withdraw approval of NADAs for furazolidone and furaltadone. Requests for a

hearing on both furazolidone and furaltadone were filed by Hess and Clark on August 31 and by Norwich on September 3.

ACTIONS TO DENY A HEARING

In a July 21, 1971, memorandum to FDA's Chief Counsel, the Director, Bureau of Veterinary Medicine, recommended that Norwich and Hess and Clark be denied a hearing on nitrofurazone and nihydrazone. The Office of Chief Counsel, on September 21, suggested that the Bureau of Veterinary Medicine evaluate the data submitted in response to the furazolidone and furaltadone notices before proceeding with withdrawal action against nitrofurazone and nihydrazone. The Office of Chief Counsel said it would be willing to proceed to withdraw approval of nitrofurazone and nihydrazone NADAs if the Bureau of Foods would state in writing that methods for detecting furazolidone and furaltadone residues could not be adapted to detect nitrofurazone and nihydrazone residues.

In an October 28, 1971, memorandum to the Bureau of Veterinary Medicine, a Bureau of Foods chemist stated that it would be pure conjecture as to whether the furazolidone residue detection method could be adapted to detect nitrofurazone and nihydrazone residues. The memorandum did not state whether the furaltadone residue detection method could be adapted to detect nitrofurazone and nihydrazone residues.

FDA's Associate Chief Counsel for Veterinary Medicine told us that he was not aware of the October 28 memorandum, but that it would not have provided adequate grounds for denying a hearing because it did not specifically state why the furazolidone residue detection method was not adaptable to nitrofurazone and nihydrazone.

In a December 28, 1971, memorandum, the Director, Bureau of Veterinary Medicine, asked FDA's Chief Counsel for instructions on the proper course of action regarding nitrofurans. The Director stated that no definite conclusions could be reached on the acceptability of the proposed methods for detecting furazolidone and furaltadone residues or on their adaptability for detecting nitrofurazone and nihydrazone residues because the Bureau of Foods had a number of questions concerning these methods that needed to be resolved by Norwich.

At a February 17, 1972, meeting with the Bureau of Veterinary Medicine, the Office of Chief Counsel suggested that the Bureau of Foods contact Norwich to resolve its

questions on the furazolidone and furaltadone residue detection methods. The Office of Chief Counsel stated that FDA need not prove that the methods of analysis were not good, only that Norwich had not proven to FDA's satisfaction that they were good.

The Bureaus of Foods and Veterinary Medicine met with Norwich on March 8, 1972, to discuss the Bureau of Foods' questions concerning the furazolidone and furaltadone residue detection methods. Subsequently, on April 5, Norwich submitted to FDA revised methods for detecting furazolidone and furaltadone residues.

On April 26 the Bureau of Foods notified the Bureau of Veterinary Medicine that, with a few changes, the revised methods for detecting furazolidone and furaltadone residues would be ready for physical trials to determine the methods' suitability for regulatory purposes.

Because of the forthcoming physical trials, the Bureau of Veterinary Medicine, in a May 12 memorandum, asked the Office of Chief Counsel to delay, until after the trials, action on removing furazolidone and furaltadone from the market. The Bureau also asked that action on removing nitrofurazone and nihydrazone from the market be delayed because the residue detection methods for furazolidone and furaltadone should be adaptable to the other two drugs.

After completion of the physical trials, the Bureaus of Foods and Veterinary Medicine and the Department of Agriculture met on December 19, 1972, and agreed that the trials showed that the method for detecting furazolidone residues was unacceptable, and that questions regarding the residue detection methods would require many time-consuming studies to answer.

On March 7, 1973, the Bureau of Foods advised the Bureau of Veterinary Medicine that the method for detecting furaltadone residues in milk was acceptable and that a method for detecting furaltadone residues in tissues would be needed unless Norwich could show that tissue residues resulting from using furaltadone as a mastitis treatment would not exceed 10 times the residue level in milk.

Following a meeting with the Bureaus of Foods and Veterinary Medicine on March 30, FDA's Chief Counsel determined that before FDA could justify denial of a hearing, FDA must (1) reach a final determination on nitrofuran carcinogenicity, (2) determine whether Norwich

had proven that nitrofuran residues do not occur under the conditions of use stated on the product labels, and (3) determine whether practical regulatory methods of sufficient sensitivity for detecting nitrofuran residues were available.

To resolve these issues, FDA's Chief Counsel suggested that the Bureau of Foods review (1) the mammary tissue slides from the Norwich and Hess and Clark studies, (2) all available safety data to determine if a "no effect" 1/ level could be established, and (3) all available residue data to determine whether any residues would occur in food from using the nitrofurans according to label directions.

On October 15, 1973, the Bureau of Foods, based on its reviews, concluded that furaltadone was carcinogenic, furazolidone was highly suspected of being carcinogenic, and that all four nitrofurans were tumorigenic. The Bureau recommended that:

--Furazolidone, nitrofurazone, and nihydrazone be withdrawn from the market because methods for detecting residues of the drugs sensitive to 2 ppb had not been developed.

--The method for detecting furaltadone residues in milk be accepted, but that a withdrawal period be added to preclude the possibility of furaltadone residues in edible tissues of slaughtered cows.

On October 24 FDA's Chief Counsel met with the Bureaus of Foods and Veterinary Medicine to discuss the Bureau of Foods' recommendations. It was agreed that the Bureau of Veterinary Medicine would ask Norwich to submit all available data on carcinogenicity studies, new methods for detecting furazolidone, nitrofurazone, and nihydrazone residues, and a method for detecting furaltadone residues in tissue. After receipt and review of such data, FDA was to take action against the four drugs as recommended by the Bureau of Foods on October 15. The Bureau of Foods was to prepare a summary of safety and residue data for use in preparing new Notices of Opportunity for Hearing on

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1/ A "no effect" level refers to a level of exposure to a chemical at or below which no adverse effects result from exposure to the chemical.

furazolidone, nitrofurazone, and nihydrazone. The Bureau of Veterinary Medicine was to prepare a document vacating the Notice of Opportunity for Hearing on furaltadone and providing Norwich 1 year to submit a method for detecting furaltadone residues in tissues.

The Bureau of Veterinary Medicine subsequently asked Norwich to submit additional data. Norwich submitted new carcinogenicity studies and methods for detecting residues. According to a Bureau of Veterinary Medicine official, the Bureau of Foods did not complete its review of the data obtained from Norwich until December 30, 1974.

On April 25, 1974, a Bureau of Foods official notified the Office of Chief Counsel that one of the issues Norwich raised in its response to the 1971 Notices of Opportunity for Hearing was complex and might result in differing opinions. The Bureau official stated that FDA might not be able to deny Norwich's request for a hearing until a determination was made on the validity of Norwich's claim that nitrofuran tumorigenicity was related to hormonal imbalance. (See p. 31.)

On February 28, 1975, about 16 months after it was agreed that the Bureau of Veterinary Medicine would prepare a document vacating the Notice of Opportunity for Hearing on furaltadone, FDA's Chief Counsel and the Bureaus of Foods and Veterinary Medicine met again. The Bureau of Veterinary Medicine was directed to vacate the notice on furaltadone and spell out the conditions of acceptance of the methods for detecting furaltadone residues in milk. It was also determined that FDA would publish new Notices of Opportunity for Hearing proposing withdrawal of approval of NADAs for the other three nitrofurans.

As of February 1, 1976, neither the notice permitting furaltadone to remain on the market nor the new notice proposing withdrawal of the other three nitrofurans had been issued.

REASONS FOR DEFERRING SAFETY DETERMINATION

As of February 1, 1976, more than 4 years after the 1971 Notices of Opportunity for Hearing were issued, FDA had not held a hearing to determine the safety of nitrofuran use in food-producing animals.

The Notices of Opportunity for Hearing stated that if a hearing was requested and was justified by the objections

filed in response to the notices, the issues to be discussed in the hearing would be defined, a hearing examiner would be named, and the hearing would begin within 120 days after issuance of the notice. The notices further stated that the start of the hearing could be delayed only by mutual consent of the hearing examiner and the parties requesting the hearing.

According to FDA's Associate Chief Counsel for Veterinary Medicine, FDA does not usually meet the 120-day requirement for starting hearings. He explained that before FDA can make a decision, it must determine whether the hearing requests raise valid issues justifying a hearing. He said that the time required to make such a determination and prepare for a hearing depends on the case's complexity. He emphasized that FDA must have a firm legal case before initiating or denying a hearing. According to him, it was the lack of consensus on scientific issues and the vagueness of the 1971 Notices of Opportunity for Hearing that prevented FDA from scheduling or denying a hearing on the proposed withdrawal of the nitrofuran NADAs.

In attempting to identify and resolve the scientific issues which could be raised in response to the 1971 notices, the Office of Chief Counsel has directed the Bureaus of Foods and Veterinary Medicine to continue accepting and reviewing data from Norwich concerning nitrofuran safety and methods for detecting residues.

Lack of consensus on scientific data

According to FDA's Associate Chief Counsel for Veterinary Medicine, scientific data on nitrofurans has been slow in developing and, as a result, there has been a lack of a consensus on scientific issues. He said that FDA had not resolved the issue of nitrofuran carcinogenicity.

He indicated that to have a strong case for removing nitrofurans from the market, FDA must identify and resolve any issues which Norwich or Hess and Clark may raise at a hearing. He said that FDA's Chief Counsel has questioned FDA scientists in an attempt to establish an FDA position on the scientific issues involved, but has been unable to get satisfactory answers. The Bureau of Foods has been asked to perform reviews to develop additional scientific data needed to resolve some of the issues.

The Bureau of Foods' Assistant to the Associate Director for Sciences, agreed that there was a lack of a consensus on the scientific issues when the Bureau met with Chief Counsel in October 1973. She cited the advisory committees' inability to conclude that the nitrofurans were carcinogenic and FDA's difficulty in justifying the requirement that residue detection methods be sensitive to 2 ppb. She said that the question of furazolidone carcinogenicity had been resolved by the Norwich studies submitted to FDA in November 1973 and March 1974 and that adequate justification for requiring a 2 ppb sensitivity for residue detection methods was being developed. She attributed the past year's delays to insufficient resources in the Bureau of Foods to prepare the necessary documentation and new Notices of Opportunity for Hearing proposing to withdraw NADAs for furazolidone, nitrofurazone, and nihydrazone rather than to deficiencies in the scientific data supporting withdrawal.

FDA's Associate Chief Counsel for Veterinary Medicine pointed out that there have been significant changes in scientific knowledge affecting nitrofurans since the 1971 Notices of Opportunity for Hearing. He stated that the issue of nitrofuran carcinogenicity was not raised in the 1971 notices and that significant developments in drug residue detection methods have also affected the nitrofuran case.

Notices of Opportunity for Hearing too vague

According to FDA's Associate Chief Counsel for Veterinary Medicine, when the 1971 notices on the proposed withdrawal of the nitrofuran NADAs were issued, FDA's Chief Counsel generally allowed FDA bureaus to prepare and publish "Federal Register" notices with little guidance from the Office of Chief Counsel as long as they were written in accordance with FDA's statutory authority. He stated that when the 1971 notices were issued, FDA's Chief Counsel did not attempt to identify legal issues which might arise in the future, but chose to confront them as they arose. Under this policy, Notices of Opportunity for Hearing were short and written in general terms.

The 1971 notices prepared by the Bureau of Veterinary Medicine stated only that the nitrofurans had caused tumors in laboratory animals and that a method for detecting nitrofuran residues of adequate sensitivity was not available. The notices did not describe the studies on which FDA had based its proposal to remove the nitrofurans from the market or the level of sensitivity needed.

According to FDA's Associate Chief Counsel for Veterinary Medicine, he first realized that the 1971 notices were not specific enough when he met with the Bureau of Veterinary Medicine in September 1971 to discuss the possibility of denying a hearing on nitrofurazone and nihydrazone. He stated that because the March and August 1971 notices were written in general terms, FDA could not restrict a hearing to the specific issues raised in Norwich's and Hess and Clark's requests for a hearing. He cited the diethylstilbestrol (DES) case (Hess and Clark v. FDA, 495 F.2d 975 (D.C. Cir. 1974)) in which the manufacturer successfully argued that the Notice of Opportunity for Hearing was too vague to enable it to identify the issues being raised by FDA.

The Associate Chief Counsel indicated it was difficult to prepare for or deny a hearing under a vague notice because FDA must develop scientific data adequate to resolve any issues which might be raised in a hearing. He stated that the need to develop additional scientific data has delayed action on withdrawal of the nitrofuran NADAs. He further indicated that FDA does not like to hold hearings under Notices of Opportunity for Hearing as vague as those for the nitrofurans because the expense of manpower and time required to prepare for and hold such hearings does not benefit the public.

The Associate Chief Counsel said that since late 1971 there has been a trend toward making Notices of Opportunity for Hearing more specific. He stated that the Office of Chief Counsel now takes an active part in drafting "Federal Register" notices--attempting to identify and resolve issues which might be raised at a hearing. He believed that more specific notices limit the issues which might be raised in a request for hearing and give the public a better understanding of FDA's position.

Cutoff for submissions not enforced

In attempting to identify and resolve the scientific issues which might be raised at a hearing, FDA continued to accept and review data on nitrofuran safety and methods for detecting residues after the cutoff date for such submissions. The 1971 notices gave interested parties 30 days in which to request a hearing and submit supporting data.

In an October 20, 1971, memorandum to the Director, Bureau of Veterinary Medicine, concerning the time given Norwich to respond to the 1971 notices, a Bureau official

stated that:

> "It has been over 180 days for NF-7 [Nitrofurazone] and NF-64 [Nihydrazone], and over 70 days for NF-180 [Furazolidone] and NF-260 [Furaltadone]. At this point in time I wish to know when is the cut-off date for the receipt and review of additional data? Without a cut-off date, we will be unable to provide General Counsel with a concluding summary in regard to these products."

Subsequently, the Director, Bureau of Veterinary Medicine, notified Norwich in an October 28, 1971, letter that no data would be accepted in response to the March and August 1971 notices after November 10, 1971.

An attorney from FDA's Office of Chief Counsel, however, told the Bureau of Foods in April 1973 that FDA cannot refuse to accept and review additional data until a final decision is made regarding removal of the nitrofurans from the market. Additional data concerning nitrofuran safety and methods for detecting residues subsequently submitted by Norwich has been accepted and reviewed by FDA.

FDA's Associate Chief Counsel for Veterinary Medicine told us that the October 28, 1971, letter to Norwich probably should not have been issued because it is not in accordance with FDA policy. He stated that FDA will not refuse to accept additional submissions as long as they are submitted in accordance with FDA regulations. He added that FDA will review any submission received before it begins analyzing the hearing request, but may refuse to review studies submitted after that. Furthermore, if a party requesting a hearing states that it has studies in progress, FDA will review such data when submitted. In addition, FDA will not refuse to review changes or improvements to previously submitted methods for detecting drug residues.

The Assistant to the Associate Director for Sciences, Bureau of Foods said that Norwich reports on carcinogenicity studies, submitted to FDA in November 1973 and March 1974, have resolved the question of nitrofuran carcinogenicity. (See pp. 22 to 35.) Other Norwich submissions accepted and reviewed since the cutoff date appear to demonstrate that nitrofuran residues are likely to remain in food. (See pp. 36 to 45.)

CHAPTER 3

STUDIES CONCERNING THE SAFETY OF NITROFURANS

In 1965 FDA was notified of the results of investigations by University of Wisconsin scientists which raised questions about the carcinogenicity of nitrofurans. Since that time a number of animal studies have been made to evaluate the safety of nitrofurans for use in human and animal drugs. We reviewed studies directed at the chemical's (1) tumorigenic and/or carcinogenic effects and (2) physiological effects on body functions.

INITIAL CARCINOGENICITY STUDIES

Between 1965 and 1967, the University of Wisconsin, Norwich, and Hess and Clark reported to FDA the results of six studies on the long-term toxicity of nitrofurans. A Bureau of Foods veterinarian stated that one of the studies, Hess and Clark's 2-year chronic toxicity test with furazolidone in dogs, was not adequate to determine carcinogenic potential. The other five studies, involving feeding nitrofurans to rats, are discussed below. Based on the results of the rat studies, FDA concluded that all four nitrofurans were tumorigenic and possibly carcinogenic.

University of Wisconsin studies

In 1963 two University of Wisconsin scientists visited a drug manufacturer, Abbott Laboratories, to discuss the low incidence of mammary tumors which had developed during Abbott's chronic toxicity studies with a nitrofuran. 1/ As a result of the meeting, the university scientists began studies in February and May 1964 on the chronic toxicity to rats of the Abbott nitrofuran and several other nitrofurans, including nitrofurazone. The scientists chose to study nitrofurazone because it is chemically related to the Abbott nitrofuran and they could find no evidence from published reports that nitrofurazone had been thoroughly tested for chronic toxicity.

1/The nitrofuran tested by Abbott, 2-(2-formylhydrazino)-4-(5-nitro-2-furyl)-thiazole, has not been used in human or animal drugs.

By the end of February 1965, both studies showed that a substantial number of mammary tumors had developed in the rats fed nitrofurazone. Of 44 rats exposed to nitrofurazone, 35 developed multiple mammary tumors, none of which was considered clearly malignant.

In April 1965 the university scientists met with Norwich representatives to discuss their findings on nitrofurazone. At Norwich's suggestion, a university scientist notified FDA in April 1965 of the preliminary results of their studies.

During June 1965 the university scientists held separate meetings with FDA and the National Cancer Institute to discuss their studies.

Norwich studies

As a result of its April 1965 meeting with the university scientists, in June 1965 Norwich began studying the effects of long-term feeding of nitrofurans, including nitrofurazone, nihydrazone, furazolidone, and furaltadone, to rats. In the study, 245 female Holtzman rats were divided into 7 test groups of 35 rats each. A control group was fed a drug-free diet for 53 weeks. Each of the other groups was fed a diet containing one of the nitrofurans for 45 weeks and a drug-free diet for 8 additional weeks.

A second study using 40 Sprague-Dawley rats (20 males and 20 virgin females) in each of 7 test groups was subsequently started. A control group was fed a drug-free diet for 52 weeks. Each of the other groups was fed a diet containing one of the nitrofurans for 45 weeks and a drug-free diet for 7 additional weeks. Reports on the studies were prepared in October 1966 and January 1967.

The study using Holtzman rats showed that rats fed furazolidone and furaltadone had a significantly higher incidence of grossly palpable (capable of being felt) tumors after 35 weeks of feeding when compared to control group rats. Also, rats fed nitrofurazone and nihydrazone had significantly more tumors than the control group rats at the end of the experiment.

The study using Sprague-Dawley rats showed a significantly higher incidence of tumors in the female rats in groups fed nitrofurazone, nihydrazone, furazolidone, and furaltadone when compared to female rats in the control group. Male rats fed nitrofurazone, nihydrazone, furazolidone, and the control diet had no tumor incidences. One male rat in the group fed furaltadone developed a tumor.

The tumors from the Holtzman rats fed furazolidone, furaltadone, and the control diet were examined by Norwich's consulting pathologist. The pathologist stated that there was no doubt that the incidence of fibroadenomas in rats fed furazolidone and furaltadone was drug related and noted that "the fibroadenoma are exactly like similar mammary tumors of both women and dogs." He stated, however, that he considered all of the tumors benign because there was no evidence of metastasis (transfer of disease from one organ or part to another not directly connected with it).

The consulting pathologist suggested that the rats in the Norwich study may have been predisposed to tumors because they were virgin females. He believed that thwarted reproduction and lactation predisposes rats to mammary tumors and suggested further studies to confirm the hypothesis.

Results of the Norwich studies were reported to the Bureau of Veterinary Medicine on June 2, 1967, and subsequently referred to the Bureau of Foods. The Bureau of Foods made a preliminary review of the Norwich data and, on January 27, 1969, advised the Bureau of Veterinary Medicine that the data implicated all nitrofurans as tumorigenic and carcinogenic.

In a June 1969 detailed review of the Norwich studies the Bureau of Foods concluded that 3 percent of the rats fed nitrofurazone and nihydrazone and over 10 percent of the rats fed furazolidone and furaltadone had carcinomas. The Bureau concluded that all four of the nitrofurans were tumorigenic and probably carcinogenic and that they should not be used in food-producing animals until additional long-term studies were completed.

According to the Bureau of Foods veterinarians who reviewed the Norwich studies, the incidence of tumors would have been higher and the number of rats developing malignancies greater had the study been continued for the rats' lifetime. They stated that although no metastasis was noted in the studies, the studies' short duration may have been a limiting factor.

Hess and Clark study

In February 1967, Hess and Clark submitted a "Drug Experience Report" to the Bureau of Veterinary Medicine containing a report on a 2-year chronic toxicity and three generation reproductive study of furazolidone in rats.

In the study, 60 rats were divided into 3 groups each consisting of 10 male and 10 female rats. One group was fed a furazolidone-free control diet. The diet for the other groups contained either 30 or 100 grams of furazolidone per ton of feed.

Results of the study showed that there were three times as many tumors in rats fed furazolidone when compared to rats in the control group, but concluded that none of the tumors were attributable to furazolidone. An October 1965 review of the tissue slides by a division of Hess and Clark's parent corporation concluded that

> "The incidence of tumors * * * did not suggest a drug relationship, and the types of tumors demonstrated were those which occur spontaneously and are encountered frequently in aged rats."

At the time the Hess and Clark report was submitted, the Bureau of Veterinary Medicine did not have adequate staff to review "Drug Experience Reports" and consequently was not aware of the report. The Bureau of Foods first learned of the report during a November 1968 meeting with Hess and Clark.

A Bureau of Foods veterinarian reviewed the Hess and Clark report in December 1968. He noted that there were there times as many tumors in rats fed furazolidone as compared to the control rats and that some of the tumors in rats fed furazolidone were malignant. None of the control rats' tumors were malignant. He concluded that the data on tumor incidence indicated that furazolidone was carcinogenic and nitrofurans as a class had carcinogenic potential.

SUBSEQUENT CARCINOGENICITY STUDIES

On August 30, 1968, the Bureau of Drugs notified Norwich that additional testing should be initiated immediately for all marketed nitrofuran derivatives, using a protocol developed by the Bureau of Drugs. A National Cancer Institute scientist was consulted in development of the protocol; the Bureau of Veterinary Medicine and the Bureau of Foods apparently were not consulted.

Norwich has performed six additional tumorigenicity studies using furazolidone, but has performed no additional tumorigenicity studies on nitrofurazone, nihydrazone, or furaltadone. A Bureau of Foods veterinarian stated that one of the studies, a 2-year study with dogs, was inadequate to determine carcinogenic potential. Other tumorigenicity studies have been performed by University of Wisconsin scientists and foreign researchers.

The Bureau of Foods has concluded that, on the basis of the Norwich studies, furazolidone is carcinogenic and the other three nitrofurans are highly suspect carcinogens.

Norwich studies

Norwich submitted reports on the following studies to the Bureau of Veterinary Medicine, which subsequently forwarded the reports to the Bureau of Foods for review.

Study 1--On June 18, 1971 Norwich submitted a report on a study of various factors such as virginity, breeding, lactation, and ovarian hormones in inducing mammary tumors in Sprague-Dawley rats.

The study involved three groups of rats--virgin, multiparous, and ovariectomized. Within each group, half the rats were fed a diet containing furazolidone and the other half, the control group, was fed a furazolidone-free diet. According to the report, 6 months after the start of the experiment mammary tumors began to appear in the groups fed furazolidone and steadily increased. Mammary tumors first appeared in the control rats 15 months after the experiment started. In addition, the incidence of tumors in all groups of rats fed furazolidone was significantly higher than the incidence of tumors in the control rats in each group. The report concluded that

> "* * * the data is inadequate for a complete and realistic evaluation of nitrofurans in general or NF-180 [furazolidone] in particular with regard to their carcinogenic hazard to man in the conditions of exposure."

According to a Bureau of Foods veterinarian the study results showed the same pattern of tumor incidence as previous studies. In an August 25, 1971, memorandum to the Bureau of Veterinary Medicine, the Bureau of Foods veterinarian stated that the report supported his contention that nitrofurans were potent carcinogens.

Study 2--On November 12, 1973, Norwich submitted a report on a study on the tumorigenicity of furazolidone in Sprague-Dawley rats. The study consisted of 400 rats divided into 4 groups of 50 male and 50 females rats each. A control group was fed a furazolidone-free diet. The diet of the other three groups contained furazolidone levels of 0.025, 0.05, or 0.1 percent for 18 months. All groups of rats were then maintained on the furazolidone-free diet until the mortality

rate of each group reached 90 pecent at which time the remaining 10 percent were sacrificed.

The report noted that compared to the control group (1) female rats at all feeding levels of furazolidone experienced a higher incidence and earlier development of mammary tumors, (2) female rats at the highest feeding level of furazolidone experienced a higher incidence of malignant tumors, and (3) male rats at the highest feeding level of furazolidone experienced a higher incidence of tumors.

The Bureau of Foods in its March 29, 1974, review of the report concluded that furazolidone at high levels has an apparent influence on carcinogenicity based on the significant incidence of malignant mammary tumors in female rats as compared to the control rats. The Bureau further stated that benign tumor development at all feeding levels for female rats was significant and a "no effect" level was not established. The Bureau expressed the view that the tumor development was linked to female rats possibly because of the effect of nitrofurans on hormone levels.

Study 3--On February 8, 1974, Norwich submitted a tumorigenicity evaluation of furazolidone in Fischer rats, using the same feeding levels as in study 2. The rats were maintained on a furazolidone diet for 20 months and then on a furazolidone-free diet until the mortality rate of each group reached 90 percent at which time the remaining 10 percent were sacrificed.

The report noted that compared to the control groups (1) female rats at all feeding levels of furazolidone experienced an earlier and increased incidence of mammary tumors, (2) female rats at the highest feeding level of furazolidone experienced a higher incidence of malignant mammary tumors, (3) male rats experienced an increased incidence of basal cell epitheliomas, and (4) male and female rats at the two highest feeding levels of furazolidone experienced an increased incidence of sebaceous adenomas and thyroid adenomas.

The July 8, 1974, Bureau of Foods review of the report concluded that furazolidone was carcinogenic based on the statistically significant number of mammary tumors occurring at all feeding levels of furazolidone in female rats. The veterinarian reviewing the study report indicated that although there was not a statistically significant increase in malignancies, he believed that malignancy would have been significant in the rats fed furazolidone had they not

died from other toxic effects of furazolidone. The veterinarian also indicated that only the male rats at the two highest feeding levels and the female rats at the highest feeding level showed a statistically significant increase in sebaceous adenomas.

Study 4--Norwich submitted a report on a tumorigenicity study of furazolidone in Swiss mice on February 8, 1974. The study consisted of 400 mice divided into 4 groups each consisting of 50 male and 50 female mice. A control group was fed a furazolidone-free diet. The diet of the other three groups contained furazolidone levels of 0.0075, 0.015, and 0.03 percent for 13 months. After the 13-month period all groups of mice were maintained on the furazolidone-free diet for an additional 10 months.

The report noted that compared to the control group (1) mice at the two highest feeding levels of furazolidone experienced an increase in bronchial adenocarcinomas (a cancer of the bronchial tubes) and (2) male mice at the highest feeding level of furazolidone experienced a significantly higher incidence of benign and malignant tumors. The report concluded that the lowest feeding level of furazolidone was a "no effect" level for tumorigenesis in mice.

The Bureau of Foods' Division of Mathematics reviewed the statistical data presented in the report and concluded that "there is no convincing evidence that any of the dose levels used in this study are safe." The Division also concluded that for both sexes there was a significant linear dose response relationship for total tumors and malignancies. According to a Bureau of Foods veterinarian, furazolidone is carcinogenic for both male and female mice. The veterinarian stated that the tumors in the mice were lymphoreticular, bronchial adenoma, and adenocarcinoma rather than mammary tumors as found in rats.

Study 5--On November 12, 1973, Norwich submitted a report on a 2-year, low-level feeding study on furazolidone in Sprague-Dawley rats. The study consisted of 320 rats divided into 4 groups each consisting of 40 male and 40 female rats. A control group was fed a furazolidone-free diet. The diet of the other three groups contained doses of furazolidone which gradually reached levels of .0025, .0125, and .0375 percent during a period of 2 years.

The report concluded that the lowest level of furazolidone feeding was a "no effect" level for tumor formation in female rats and that all feeding levels were "no effect" levels for male rats.

Review of this study by the Bureau of Foods' Division of Mathematics in September 1974 showed that furazolidone was related to the development of tumors and multiple tumors, particularly mammary tumors. The Division concluded that a "* * * conservative method of finding a safe dose would fix it at a level much lower than any used in this study."

On October 9, 1974, a Bureau of Foods veterinarian notified the Bureau of Veterinary Medicine of the above findings and also stated that furazolidone-treated rats showed a trend toward malignancy.

University of Wisconsin studies

After the April 1965 meeting between University of Wisconsin scientists and Norwich (see p. 23), university researchers began a series of additional studies on nitrofurans and related compounds. These studies included evaluations of the carcinogenic potential of nitrofurazone and furaltadone. Because these studies were not performed in support of an NADA they have not been submitted to or reviewed by the Bureau of Foods.

In an article published in May 1970 1/ the Wisconsin researchers and their associates reported that fibroadenomas induced by nitrofurazone were transplantable to newborn male and female rats and showed increased malignancy. Some researchers consider the transplantability of rat mammary fibroadenomas to be a criterion for cancer.

The article also reported results of followup tumorigenicity studies with clinical-quality nitrofurazone. Nitrofurazone was found to induce mammary tumors in 22 of 29 rats, indicating that the impurity in the nitrofurazone used in the earlier tests did not significantly contribute to tumorigenesis. They reported, however, that the nitro group (see footnote, p. 1) appeared to be vitally important in tumor induction because the compound without the nitro group provided a statistically insignificant incidence of mammary tumors.

1/Erturk, E., Morris, J. E., Cohen, S. M., Price J. M., and Bryan, G. T., "Transplantable Rat Mammary Tumors Induced by 5-Nitro-2-Furaldehyde Semicarbazone and by Formic Acid 2-[4-(5-Nitro-2-furyl)-2-thiazoyl] hydrazide," Cancer Research, May 1970, vol. 30, pp. 1409-1412.

University of Wisconsin researchers and their associates reported in an article published in August 1973 1/ that levo-furaltadone-hydrochloride--a chemical compound closely related to furaltadone--was strongly carcinogenic, inducing a high incidence of breast adenocarcinomas and a lower incidence of lymphoblastic lymphomas (malignant tumors of the lymph glands). Transitional cell carcinomas were also reported. The article stated that the breast tumors appeared earlier than in the control group and multiple breast tumor masses were usually found in each rat. The researchers stated that the lymphoblastic lymphomas and transitional cell carcinomas were highly significant because they were uncommon in rats.

Foreign studies

Although studies on furazolidone tumorigenicity have been performed in Canada and Japan, a Bureau of Foods veterinarian concluded that the studies were either incomplete or inadequate.

In December 1970 an official in Canada's Department of National Health and Welfare submitted an interim report to FDA on a study of the tumorigenic effects of furazolidone in Wistar rats. Bureau of Foods veterinarians stated the study was never completed due to the death of the researcher, but that the interim report showed that furazolidone-induced tumors were found in the rats.

In January 1971 Norwich submitted a Japanese report on nitrofurans in which male Wistar rats fed furazolidone for 13 months showed no evidence of tumorigenicity. A control group of six rats was fed a furazolidone-free diet. The diet of three groups of six rats each contained furazolidone at levels of .001, .01, and .02 percent. A Bureau of Foods veterinarian stated that the sex of the rats, low dosages, short duration of the test, and small number of animals in each group negates the validity of the conclusions.

PHYSIOLOGICAL STUDIES

Physiological studies identify possible changes in body functions and processes resulting from use of a

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1/Cohen, S. M., Erturk, E., Von Esch, A. M., Crovetti, A. J., and Bryan, G. T., "Carcinogenicity of 5-Nitrofurans, 5-Nitroimadazoles, 4-Nitrobenzenes, and Related Compounds," Journal of the National Cancer Institute, Aug. 1973, vol. 51, no. 2, pp. 403-417.

chemical, trace the chemical's movement in the body, and examine the body's disposition of the chemical. Such studies are important in analyzing the results of other studies, such as those for carcinogenicity.

We reviewed physiological studies on nitrofurans including studies on their effects on the endocrine glands and their metabolism in the body. The results of these studies are summarized below.

Endocrinology studies

Endocrinology is a branch of biological science which studies the endocrine glands (such as the thyroid and pituitary glands) and their secretions in relation to body processes and functions. Secretions of the endocrine glands pass into the blood or lymph, which transport the secretions to the body organs whose functions they regulate.

In a July 23, 1969, letter to the Bureau of Veterinary Medicine, Norwich hypothesized that near-toxic doses of furazolidone administered over long periods might produce an effect on estrogen (a female sex hormone) synthesis which might ultimately result in the earlier appearance of spontaneous tumors. Norwich maintained that such an effect would not occur when lower, nontoxic doses of furazolidone were administered to rats or when higher doses were given to species with estrogen/progesterone ratios more closely approximating man's. To test this hypothesis, Norwich began studying the effect of furazolidone on steroidogenesis (the production of steroids including bile acids and sex hormones) in rats.

Norwich again notified the Bureau of Veterinary Medicine on May 11, 1970, that it believed that tumorigenic effects of furazolidone were limited to a particular species, strain, and sex of test animal; i.e., female Sprague-Dawley rats. Citing preliminary results from studies terminated after 9 months due to the accidental death of the test animals, Norwich stated that the tumorigenic effects were caused by action of the drug on the reproductive cycle, perhaps through alteration of the progesterone/estrogen balance. Norwich noted that furazolidone produced greater changes in adrenal progesterone levels in mammary-tumor-susceptible Sprague-Dawley rats than in tumor-resistant Fisher rats.

At a meeting with the Bureau of Drugs in September 1972, Norwich maintained that there was no increase in the number of malignant mammary tumors due to administration of nitrofurans and no increase in tumors in other organs. Norwich

officials indicated they hoped to show that the effects on the rat reproductive system which indirectly caused an earlier appearance of mammary tumors would not occur in man because of his different chemical makeup.

In March 1973 Norwich sent the Bureau of Veterinary Medicine a report on a study to determine why nitrofurans induce mammary tumors. According to the report, furazolidone and nitrofurazone can inhibit function of the adrenal glands. The adrenal glands produce sex hormones, hormones affecting body metabolism, and adrenaline. Both furazolidone and nitrofurazone were shown to block the conversion of progesterone to corticosterone in the adrenal glands. Norwich concluded that the effects of furazolidone on adrenal functions might be a factor in the induction of rat mammary tumors.

A June 1973 Bureau of Foods review of the report confirmed that the induction of tumors resulted from furazolidone's effects on the adrenal glands, but stated that the results were not useful in establishing a "no-effect" level. The Bureau concluded that the study proved that the tumorigenic response was related to pharmacological effects of furazolidone other than the direct chemical effect.

Another report submitted to the Bureau of Veterinary Medicine by Norwich in March 1973 concerned the effects of estrone (an estrogen hormone) and furazolidone on tumor formation. The study on which this report was based attempted to determine whether furazolidone increased or depressed the tumorigenicity of estrone. According to the report, estrone levels that are carcinogenic are too toxic for use in drug combination comparisons. The report concluded that the study did not help explain the mechanism by which furazolidone induces the early onset of mammary tumors.

A Bureau of Foods veterinarian stated in a June 1973 memorandum that the study demonstrated that furazolidone plus estrone in the diet of female Sprague-Dawley and Fisher female rats increased the incidence of mammary masses. He stated, however, that it was not clear how these results could be used in establishing safe-residue levels of furazolidone in food.

At a December 10, 1973, conference with officials of FDA and HEW's National Institutes of Health, Norwich explained its hypothesis on hormonal activity and submitted a written summary of pertinent data.

The Bureau of Foods asked endocrinologists from the National Institutes of Health and the Bureau of Drugs to comment on Norwich's data and hypothesis. The National Institutes of Health endocrinologist stated that the Norwich presentation was unconvincing and poorly supported. The Bureau of Drugs endocrinologist stated that the Norwich hypothesis was not without foundation; however, he also stated that much of the hypothesis was more speculative than could be established by fact.

The Bureau of Foods' Assistant to the Associate Director for Sciences said the Norwich hypothesis is no longer an issue because of the results of the 1973 and 1974 Norwich carcinogenicity studies. She stated that induction of nonmammary tumors in rats and mice fed furazolidone cannot be presumed as a secondary effect due to hormonal imbalance.

Metabolism studies

Metabolism studies determine what compounds, or metabolites, a substance breaks down to in the body; how fast and into which organs the components are dispersed; and how fast they are eliminated. Because animal drugs, such as nitrofurans, may be rapidly metabolized in the animal's body, little residue of the original drug may remain in animal tissue, milk, or eggs. Thus it is important to identify the metabolites, their toxicological properties, and their disposition in the animal.

In a 1967 article on nitrofurans 1/ it was reported that nitrofurazone is metabolized into a hydroxylamine and then into an amine. The compounds detected in the urine of animals fed nitrofurazone included unchanged nitrofurazone, an hydroxylamine, and other nitrofurans.

The 1967 article and data submitted to FDA by Norwich in 1970 showed that nihydrazone metabolites include other nitrofurans and a hydrazine derivative.

1/Miura, K., and Reckendorf, H. K., "The Nitrofurans," Progress in Medicinal Chemistry, Plenum Press, New York, 1967, vol. 5, pp. 320-381.

In a 1971 Japanese report 1/ on the metabolic fate of nitrofurans, nitrofurazone, containing a carbon-14 radioactive tracer, was administered to rats. The report indicated that most of the radioactivity was excreted within 48 hours after the nitrofurazone was administered. In addition, less than 1 percent of the radioactivity recovered from the urine, feces, and bile was unchanged nitrofurazone, indicating substantial metabolism of nitrofurazone in the rat.

In a 1973 article 2/ on metabolism of a nitrofuran, University of Wisconsin researchers stated that nitrofurans were generally rapidly metabolized and excreted. They noted that nitrofuran metabolism involved formation of an aminofuran metabolite with a hydroxylaminofuran metabolite as an intermediate. The article further stated that metabolism had been postulated as necessary for the carcinogenicity of nitrofurans with the N-hydroxylaminofuran metabolite as the reactive intermediate.

A 1974 article 3/ reporting the results of a study on the mutagenicity of nitrofurans stated that all 22 nitrofurans tested, including nitrofurazone and furazolidone, were mutagenic in E. coli bacteria. The article stated that the ultimate mutagen is likely to be a metabolite rather than the nitrofuran itself.

Two Bureau of Drugs pharmacologists suggested in a January 15, 1975, memorandum that a metabolite may possibly be the ultimate carcinogen. He stated that:

1/Tatsumi, K., Ou, T., Yoshimura, H., and Tsukamota, H. "Metabolism of Drugs. LXXIII. the Metabolic Fate of Nitrofuran Derivatives. (1) Studies on the Absorption and Excretion," Chem. Pharm. Bull, 1971, vol. 19, pp. 330-334.

2/Cohen, S. M., Alter, A., and Bryan, G. T., "Distribution of Radioactivity and Metabolism of Formic Acid 2-[4-(5-nitro-2-furyl)-2-14 C-2-thiazolyl] hydrazide following Oral Administration to Rats and Mice," Cancer Research, November 1973, vol. 33, pp. 2802-2829.

3/McCalla, D. R. and Voutsinos, D., "On the Mutagenicity of Nitrofurans," Mutation Research, 1974, vol. 26, pp. 3-16.

"The nitro group of furazolidone can be reduced by liver enzymes; a hydroxylamino intermediate would be suspect. Metabolites which are hydrazine derivatives would also be suspect, since a number of compounds of this type are known to possess carcinogenic activity."

We discussed the toxicological significance of nitrofuran metabolites with a Bureau of Foods veterinarian. He stated that a metabolite may be just as toxic or carcinogenic as the nitrofuran itself and that many hydroxylamines and hydrazine derivatives have been shown to be carcinogenic. He also stated that if the nitrofuran metabolizes into other nitrofurans, those nitrofurans would also be suspect carcinogens.

CHAPTER 4

RESIDUES OF NITROFURANS AND THEIR METABOLITES

Residues of animal drugs and/or their metabolites may remain in meat, milk, and eggs after treatment of the animal. Long-term, low-level public exposure to residues of animal drugs may occur through consumption of meat, milk, or eggs from treated animals.

A zero tolerance has been set for residues of furazolidone in swine tissues, furaltadone in milk, and nihydrazone in chicken tissues and eggs. Tolerances have not been set for residues of furazolidone in eggs and rabbit, chicken, and turkey tissues and nitrofurazone in swine, chicken, and turkey tissues.

On the basis of the studies discussed previously, FDA considers furazolidone a carcinogen and the other three nitrofurans highly suspect carcinogens. To comply with the provisions of the Delaney Clause, FDA has required the holders of nitrofuran NADAs to show that no nitrofuran residues are present in food using a method of analysis capable of detecting 2 ppb of nitrofuran residue in animal tissue and 0.2 ppb in milk.

There are two basic methods used to detect drug residues--radioactive tracer and chemical. Radioactive tracer methods involve the experimental feeding of a drug containing radioactive material such as carbon-14. By measuring the amount of radioactivity remaining in the animal, the extent of drug or metabolite residues can be determined.

Chemical methods are used for regulatory purposes and involve extracting and analyzing the drug from treated animals through chemical means. The Bureau of Foods' Assistant to the Associate Director for Sciences said that neither FDA nor the Department of Agriculture have tested meat, milk, or eggs for nitrofuran residues because no acceptable methods for such detection have been approved by FDA.

We reviewed data on (1) nitrofuran residues in meat and milk, (2) proposed restrictions on nitrofuran use, and (3) residues of nitrofuran metabolites in meat and milk.

NITROFURAN RESIDUES IN MEAT AND MILK

To allow natural depletion of drug residues from the animal--thus limiting human exposure to the residues--the drug is withdrawn from the animal before the animal is slaughtered or its milk taken for food. Depletion studies measure the amount of drug residue at succeeding time periods. The length of the withdrawal period is determined by the time required for residues to deplete to the established tolerance.

The conditions of use approved in the nitrofuran NADAs do not include a requirement that nitrofurans be withdrawn from the feed of swine, chickens, and turkeys before slaughter. Dairy cattle are required to be withdrawn from furaltadone 36 hours before milk is taken for food. The conditions of use approved in the nitrofuran NADAs were based on depletion data showing that no nitrofuran residues remain in food under those conditions of use.

Improved methods for detecting nitrofuran residues have made it possible to detect residues which could not be detected when the nitrofurans were originally approved for marketing.

In January 1971 Norwich and Hess and Clark submitted to the Bureau of Veterinary Medicine supplemental NADAs for their nitrofuran products requesting that labels of nitrofuran products be amended to provide withdrawal periods for swine, turkeys, and chickens, and longer withdrawal periods for dairy cattle. The companies proposed that the regulations be amended to require that (1) swine, turkeys, and chickens be withdrawn from furazolidone or nitrofurazone 5 days before slaughter, (2) chickens be withdrawn from nihydrazone 4 days before slaughter, and (3) dairy cattle be withdrawn from furaltadone 48 hours before milk is taken from them for food purposes.

The Bureau of Veterinary Medicine told Norwich and Hess and Clark that it could not approve the supplemental NADAs until the question of nitrofuran safety had been resolved, but agreed to the use of a revised label until the issue was resolved. Subsequently, Norwich and Hess and Clark revised the labels of their nitrofuran products in accordance with the proposed supplemental NADAs.

Available data indicates that nitrofuran residues may remain in food even if the withdrawal periods contained on product labels are followed.

Furaltadone in milk

In March 1971 Norwich submitted to FDA a report on a study of the rate of furaltadone depletion in milk. In the study, Norwich measured the furaltadone residues in the milk of a cow using a method of analysis capable of detecting as little as 0.2 ppb of furaltadone in milk. Results of the study showed that a residue of 1 ppb of furaltadone remained 48 hours after the last drug treatment. Furaltadone residues were less than 0.2 ppb after 60 hours.

Norwich submitted to FDA a report on a second furaltadone depletion study in July 1971. According to the report, less than 0.2 ppb of furaltadone was present in the milk of two of the five cows involved in the study 36 hours after the last furaltadone treatment. Furaltadone residues of up to 1.4 ppb were detected in milk of the other three cows 48 hours after the last treatment. No furaltadone residues were detected in the milk of any of the cows after 60 hours.

In an October 6, 1971, evaluation of various data concerning furaltadone, a Bureau of Foods veterinarian stated that from the limited depletion data available it appeared that at least a 60-hour withdrawal period would be necessary to insure that furaltadone residues in milk were less than 0.2 ppb. On October 29 Norwich submitted to FDA's Hearing Clerk a report indicating that furaltadone residues in milk were less than 0.2 ppb 48 hours after the cow was last treated with the drug.

In April 1972 the Bureau of Foods notified the Bureau of Veterinary Medicine that Norwich should be required to submit new depletion data because of the significant changes that had occurred in the methods for detecting furaltadone residues in milk. The FDA files we reviewed, however, did not contain any further correspondence between FDA and Norwich regarding new depletion data. According to a Bureau of Veterinary Medicine official, this data will not be requested until the 1971 Notice of Opportunity for Hearing is vacated.

Furazolidone in tissues

In July 1969 Norwich submitted to the Bureau of Veterinary Medicine a report on a study of the depletion of furazolidone residues in chicken tissues using a radioactive tracer method. This report and supplemental data subsequently submitted to the Bureau showed that furazolidone residues in chicken tissue were less than 2 ppb in chickens with a 3-day withdrawal period.

Also, in September 1971 Norwich submitted to FDA's Hearing Clerk a report on a study on the depletion of furazolidone residues in chicken, pork, and turkey tissue using the chemical method. According to the report, furazolidone residues of 2 ppb were found in turkey skin with fat 5 days after withdrawal from the drug, but residues of less than 2 ppb remained in all other tissues from turkeys and all tissues from chicken and pork after the 5-day withdrawal. Bureau of Foods chemists notified the Bureau of Veterinary Medicine in October 1971 that the depletion data submitted by Norwich using the chemical method did not support Norwich's label instruction calling for a 5-day withdrawal period for furazolidone used in chickens, swine, or turkeys. The chemists stated that:

> "It should be noted that depletion data and/or data used to establish suitable withdrawal times for Furazolidone (NF-180) in animal tissues can be utilized only after valid methods of analysis are accepted. The firm has generated such data with the new methodology, however, in our judgment it does not establish a five-day withdrawal time for Furazolidone. Examination of the data indicates that the drug can be detected at five days in skin and fat samples from 'dosed' animals and in fact exceeds the 2 ppb level in the turkey studies * * * A longer withdrawal time is indicated."

In November 1971 Norwich submitted to FDA's Hearing Clerk a report on a study of furazolidone depletion in turkey tissue. Norwich reported that no furazolidone residues were found in muscle, liver, or kidney after 5 days withdrawal, but stated that "residues of furazolidone in samples of skin with fat are equivocal."

Results of a February 1972 Norwich study on depletion of furazolidone in turkey skin with fat showed that furazolidone was detected in all samples of skin with fat up through 13 days after withdrawal from the drug.

Nihydrazone in tissues

In October 1969 Norwich submitted to the Bureau of Veterinary Medicine a report on a study of depletion of nihydrazone residues in chicken tissue using a radioactive tracer method of analysis. Some nihydrazone residues in excess of 2 ppb were found in some samples of all types of tissues with no withdrawal. Only skin with fat had nihydrazone residues over 2 ppb after 1, 2, or 3 days withdrawal. No residues were detected after 4 days withdrawal.

A Bureau of Foods chemist's review of the Norwich report confirmed that nihydrazone residues were less than 2 ppb after 5 days withdrawal. The chemist noted, however, that the accuracy of the radioactive tracer method had not been validated. Norwich subsequently submitted data to support the sensitivity of its method of analysis. In May 1970 the Bureau of Foods determined that the data submitted by Norwich was adequate to support the claimed 2 ppb sensitivity of the radioactive tracer method.

In November 1971 Norwich submitted another report to FDA on a study of depletion of nihydrazone residues from chicken tissue. Chickens were given nihydrazone in their feed for 8 weeks. According to the report, nihydrazone residues of 2 ppb or greater were detected in one of eight liver samples and one of seven samples of chicken skin with fat.

Nitrofurazone in tissues

In November 1971 Norwich submitted to FDA's Hearing Clerk a report on a study of the rate of nitrofurazone depletion in chicken tissues using the chemical method Norwich proposed for regulatory purposes. According to the report, nitrofurazone residues of more than 2 ppb were found in one of two kidney samples after a 5-day withdrawal period, but residues of less than 2 ppb remained in all other chicken tissues after the 5-day withdrawal.

According to the Bureau of Foods' Assistant to the Associate Director for Sciences, no data has been submitted on nitrofurazone depletion in turkey and swine tissues using a method sensitive to 2 ppb.

PROPOSED RESTRICTIONS ON NITROFURAN USE

In addition to adding or extending withdrawal periods for nitrofurans used in swine, chickens, turkeys, and dairy cattle, the supplemental NADAs submitted to FDA by Norwich and Hess and Clark in January 1971 proposed that the nitrofurans be eliminated from several uses. Use of furazolidone in the feed of laying hens and rabbits was deleted from furazolidone labels in 1971. A warning not to feed furazolidone to replacement chickens (those chickens being raised to become laying hens) over 14 weeks of age was added to the labels.

Because FDA had not approved the supplemental NADAs proposing the labeling changes, FDA's Associate Chief Counsel for Veterinary Medicine stated that he would not attempt to enforce the restrictions voluntarily placed on nitrofuran labels by Norwich and Hess and Clark.

Although since 1971, furazolidone labels have not proposed that it be used in the feed of laying hens and rabbits, FDA files indicate that furazolidone is still being sold for use in laying hens and rabbits.

On October 3, 1972, an official from the American Feed Manufacturers Association sent a memo to the Association's feed contacts notifying them that "From a strictly legal standpoint, it is still permissible to use furazolidone in both layer and rabbit feeds."

In a February 8, 1973, letter to FDA's Division of Federal-State Relations, a Maine Department of Agriculture official stated that some feed salesmen and manufacturers were telling their customers that they could still use furazolidone in laying hens. The official stated that some feed labels still contained directions for use in laying hens.

In a March 6, 1973, telephone conversation between officials from the Bureau of Veterinary Medicine and Norwich the letter from the Maine official was discussed. The Norwich official stated that furazolidone use in laying hens and rabbits was contrary to the company's wishes.

On March 7 Norwich sent a memorandum to all sales personnel notifying them that they "would be fired" if they promoted "off label" uses of any Norwich product. The memorandum quoted a June 25, 1971, Norwich memorandum instructing its sales personnel to discontinue all promotion of furazolidone in laying hens and rabbits.

An April 1974 FDA inspection of a New York feed mill revealed that the mill was producing furazolidone-medicated rabbit feed. The company advised FDA by letter dated April 26, 1974, that the company had been marketing rabbit feed containing furazolidone for many years and that other larger companies were still manufacturing and selling rabbit feed containing furazolidone. On April 29, however, the company notified FDA that it had discontinued using all drugs in rabbit feed.

In an October 18, 1974, letter to the U.S. Department of Agriculture, an official from the Georgia Department of Agriculture requested a method for detecting furazolidone residues in eggs. The letter stated that "It appears that we could have a problem of this drug being fed to laying chickens * * *."

We contacted the Georgia Department of Agriculture to determine the extent of the problem in Georgia. The Georgia

State Chemist told us that no effort had been made to analyze eggs for furazolidone residues because the U.S. Department of Agriculture could not give them an adequate detection method. A Georgia feed mill inspector said that he had been able to stop the major egg producers from using furazolidone in laying hens, but had been unable to prevent the major producers from using furazolidone in replacement chickens over 14 weeks of age. He stated that eggs for food purposes are being taken from replacement chickens after a 5-day withdrawal period.

Residue data indicates that significant furazolidone residues may exist in eggs from hens maintained on a feed containing the drug. In August 1969 Norwich submitted to FDA a report on a study of furazolidone residues in eggs showing residues averaging 152 ppb at the maximum feeding level permitted under the approved NADAs. The FDA files we reviewed contained no data on furazolidone residues in rabbit tissue.

METABOLITE RESIDUES

Methods for detecting residues of furaltadone and furazolidone are designed to detect residues of only the unaltered nitrofuran. Bureau of Foods scientists believe that residues of nitrofuran metabolites, including hydroxylamines, hydrazine derivatives, and other nitrofurans, could be present in meat and milk and that residues of these metabolites might be carcinogenic. (See p. 35.) Norwich, however, has not been required to develop methods to detect residues of these metabolites.

According to the Bureau of Foods' Assistant to the Associate Director for Sciences, the radioactive tracer studies done by Norwich did not include data on total radioactivity to enable measurement of residues of the drug and its metabolites. She indicated that the Norwich depletion studies were done by a "reverse isotope dilution" technique which only measured residues of the parent drug and not the metabolites. She considered this to be a major deficiency in the Norwich radioactive tracer studies.

In an August 14, 1969, report to the FDA Commissioner, the Interdepartmental Technical Panel on Carcinogens recommended that studies be performed on the storage and localization of nitrofurans and/or their metabolites in rats and mice. Such studies identify tissues in which drug-related residues may build up. The panel also recommended that a 21-day withdrawal period be adopted to prevent transfer of the metabolites to humans. A member of the Interdepartmental Technical Panel later approved a 5-day withdrawal

period if adequate data was available showing the absence of significant residues with the shorter withdrawal time. Although FDA regulations have not been changed to extend withdrawal periods, the 5-day withdrawal period was voluntarily placed on nitrofuran labels by Norwich and Hess and Clark. (See p. 37.)

At a December 1972 conference on nitrofurans, the Bureau of Veterinary Medicine, the Bureau of Foods, and the U.S. Department of Agriculture agreed that the following questions needed to be answered:

> "1. What is the metabolic fate of the drugs in the target species?
>
> "2. Is there a degradation of the drugs or its (sic) metabolites in slaughtered tissues? If so, what are the degradation products that would reach the consumer?"

Following the conference, the Director of the Bureau of Foods' Division of Chemistry and Physics recommended that the nitrofuran manufacturers be required to demonstrate that no significant degradation of nitrofurans occurs after slaughter or that no degradation products of toxicological concern are present in meat, milk, or eggs. The Deputy Director, Division of Toxicology, Bureau of Foods, concurred in the recommendation.

Although FDA asked Norwich for some additional data on metabolites of furazolidone, nihydrazone, and furaltadone, FDA files indicate that quantitative data on the levels of metabolite residues was not submitted. The FDA files we reviewed did not contain any record of FDA requests for, or Norwich submissions of, metabolism data for nitrofurazone.

FDA's efforts to obtain metabolism data for nihydrazone, furazolidone, and furaltadone are discussed below.

Nihydrazone metabolites

In December 1969, the Bureau of Foods notified the Bureau of Veterinary Medicine that a Norwich report on a study of depletion of residues submitted to FDA in October 1969 measured nihydrazone residues but not residues of its metabolites. In response to a Bureau of Veterinary Medicine request, Norwich, in March 1970, submitted data identifying the major metabolites of nihydrazone, including another nitrofuran and a hydrazine derivative.

A Bureau of Foods veterinarian said the Norwich data demonstrated that metabolites are formed in the tissue of chickens fed nihydrazone. In his June 1970 memorandum to the Bureau of Veterinary Medicine, the veterinarian stated that "* * * Qualitative data, as a minimum, should be submitted to show what is the complete residue." In July 1970 the Bureau of Veterinary Medicine asked Norwich to furnish qualitative data on nihydrazone metabolites.

In a January 1971 internal memorandum, the Bureau of Foods stated that the metabolism data requested in July 1970 had not been received. The memorandum stated that the data available on nihydrazone metabolites was "quite sketchy" both in terms of the metabolites formed and the residues remaining.

The FDA files we reviewed did not contain any further FDA requests for, or Norwich submissions of, metabolism data for nihydrazone.

Furazolidone metabolites

In August 1969 the Bureau of Foods told the Bureau of Veterinary Medicine that Norwich should be required to submit radioactive tracer data showing the extent of furazolidone metabolite residues in chicken tissue and a chemical method of analysis to detect such residues if they are significant. The Bureau of Veterinary Medicine notified Norwich of the need for additional metabolism data.

Norwich notified the Bureau of Veterinary Medicine in October 1969 that it was working on methods of analysis for two furazolidone metabolites, NF-362 and NF-682, and promised to submit the data as soon as the methods were completed. The FDA files we reviewed contained no data on the extent of residues of these two metabolites--both of which are nitrofurans.

The FDA files we reviewed did not contain any further requests for, or Norwich submissions of, metabolism data for furazolidone.

Furaltadone metabolites

On October 15, 1973, the Bureau of Foods decided that FDA should not withdraw approval of the furaltadone NADAs because Norwich had developed a method of analysis capable of detecting 0.2 ppb of furaltadone in milk. They recommended, however, that Norwich be required to:

"* * * submit a metabolism study in dry cows which will determine any systemic residue in tissue from the mastitis treatment, and studies in lactating and dry cows which will determine the nature of the residue in tissue and milk and the depletion kinetics of significant residues, * * * If metabolites are formed which may be of toxicological concern at the levels present, requirements for additional studies may be necessary."

The Bureau of Veterinary Medicine has not requested Norwich to perform the metabolism studies recommended by the Bureau of Foods. According to a Bureau of Veterinary Medicine official, FDA will not formally request the studies until the 1971 Notice of Opportunity for Hearing is vacated. The Assistant to the Associate Director for Sciences, Bureau of Foods, told us that Norwich had been informally requested to perform the studies, however, she could not recall when the request was made. As of February 1, 1976, the results of such studies had not been submitted to FDA.

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

An accurate assessment of the health risk created by animal drugs such as nitrofurans is particularly important because of the possibility of long-term, low-level public exposure to residues of such drugs and/or their metabolites through consumption of meat, milk, or eggs from treated animals.

FDA regulations require that FDA withdraw its approval to market an animal drug if scientific data shows the drug to be unsafe under the conditions of use approved in the NADA. In addition, the FD&C Act requires that FDA prohibit the use of an animal drug shown to induce cancer in humans or animals unless it can be shown that no residues of the drug will be found in food.

If the Secretary, HEW, determines that the use of an animal drug as intended creates an imminent hazard to the health of man, he may immediately suspend approval to market the drug and provide for an expedited hearing on the suspension.

Although FDA has been aware of the possible tumorigenicity and/or carcinogenicity of nitrofurans since 1965, it has not effectively acted to establish the safety of nitrofurans for the approved uses. On the basis of study reports submitted to FDA between 1965 and 1967, FDA concluded that the nitrofurans were tumorigenic and possibly carcinogenic.

In 1971 FDA issued Notices of Opportunity for Hearing proposing to withdraw approval of the NADAs for furazolidone, furaltadone, nitrofurazone, and nihydrazone. As of February 1, 1976, FDA, however, had neither held nor denied a hearing on the proposed withdrawal of the nitrofuran NADAs.

FDA concluded, on the basis of additional scientific studies submitted to FDA in 1973 and 1974, that furazolidone was a carcinogen and that nitrofurazone, nihydrazone, and furaltadone were highly suspect carcinogens.

Other studies have demonstrated that nitrofuran residues may remain in food when the drugs are used in accordance with label directions. However, there are no approved regulatory methods for detecting nitrofuran residues in food. As a result, no tests have been performed to determine the extent of such residues in marketed food products.

Moreover, the possible health effects of nitrofuran metabolites have not been adequately studied. Available data indicates that nitrofurans metabolize rapidly and that some of the metabolites may be carcinogenic. FDA, however, has not obtained data on the extent of the metabolite residues in food.

Permitting the continued use of nitrofurans for an extended period while methods for detecting residues of nitrofurans and their metabolites are being developed may create an imminent hazard to the public health. To minimize such risk, FDA should consider suspending approval of those uses of furazolidone, furaltadone, nitrofurazone, and nihydrazone where it has not been demonstrated, by appropriately sensitive methods of detection, that no residues of the drug or its active metabolites remain in food from treated animals.

RECOMMENDATION TO THE SECRETARY, HEW

We recommend that the Secretary, HEW, promptly consider the need to suspend those uses of furazolidone, furaltadone, nitrofurazone, and nihydrazone where it has not been demonstrated that no residues of the drug or its active metabolites remain in food from treated animals.

AGENCY COMMENTS

HEW advised us that because of the nature of the facts involved, the FDA Commissioner has not recommended use of the immediate suspension provision in the nitrofuran situation where other remedies are available under the law. (See app. I.) The Commissioner believes that publication in the near future of a revised Notice of Opportunity for Hearing is the best course of action to resolve the nitrofuran safety question. HEW said FDA is pursuing this approach in the conviction that the continued use of nitrofurans during the time required for administrative resolution does not pose an imminent hazard to the health of man.

HEW stated that immediate suspension of the use of an approved product before a hearing on its safety is the most stringent procedure available to the Secretary for removing a product from the market. HEW said in order to take this course of action, the law requires the Secretary to find that there is an imminent hazard--defined by FDA as a public health situation that (1) should be corrected immediately to prevent injury and (2) should not be permitted to continue while a hearing or other formal proceeding is being held. According to HEW, FDA has always construed this standard strictly, and under the standard, nitrofurans do not pose an imminent hazard.

FDA, according to HEW, takes action against food, drugs, cosmetics and devices that are adulterated or misbranded, some of which pose an immediate threat to the public health. Examples of such threats include salmonella contamination of a food or metal filings in a drug tablet. HEW said that in a situation of this kind, the violation of the act is obvious; the danger to the public health is certain. The distinguishing characteristic about these situations, according to HEW, is that a particular lot of a food, drug, cosmetic or device is clearly adulterated or misbranded--a case quite different from the nitrofuran situation.

HEW said the safety of a drug that has once been shown to be safe may later be called into question on the basis of evidence accumulated during several years of use. In the past, such evidence has never become available so suddenly or decisively as to justify such precipitous action as immediate suspension before a hearing on the drug's safety. In the case of nitrofuran residues in the edible tissues of animals, FDA, according to HEW, does not believe the evidence demonstrates that such residues constitute an imminent hazard. Nor have recent court decisions concerning imminent hazard determinations, including Environmental Defense Fund, Inc. v. Environmental Protection Agency, presuaded FDA to change its judgment concerning the current status of nitrofurans, since FDA believes the facts in the nitrofurans case are materially different.

Although the decision to suspend a product as an imminent hazard rests with the Secretary, HEW, we believe the FD&C Act and the court decisions referred to above support the use of an interpretation of imminent hazard that is more liberal than HEW's. As used in the animal drug provisions of the FD&C Act, imminent hazard does not, as FDA has suggested, refer to the safety of a particular lot of an adulterated or misbranded animal drug, but to the safety of a drug under the conditions of use approved in the NADA. Moreover, HEW's contention that in an imminent hazard situation the danger to the public health is certain does not appear to be consistent with FDA's definition of imminent hazard which states that an imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. (See p. 5.) The definition further states that the occurrence of the final anticipated injury is not essential to establish that an imminent hazard exists.

In the case of Environmental Defense Fund, Inc. v. Environmental Protection Agency (510 F.2d 1292 (D.C. Cir. 1975)) the court upheld the suspension of two pesticides as an imminent hazard, stating:

"We have cautioned that the term 'imminent hazard' is not limited to a concept of crisis: 'It is enough if there is substantial likelihood that serious harm will be experienced during the year or two required in any realistic projection of the administrative process.' * * * [The Federal Insecticide, Fungicide, and Rodenticide Act] does not require the [EPA] Administrator to establish that the product is unsafe, but places '[t]he burden of establishing the safety of a product * * * at all times on the applicant and registrant.' Environmental Defense Fund, Inc. v. EPA, supra, 150 U.S. App. D.C. at 352, 465 F 2d at 532." 510 F 2d at 1297 [court's emphasis].

The definition of imminent hazard used by the Environmental Protection Agency is similar to FDA's definition, and, according to the EPA Administrator, is based on the legislative history of the FD&C Act.

Accordingly, we believe the more liberal interpretation of imminent hazard supported by the court could be applied by HEW in its consideration of suspension actions.

CHAPTER 6

SCOPE OF REVIEW

We reviewed pertinent legislation, regulations, and practices relating to FDA's regulation of animal drugs; examined FDA records relating to the past and present regulatory status of the nitrofurans; and reviewed reports of scientific studies on the safety of the nitrofurans and on the depletion of nitrofuran residues in food.

We also interviewed officials from FDA's Bureaus of Drugs and Veterinary Medicine and Office of Chief Counsel, Rockville, Maryland, and Bureau of Foods, Washington, D.C.; the U.S. Department of Agriculture, Washington, D.C.; and several State departments of agriculture.

Our review of the regulatory status of the nitrofurans was primarily confined to the period since 1965 when the question of nitrofuran carcinogenicity was first raised. We reviewed all correspondence, memoranda, and other documents pertaining to nitrofuran usage in animal drugs which could be located in FDA and U.S. Department of Agriculture files.

APPENDIX I

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON, D.C. 20201

January 28, 1976

Mr. Gregory J. Ahart
Director, Manpower and
Welfare Division
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Nitrofurans: Use of Carcinogenic Drugs in Food Producing Animals May Pose Hazard to Public Health." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

John D. Young
Assistant Secretary, Comptroller

Enclosure

APPENDIX I

DEPARTMENT COMMENTS ON THE DRAFT GAO REPORT ENTITLED, "NITROFURANS: USE OF CARCINOGENIC DRUGS IN FOOD PRODUCING ANIMALS MAY POSE HAZARD TO PUBLIC HEALTH"

GAO RECOMMENDATION:

We recommend that the Secretary, HEW, promptly consider the need to suspend those uses of furazolidone, furaltadone, nitrofurazone, and nihydrazone where it has not been demonstrated that no residues of the drug or its active metabolites remain in food from treated animals.

DEPARTMENT COMMENT:

The Department has authority under the Federal Food, Drug, and Cosmetic Act to remove products from the marketplace through several procedures. This recommendation calls for invoking the most stringent of these procedures, namely, to suspend immediately the use of an approved product prior to a hearing on its safety. In order to take this course of action, the law requires the Secretary to find that "there is an imminent hazard to the health of man. . ." To establish the criteria for such a finding, the Food and Drug Administration (FDA) has defined an "imminent hazard" as "a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held." (21 C.F.R. §3.73) It has always construed this standard strictly, and under the standard, nitrofurans do not pose an "imminent hazard to the health of man."

Every day the Food and Drug Administration takes action against food, drugs, cosmetics and devices that are adulterated or misbranded. Some of these do pose an immediate threat to the public health, for example, salmonella contamination of a food, or metal filings in a drug tablet. In a situation of this kind, the violation of the Act is obvious; the danger to the public health is certain. The distinguishing characteristic about these situations is that a particular lot of a food, drug, cosmetic or device is clearly adulterated or misbranded. That is quite different from the nitrofuran situation.

Before any new human or new animal drug (such as nitrofurans) is approved by FDA, the drug must be shown to be safe and effective for its intended use. Sometimes the safety of a drug that has once been shown to be safe is later called into question on the basis of evidence accumulated during several years of use. In the past, such evidence has never become available so suddenly or decisively as to justify such precipitous action as immediate suspension prior to a hearing on the drug's safety. In the case

of nitrofuran residues in the edible tissues of animals, the Food and Drug Administration does not believe the evidence demonstrates that such residues constitute an imminent hazard. Nor have recent court decisions concerning "imminent hazard" determinations, including Environmental Defense Fund, Inc., v. Environmental Protection Agency, persuaded FDA to change its judgement concerning the current status of nitrofurans, since the facts in this case are materially different.

Therefore, because of the nature of the facts involved, the Commissioner has not recommended use of the immediate suspension provision in the nitrofuran situation where other remedies are available under the law. The Commissioner believes that publication in the near future of a revised Notice of Opportunity for Hearing is the best course of action to resolve the nitrofuran safety question. The Agency is pursuing this approach in the conviction that the continued use of nitrofurans during the time required for administrative resolution does not pose an "imminent hazard to the health of man."

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