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REPORT BY THE

Comptroller General

OF THE UNITED STATES

Does Nitrite Cause Cancer? Concerns About Validity Of FDA-Sponsored Study Delay Answer

The Food and Drug Administration and the Department of Agriculture are faced with a dilemma regarding nitrite--a substance widely used to preserve, color, and flavor meat products. Using nitrite may pose a long-term cancer risk or other health problems. Not using it could increase risks from botulism food poisoning.

Federal law provides that any additive to food shown to cause cancer must be eliminated from use. A substantial unresolved question about the safety of a food additive is also a basis for its removal from use. There is no acceptable chemical substitute for nitrite as a preservative.

The validity of the study indicating that nitrite causes cancer has been questioned. Efforts are underway to resolve the questions.

GAO's review was requested by seven members of the House of Representatives.

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

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The Honorable Charles E. Grassley
The Honorable William C. Wampler
The Honorable Tom Hagedorn Thomas M.
The Honorable James G. Martin
The Honorable Richard Nolan M.
The Honorable Charlie Whitley Charles O.
The Honorable Ike Skelton
House of Representatives

GGD-79-99 This report discusses a controversial study conducted by the Massachusetts Institute of Technology for the Food and Drug Administration (FDA). AGC 00148 FDA concluded that the study results suggest that nitrite causes cancer; however, the manner in which the study was conducted and the validity of FDA's conclusion have been questioned by both Government and non-Government scientists. Assuming that the conclusion is valid, FDA and the Department of Agriculture are faced with a unique and difficult regulatory dilemma--nitrite's continued use may pose a potential long-term cancer risk, while its removal may increase risks from botulism food poisoning. There is currently no acceptable chemical substitute for nitrite, which is used to preserve, color, and flavor large quantities of pork, beef, poultry, and fishery products.

We reviewed FDA's (1) award and monitoring of the nitrite study contract, (2) evaluation of the researcher's pathology diagnoses, (3) design and evaluation of the study, and (4) inspection of the researcher's laboratory practices.

The accuracy of the researcher's pathology diagnoses has become FDA's primary concern; therefore, on March 30, 1979, FDA awarded a contract to review all animal tissue slides from the nitrite study and to determine the validity of the researcher's diagnoses. Until this evaluation is completed, the validity of FDA's conclusion will remain in doubt.

As requested, we did not take the time to obtain formal agency comments on the report. However, we did discuss it with FDA and Department of Agriculture representatives and have included their comments where appropriate. Written comments from the nitrite study researcher are included as appendixes IV and V.

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Comptroller General
of the United States

REPORT BY THE
COMPTROLLER GENERAL
OF THE UNITED STATES

DOES NITRITE CAUSE CANCER? CONCERNS ABOUT VALIDITY OF FDA-SPONSORED STUDY DELAY ANSWER

D I G E S T

A recent Massachusetts Institute of Technology study has indicated that nitrite may cause cancer. Under Federal law:

--Any substance determined to cause cancer in humans or animals may not be used as a food additive. (Delaney Clause)

--A substantial unresolved question about the safety of a food additive is also a basis for its removal from use. (General Safety Clause)

Nitrite has been used for years to preserve, color, and flavor meat, poultry, and fish. More importantly, it protects against the formation of botulism toxin, a deadly food poison. Consequently, the Food and Drug Administration (FDA) and the Department of Agriculture are presented with a unique regulatory dilemma in that nitrite's use protects consumers against one serious problem--botulism poison--yet may cause another--cancer. There is currently no acceptable chemical substitute for nitrite.

Because nitrite is widely used, important, and lacks an acceptable chemical substitute, FDA, with Department of Agriculture concurrence, planned to phase out its use over several years. The Department of Justice determined, however, that no authority exists for such a phaseout and that removal of a cancer-causing substance may not be delayed. (See pp. 33 to 37.)

Reviews by scientists inside and outside of Government have raised questions about the nitrite study's validity. Efforts are underway to resolve these questions. (See pp. 21 to 28 and 32 and 33.)

Legislation has been proposed that would provide authority to phase out nitrite's use over a period of years to allow time to develop a substitute. (See pp. 37 and 38.)

NITRITE STUDY CONTRACTOR PERFORMANCE NOT ADEQUATELY MONITORED

FDA officials monitor contractor performance to ensure compliance with contract provisions. Site visits to the nitrite researcher's laboratory were to be used to assess contractor performance. However, the researcher's laboratory was not visited until the animal testing phase--a critical phase of the study--was nearly completed.

Progress reports were to be the primary tool for monitoring the study, but the researcher submitted some reports late and did not submit others. Agency officials did not follow up with the researcher when reports were late or not submitted and did not make a prompt written evaluation of reports received.

More effective monitoring through better use of site visits and requiring prompt submission and evaluation of progress reports during contract performance could identify problems earlier.

FDA officials told GAO that followup practices to ensure prompt receipt and evaluation of progress reports have been strengthened. Because this review was limited to the nitrite study contract, GAO was unable to evaluate the overall effectiveness of these practices. (See ch. 3.)

PATHOLOGY DIAGNOSES IN QUESTION

Pathology diagnoses provide the basic information used to assess the cancer-causing potential of a substance. FDA's review of long-term study results does not usually include a reexamination of animal tissue slides which, along with notes from the physical (gross) examination of the animal, are the basis for the diagnoses.

The interagency working group charged with assessing the nitrite study requested two of its pathologists to independently review tissue slides from about 25 percent of the animals that the researcher had diagnosed as having cancer. Diagnoses by these two pathologists basically agreed with one another, but substantially disagreed with the researcher's diagnoses.

As a result, FDA determined that an impartial review of all the animal tissue slides by a group of expert pathologists was needed. On March 30, 1979, FDA awarded a contract to the Universities Associated for Research and Education in Pathology, a nonprofit consortium of universities, for that purpose. That contract is expected to be completed in late February 1980.

Verification of the accuracy of pathological diagnoses for all FDA-sponsored studies on which regulatory action is contemplated is needed since conclusions drawn from them may shape far-reaching regulatory decisions. (See ch. 4.)

GUIDELINES ARE NEEDED

FDA does not have guidelines for design, data recording and reporting, and statistical evaluation for long-term toxicity studies like the nitrite study. Design and data requirements of each long-term study are planned by a group of scientists selected to oversee that study. Members of this group vary from study to study.

The nitrite study design did not anticipate the possibility that animals from the same litters would tend to respond alike (litter effects) or the impact this could have on the assessment of risk associated with nitrite. As a result, FDA may have overstated the risk in using nitrite.

The contract for the nitrite study did not specify the types of data the agency would need to evaluate study results. Therefore, some data were submitted late or not recorded.

Statistical analyses are used to quantify the strength of experimental evidence. The statistical procedures used are particularly important since they can influence the determination about a substance's cancer-causing potential. Some reviewers of the nitrite study have criticized the statistical procedures used in evaluating test data. Such procedures included:

--The comparison of combined data from all animals fed nitrites with combined data from all animals not fed nitrites.

--The use of an inappropriate control group in evaluating some data from nitrite-fed animals.

--The failure to adjust study results for differing animal life-spans, which can affect their chances of developing tumors.

Statistical evaluation guidelines are needed to ensure that study evaluations are performed consistently and without bias. (See ch. 5.)

LABORATORY INSPECTION IDENTIFIES SERIOUS PROBLEMS

An FDA inspection of the nitrite researcher's laboratory during a pilot test of proposed Good Laboratory Practices regulations revealed a number of deviations from acceptable procedures, including

--possible contamination of the laboratory environment,

--a feeding mixup which may have jeopardized the study's validity, and

--failure to follow the studies' protocols.

Although the researcher's explanations for the deviations were initially accepted, the interagency working group on nitrites has determined that they require further consideration.

FDA has issued instructions requiring that all contracts for toxicological safety studies comply with Good Laboratory Practices regulations. (See ch. 6.)

RECOMMENDATIONS

The Secretary of Health, Education, and Welfare should direct the FDA Commissioner to:

--Establish guidelines on when site visits are appropriate during long-term toxicity studies.

--Develop a system for ensuring the accuracy of pathological diagnoses for FDA-sponsored studies on which regulatory action is contemplated and consider the need for verifying tissue slide diagnoses as part of that process.

--Develop guidelines for design and data collection and reporting of long-term toxicity studies and establish standards and methods for statistically evaluating such studies.

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FDA officials stated during informal discussions that they would establish guidelines on conducting site visits and explore the merits of developing a system to ensure the accuracy of pathological diagnosis for FDA-sponsored studies. They generally agreed that guidelines can be helpful in designing and evaluating long-term toxicity studies; however, they noted the difficulty in developing a single set of guidelines that would receive universal approval by the scientific community.

We informally discussed a draft of this report with officials of the Department of Agriculture's Food Safety and Quality Service. They suggested that the discussion of the relationship between their responsibilities and FDA's be made more descriptive.

The nitrite study's researcher provided written comments, which are included as appendixes IV and V. The researcher's responses to comments and findings resulting from reviews of his study are quoted throughout the report.

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ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
GLP	Good Laboratory Practices
HEW	Department of Health, Education, and Welfare
IAWG	Interagency Working Group
MIT	Massachusetts Institute of Technology
MON	Memorandum of Need
NCI	National Cancer Institute
NIH	National Institutes of Health
ppm	parts per million
PAG	Project Advisory Group
UAREP	Universities Associated for Research and Education in Pathology
USDA	United States Department of Agriculture

CHAPTER 1

INTRODUCTION

"The use of nitrite to preserve and to color and flavor cured meats, poultry and fish has been the source of scientific debate and public controversy for a decade.

"Since the early 1960's, scientists have known that nitrite combined with certain chemicals can form nitrosamines, a family of chemicals known to produce cancer in test animals.

"We are now confronted with new concerns about nitrite. A study recently completed for FDA [Food and Drug Administration] by the Massachusetts Institute of Technology [MIT] strongly suggests that nitrite produces cancer of the lymphatic system in test animals. The mechanism is clearly distinct from that of nitrosamines."

So states an August 11, 1978, announcement made jointly by FDA, a component of the Department of Health, Education, and Welfare (HEW), and the United States Department of Agriculture (USDA). The announcement further states that

"* * * nitrite also protects against the formation of botulinum toxin, a deadly food poison. We thus are presented with a difficult balance of risks.

"We must weigh the risk associated with nitrite added to food against the health risk from not adding it. On the one hand, nitrite makes it possible for cured meats, poultry and fish to be processed, transported, stored and sold without careful attention to refrigeration. On the other hand, nitrite may pose a potential cancer risk to humans.

"In the past we have moved without hesitation to ban outright a number of food additives when they pose a hazard to human health. In such cases FDA is bound by law to eliminate these substances, and has always done so in the past with the firm conviction that this action is sound law, responsible regulation and wise health policy. Similarly, USDA is bound by law to

eliminate from the foods under their jurisdiction substances which are harmful.

"In this case the need to balance two kinds of health risks--one by taking nitrite out of food and the other by leaving it in--creates a difficult challenge."

The announcement and the concurrent release of the MIT study for external scientific scrutiny led to a number of questions about the conduct of the study and the methods used to ensure the validity of it and others like it. In an October 14, 1978, letter, Representatives C. E. Grassley, W. C. Wampler, T. Hagedorn, J. G. Martin, R. Nolan, C. Whitley, and I. Skelton requested that we review FDA and USDA activities related to nitrite regulation. In response to this request and later discussions with staff members of some of these representatives and the House Committee on Agriculture, this report discusses

--FDA's award of the noncompetitive contract to MIT for the nitrite study;

--FDA's monitoring of the contract;

--FDA and USDA methods and procedures for evaluating and making regulatory decisions on newly developed scientific data and, in particular, the methods and procedures applied to the MIT nitrite study; and

--the circumstances surrounding FDA's laboratory audit of the MIT study and the resolution of questions it raised.

SOURCES AND USES OF NITRITE

For thousands of years, people have been eating meat cured with salt. Such meat develops a characteristic "cured" flavor and color and is preserved for later consumption by delaying normal spoilage. Early users, however, did not realize that nitrate, present as a natural impurity in the salt, was a key ingredient in this process. Scientists in the early 1900s determined that some of the nitrate in the salt was changed to nitrite in the meat and that the nitrite reacted with the meat to produce the desired effects. Because it was difficult to control the amount of nitrite produced by conversion from nitrate, meat producers sought approval to add nitrite directly to meat. In 1925 USDA formally approved this use of nitrite but established a maximum allowable

residual level for nitrite of 200 parts per million (ppm) 1/ to protect against its acute toxic effects.

Later scientists recognized another valuable benefit from using nitrite for meat preservation. Nitrite retards the growth of Clostridium (C.) botulinum. These bacteria, under certain conditions, can produce the deadly toxin responsible for food poisoning known as botulism.

C. botulinum spores are widely distributed in nature, principally in soil, but also in the bottom sediments of streams, lakes, and coastal waters and in the intestinal tracts of mammals, fish, and shellfish. All raw food materials must be considered contaminated with C. botulinum spores since they all come in contact with airborne dust that carries the spores.

By themselves, the C. botulinum spores in the environment or in food do not present a hazard. A hazard does arise, however, when food containing the spores is held under conditions that allow the spores to germinate, grow, and produce the toxin that causes botulism. Such conditions can be found in food that has been inadequately processed, preserved, refrigerated, or cooked. The spores can grow and produce their toxin without a foul odor or other warning sign of contamination.

Food scientists have demonstrated that nitrite inhibits the growth of C. botulinum. In experiments over the past 10 years, nitrite has repeatedly been shown to reduce sharply the formation of toxins when spores of C. botulinum were intentionally inserted into perishable cured meats and smoked fish during or after preparation. Toxins in samples of bacon, hotdogs, sausage, smoked chubs, and whitefish decreased as the concentration of nitrite increased. Without added nitrite, most of the samples became toxic.

Today almost all curing is done by directly adding sodium nitrite to food products. Nitrite is used in processed meat (e.g., bacon, sausage, canned ham, frankfurters), poultry, and fish; certain imported cheeses; pet food; and home curing.

The amount of processed red meat products containing nitrate or nitrite available for sale in the United States

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1/See pages 8 and 9 for USDA's latest restrictions on nitrite's use.

in 1976 was 6.84 billion pounds of pork and 2.56 billion pounds of beef by carcass weight. This represented 55 percent of the total pork output and 10 percent of the total beef output processed under Federal inspection during that year. Fifteen million pounds of nitrite-treated fishery products were also produced in 1976.

Meat, poultry, and fish with nitrite added is not the only food source of human exposure to nitrite. Although raw food products do not ordinarily contain large amounts of nitrite, when food naturally rich in nitrate is acted upon by bacteria the level of nitrite increases. Therefore, any food containing natural or added nitrate will eventually contain nitrite. Celery, radishes, beets, and leafy vegetables (lettuce, cabbage, spinach, and broccoli) are especially rich sources of nitrate. Most natural sources of drinking water also contain nitrate.

Estimates indicate that from 80 to 98 percent of the nitrite to which the human body is exposed is produced by the body itself. Nitrite is produced from conversion of nitrate to nitrite in the mouth and digestive tract, and from the generation of nitrate and nitrite from other nitrogen-containing compounds in the intestines. Studies have shown that subjects on carefully measured diets can excrete several times as much nitrate as they take in and have suggested that nitrites can be produced in the intestines from nitrogen-containing compounds other than nitrate. One scientist estimates that, of the total amount of the body's exposure to nitrite in a single day, about 3 percent comes from food additive nitrite, 15 percent from salivary nitrite, and 82 percent from intestinal nitrite. The latter two sources are completely independent of food additive nitrite.

Thus, the amount of nitrite intentionally added to meat, poultry, and fish represents only a small portion of the total to which the human body is exposed. Current legislation requires, however, that all substances intentionally added to food must be safe.

NITRITE REGULATION

FDA and USDA are responsible for regulating nitrite. FDA has the major responsibility for assuring the safety and wholesomeness of the Nation's food supply, except for meat and poultry subject to Federal meat and poultry inspection laws, which are the primary responsibility of USDA. (See app. I for nitrite's approved uses, intended purposes, legal status, and dates of approval.)

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (FD&C Act), as amended on September 6, 1958, by the Food Additives Amendment (21 U.S.C. 348), requires FDA to establish regulations prescribing the conditions under which a food additive may be safely used. The act defines a "food additive" as any substance which becomes or may be expected to become a component of food, either directly or indirectly, or which may otherwise affect the characteristics of the food. Before a regulation can be established, the additive must be shown to be safe and functional for its intended uses (i.e., it must accomplish the effect for which it is to be used--preservatives must preserve).

The act states, however, that no food additive shall be deemed safe if it is found to be carcinogenic (induce cancer) when ingested by man or animal or if it is found, after tests which evaluate the safety of food additives, to induce cancer in man or animal. This provision is commonly known as the Delaney Clause. Under this provision if a substance is shown, based on scientific analysis, to induce cancer when fed to test animals, FDA cannot allow its use.

In addition, if after its approval, a substance is found, by adequate scientific evidence, to be carcinogenic, its use must be banned. If the evidence is not sufficient to prove that the substance is carcinogenic but does raise substantial unresolved questions about its safety, the general safety clause of the act (21 U.S.C. 348(c)(3)(A)) would require the banning of the substance.

The requirements for revoking approval of a food additive are not as demanding under the general safety clause as under the Delaney Clause. Instead of proof that a substance causes cancer, FDA is required only to present new evidence raising a substantial unresolved question about the safety of an approved substance. FDA does not have the burden of proving that a substance causes cancer or that it is otherwise unsafe; FDA has only to present new evidence that raises a substantial safety question. The burden then is on the manufacturer to resolve the question by showing that the substance is safe.

In interpreting these provisions of the law, FDA officials told us that, even if defects in a study do not allow it to be used as valid evidence for the conclusion that a food additive induces cancer in laboratory animals, the study may nevertheless be sufficient to raise a substantial question as to whether the substance induces cancer. If defects in such a study are not so serious as to make all aspects of the study invalid, the act requires that the substance in question be banned.

Since September 1958, FDA has issued food additive regulations approving the use of either nitrite or nitrate in fish (sable, salmon, shad, smoked tuna, and smoked chub), home cures, canned pet food, cod roe, and indirect uses.

The Food Additives Amendment exempts certain categories of food ingredients from the definition of "food additive." One such category are those substances that have "prior sanctions." A substance has a prior sanction if its use in food was sanctioned or approved by FDA or USDA before September 6, 1958, the effective date of the amendment. Such approvals were granted under provisions of the FD&C Act, the Poultry Products Inspection Act (21 U.S.C. 451 et seq.), and the Federal Meat Inspection Act (21 U.S.C. 601 et seq.).

Because prior sanctioned substances are not covered by the definition of "food additive," the provisions of the Food Additives Amendment, including the Delaney Clause, do not apply to them. The three laws under which prior sanctions were granted provide, however, that the public is to be protected from adulterated food products. They state that food is adulterated if "it bears or contains any poisonous or deleterious substance which may render it injurious to health." Thus, if competent scientific evidence demonstrates a reasonable possibility that some consumers may be harmed by eating food containing a prior sanctioned substance, the food is adulterated and cannot be introduced into the food supply.

USDA is responsible for assuring that the Nation's meat and poultry supply is safe, wholesome, and properly labeled. While FDA has primary responsibility for approving the use of substances identified as food additives, USDA has the additional responsibility to determine that an FDA-approved additive may be used in meat and poultry products. This responsibility includes determining that the approved additive will serve a useful purpose and establishing a minimum amount of the additive necessary to achieve that purpose. USDA also restricts and monitors the use of approved additives to assure that requirements for safe use are met.

In 1925 USDA approved the use of nitrite in meat products (hotdogs, bacon, luncheon meats, etc.), thus establishing its current prior sanctioned status for that use.

Another use for nitrite is in poultry products. Until April 1977 it was generally assumed that USDA had approved the use of nitrite in poultry products before September 6, 1958, thus establishing a prior sanction basis for that use.

In April 1977, however, USDA advised FDA that it was unable to find convincing evidence that it had officially approved the use of nitrite in poultry products under the Poultry Products Inspection Act before 1958 and that no valid prior sanction existed.

In response to USDA's disclosure, FDA issued a notice in the September 2, 1977, "Federal Register" in which it encouraged the submission of petitions requesting that nitrite's continued use be temporarily approved pending the conduct of additional safety studies.

A food company and representatives of poultry trade associations later brought legal action in a U.S. district court challenging USDA's finding that no prior sanction approval existed for using nitrite in poultry products and FDA's efforts to issue food additive regulations for those uses. 1/ That case was dismissed in March 1979.

NITROSAMINES--A RELATED SAFETY CONCERN BUT DIFFERENT REGULATORY ISSUE

Since the late 1960s scientists have known that nitrite can combine, both before and after ingestion, with other chemicals called amines or amides, to form a family of chemical substances known as nitrosamines. Nitrosamines may be produced in the parts-per-billion range when bacon cured with nitrite is cooked well-done. Lower concentrations have been found in certain other nitrite-cured meat products heated at temperatures lower than those at which bacon is cooked. Relatively low concentrations have also been reported in various other foods containing amines or amides to which nitrite has not been added.

According to scientists, nitrosamines as a group are among the most potent carcinogens known. Over 80 percent of the more than 100 nitrosamines tested are powerful carcinogens. They include agents that have induced cancer during experiments in almost all animal organs and tissues and in over 20 species of animals. Experiments have shown that nitrosamines can produce in animals almost all of the common cancers of man.

1/Tyson Foods, Inc., et al. v. United States Department of Agriculture and United States Department of Health, Education, and Welfare, U.S. District Court for the Western District of Arkansas, Fayetteville Division (Civil Action No. F-77-5059).

Nitrosamines are not permitted to be knowingly added to food at any level. However, since FDA and USDA do allow the addition of nitrite to many foods and since nitrosable (capable of combining with nitrite) amines are normal components of food, nitrosation (the combination of nitrite and food amines to form nitrosamines) can occur either in food before ingestion or in the body after ingestion. It is therefore likely that many foods, including cured meats, contain detectable amounts of potentially carcinogenic nitrosamines.

Safety concern since the late 1960s has concentrated on the means of formation, levels of occurrence, and relative toxicity of nitrosamines. This concern has led to FDA and USDA policies directed toward eliminating nitrosamines which form in meat and poultry products before ingestion. A fundamental part of this policy is reducing the amount of nitrite/nitrate that can be added to food.

FDA and USDA have initiated regulatory action to deal with the risks associated with nitrosamines. In the September 2, 1977, "Federal Register," FDA proposed requiring that manufacturers of processed poultry products to demonstrate that their products contain no preformed nitrosamines (nitrosamines that form during heating of the food). On May 16, 1978, USDA issued a final rule setting the amount of nitrite to be added to bacon at 120 ppm. 1/ The regulation also provided for a compliance program beginning June 15, 1978, that required bacon to be free of preformed nitrosamines when tested at 10 parts per billion, the lowest amount confirmable by commercial technology available at that time.

On May 16, 1978, USDA also issued a proposed rule to become effective as a final rule no more than 1 year later, to further reduce the amount of nitrite to be added to bacon from 120 ppm to 40 ppm. 2/ This additional reduction, according to a USDA official, was intended to assist in nitrosamine reduction while maintaining protection against botulism by requiring the use of potassium sorbate as a preservative in bacon. However, on May 15, 1979, USDA issued a notice in the

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1/The amount of sodium nitrite to be added to bacon was set at 120 ppm and the amount of potassium nitrite was set at 148 ppm.

2/The amount of sodium nitrite to be added to bacon was to be reduced to 40 ppm and the amount of potassium nitrite was to be reduced to 49 ppm.

"Federal Register" delaying the effectiveness of the final rule on the amount of nitrite in bacon because its sorbate safety studies were inconclusive. Several cases of adverse reactions to sorbate were reported during the tests, and FDA has begun investigating these reactions. No final action is expected regarding the amount of nitrite allowed in bacon until the investigations are completed.

CONTRACTS FOR NITRITE STUDIES IN COMPLIANCE WITH REGULATIONS

Two studies have raised questions about the safety of nitrite--a study related to the nitrosamine issue and the follow-on study mentioned in the August 11, 1978, FDA/USDA announcement. Both studies were conducted by MIT under noncompetitive contracts awarded by FDA. Our review of procurement regulations showed that FDA's award of these two contracts complied with regulations in effect at the time.

FDA's concern that nitrite would react with amines in foods to produce nitrosamines in the digestive tract resulted in a noncompetitive study contract (No. FDA-71-81) for about $500,000 awarded to MIT on June 29, 1971. The study was to

--determine whether continuous exposure to nitrite and morpholine (an amine) at low concentrations in the diet will induce tumors in rats, rabbits, and hamsters and

--compare the effect of nitrite and morpholine fed in the same diet to rats, rabbits, and hamsters with a control group of rats, rabbits, and hamsters fed a known carcinogen, N-nitroso-morpholine (a nitrosamine).

Federal Procurement Regulations set general Government procurement policies. HEW Procurement Regulations, which implement and supplement the Federal Procurement Regulations (41 CFR 3.802-50), provided in 1971 that, if one organization or individual has exclusive or predominate capability by reason of experience, specialized facilities, or technical competence to perform the work within the time required and at a reasonable price, a proposal could be solicited from only this source. They also provided that a document entitled "Justification for Noncompetitive Procurement" should be prepared, fully justifying the selection.

The Justification for Noncompetitive Procurement for the MIT study was dated April 7, 1971, and signed by the acting director, Division of Toxicology, Bureau of Foods. The justification states:

"Other laboratories may be fully capable of carrying out one or another aspect of the proposed work, however, to my knowledge, it is unlikely that there is any laboratory that has had the experience and competence in all of the various aspects as have been described above.

"The work in the MIT laboratory for the last nine years has involved the use of the highly purified diets required for this work, with a high degree of success in keeping animals for the lifetime periods required for carcinogenesis investigations. To my knowledge, there is no other laboratory with similar experience."

In addition, two of the four scientists at MIT who were to work on the study possessed experience which was described as "unavailable elsewhere" and "indispensable."

The study began on July 1, 1971, and on January 25, 1974, two MIT researchers briefed FDA scientists on their preliminary findings. The memorandum of the briefing states that:

--Unexpected results were seen in the rat group fed sodium nitrite--a 27-percent incidence of malignant lymphoma compared to the 2-percent incidence normally seen in this strain of rats.

--These results are at variance with several other feeding studies in which nitrite was used with no evidence of cancer.

--The question remaining was whether nitrite alone, or the agar-based semisynthetic diet interacting with the nitrite, produced the results seen.

At the time of the preliminary briefing, the MIT researchers agreed to submit a proposal for further research on nitrite using the same strain of rats. The final report dated March 14, 1975, showed that lymphomas 1/ or

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1/Lymphomas are tumors of the lymphatic system and in the MIT studies refer to malignancies. The lymphatic system is an interconnected system of spaces, vessels, and cells between tissues and organs through which lymph circulates throughout the body. Lymph is a liquid that removes bacteria and certain protein from the tissues, transports fat from the intestines, and supplies white blood cells to the blood.

leukemias 1/ occurred in about 27 percent of rats fed nitrite alone--about 19 percent developed lymphomas and about 8 percent developed leukemias. 2/ Previous studies using nitrite alone had shown negative results. The MIT study was therefore the first indication of possible carcinogenicity from the use of nitrite in foods. In March 1974, MIT researchers responsible for the nitrite/morpholine study and Bureau of Foods' scientists met to discuss the protocol (study design) for a follow-on study to address the safety of nitrite alone because of its obvious importance as a food additive. Both Bureau scientists and the MIT nitrite study researcher, a veterinary pathologist, 3/ told us that the design of this experiment was a joint MIT-FDA effort.

The protocol provided that the same Charles River strain of Sprague-Dawley rats and the same diet base of the nitrite-fed rats in the first MIT study were to be used in the follow-on study. About 1,400 treated rats and about 600 control rats were to be divided into 18 groups--7 control groups and 11 treatment groups--with each group on a different diet base or nitrite dose. Two types of control groups--negative and positive--were included. The five negative control groups were given untreated feed. The two positive control groups were fed urethane--a known carcinogen expected to cause a 30-percent lymphoma incidence. The 11 treatment groups were fed various levels of nitrite in their diet.

The researcher and FDA officials described the study as actually being six studies in one. Each study was arranged as follows:

--Study one fed nitrite in a semisynthetic agar gel diet, a gelatinlike substance.

1/Leukemia is the body's production of abnormal amounts and types of white blood cells--cancer of the blood cells.

2/The portion of the study using rabbits was terminated early because the animals had not shown any effect from nitrite exposure 15 months after the study began, and the portion of the study using hamsters was terminated because a large number of the test animals died from causes not related to nitrite exposure.

3/Veterinary pathology is a branch of medicine that studies the essential nature of a disease in animals, especially the structural and functional changes in tissues and organs of the body which cause or are caused by disease.

--Study two fed nitrite in drinking water.

--Study three fed nitrite in a standard laboratory rat chow.

--Study four fed nitrite in a dry form of the agar gel diet, a powdery substance.

--Study five was composed of mother rats that gave birth to offspring used in two feeding groups, one of which was fed nitrite beginning about 5 days before they gave birth.

--Study six fed nitrite in an agar gel diet after the animals were weaned.

Treated animals used in studies one through four were exposed to nitrite in utero, that is, during prenatal development. A noncompetitive contract (No. FDA 74-181) dated June 24, 1974, for about $500,000 was awarded to MIT for this study. FDA officials told us that the second study had to be done at MIT, because of the possibility that the first study's positive findings were in some way related to the MIT environment and because of MIT's expertise gained in the first study.

HEW regulations that governed the award of a noncompetitive contract in 1974 had remained unchanged since 1971, when the nitrite/morpholine study contract was awarded. The Justification for Noncompetitive Procurement states:

> "The need for this contract is an outgrowth of findings from earlier work done at MIT under Contract No. FDA 71-81. The questions to which answers are sought are, in part, actually related to the MIT environment. For this reason, one study of the type envisioned must be performed at MIT."

The results from this study (see app. II for a summary), which ultimately cost $548,527, justified, according to FDA officials, the conclusion that nitrite induced cancer in treated animals and led to the joint FDA/USDA announcement of August 11, 1978. (See p. 1.)

CHAPTER 2

NITRITE'S FUTURE USE IN FOODS UNCERTAIN

After hearing the MIT nitrite study's conclusions, the FDA Commissioner decided that the normal agency procedures used to evaluate research and to choose a regulatory option were inappropriate. Instead, he appointed a special task force for those purposes. FDA's task force review concluded that (1) nitrite causes cancer and (2) the use of nitrite should be phased out over a period of years. While the task force effort included a scientific review of the MIT study, serious concerns about the scientific integrity of the study were not raised during the task force deliberations. Later scientific reviews, however, did raise serious questions about the validity of the study's conclusions.

The FDA/USDA plan to phase out the use of nitrite was submitted to the Secretary of HEW, who requested an opinion on the legality of the plan from the Attorney General. After 7 months the Department of Justice decided the phaseout was illegal. To avoid being forced to ban nitrite immediately, FDA and USDA proposed legislation providing a moratorium on such a ban until a commercially feasible substitute has been developed.

MIT STUDY INDICATES NITRITE MAY CAUSE CANCER

Because of nitrite's importance in the Nation's food supply and the safety questions raised by the nitrite study results, on May 2, 1978, the MIT researcher briefed senior FDA and USDA officials on the study's findings. Among those in attendance were the FDA Commissioner; the Acting Director of the Bureau of Foods; the Assistant Secretary, Food and Consumer Services, USDA; and the Administrator, Food Safety and Quality Services, USDA. Scientists from both agencies also attended.

An FDA memorandum summarizing information presented during the briefing states that:

--Animal feeding studies and clinical observations were completed and data were being analyzed.

--Lymphoreticular tumors and enlarged spleens had been indicated to be associated with exposure to nitrite in the diet.

--The types of tumors observed in this study were different than those produced by nitrosamines.

The FDA Commissioner described this briefing as an intense 2-hour discussion of the study data. By the end of the briefing, he was convinced that nitrite causes cancer and that the agency was faced with a serious problem.

FDA TASK FORCE ASSIGNED TO CONSIDER SAFETY OF NITRITE

After the May 2, 1978, briefing the Commissioner directed that the usual FDA review procedures which lead to regulatory action be omitted and instead an informal review be initiated by a task force composed of FDA personnel of his selection. 1/ The Chief Counsel was responsible for overall development of the regulatory policy, and the Acting Director, Bureau of Foods, was responsible for directing the scientific review of the study.

According to FDA officials, the Commissioner decided to use a task force to consider the scientific, regulatory, and legal aspects of the nitrite problem for at least two reasons. First, everyone associated with the matter recognized that a finding that nitrite causes cancer would present FDA and USDA with one of the most difficult regulatory problems they had ever faced. Second, if released prematurely or without a careful exposition of what the two agencies intended to do, the MIT study could have created substantial public concern and possible panic.

The FDA officials pointed out that in recent years FDA and other agencies have used the task force approach to handle certain difficult and sensitive regulatory problems. The Deputy Commissioner said the agency used a task force to review safety and regulatory options for such substances as saccharin, diethylstilbestrol (DES), and Red No. 40.

The task force was composed solely of FDA personnel even though both FDA and USDA have responsibilities for regulating the nitrite content in foods. Both agencies agreed that USDA would not participate in the review of the MIT nitrite study results because (1) FDA funded the study, (2) according to existing laws, initial food additive safety

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1/The task force included the Commissioner; the Deputy Commissioner; the Chief Counsel; the Special Assistant to the Commissioner; the Executive Assistant to the Commissioner; the Acting Director, Bureau of Foods; the project officer for the MIT nitrite contract; and a toxicologist from the Division of Toxicology, Bureau of Foods.

determinations are made by FDA, and (3) USDA had limited its expansion of expertise in toxicology to minimize redundancy between the two agencies.

USDA and FDA officials told us that neither agency has a a formal, written policy setting forth procedures for evaluating new scientific information concerning the safety of food additives. The nature of the informal review process for such information, according to an FDA official, usually involves a sequence of reviews within the agency to identify the strengths and weaknesses of the data and the possible regulatory alternatives.

The Bureau of Foods is responsible for evaluating new scientific information on the safety of food additives. Bureau officials told us that the division sponsoring the study decides how to review the data. If cancer is involved, the Division of Toxicology, 1/ begins the review. The study is then forwarded to the Cancer Assessment Committee, 2/ which was established to provide rigorous review of cancer data. The committee reviews all experimental evidence, evaluates its significance, and either takes appropriate action to resolve outstanding problems or requests regulatory action. If the committee members believe a substance has major scientific, economic, and regulatory significance, they will recommend formation of an interagency working group composed of eminent Government scientists 3/ to evaluate the experiment's scientific merit. The group will present its evaluation to the Director of the Division of Toxicology who, with other Bureau officials, will confer with the Bureau of Foods' Director to decide upon the regulatory options

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1/Toxicology is the scientific study of poisons. It is concerned with the adverse effects of chemicals or other substances on living organisms and the assessment of the likelihood that such adverse effects will occur under specified conditions of use or exposure.

2/The committee's official title is the Cancer Data Review Committee. Members represent the Divisions of Toxicology, Pathology, Mathematics, Chemistry, and Physics and the Epidemiology Staff, when appropriate. The Chairman is the Associate Director for Regulatory Evaluation, Division of Toxicology. The Division Director is an ex-officio member.

3/Interagency working group members are drawn from FDA, USDA, the National Institutes of Health (NIH), and other agencies, as needed.

available to FDA. 1/ If application of the Delaney Clause (see p. 5) seems appropriate, the matter will be brought directly to the Commissioner's attention.

In the case of the MIT nitrite study, the Commissioner's decision to use a task force resulted in these normal procedures being initially ignored. He gave three reasons for his decision: (1) nitrite is added to 7 percent of the Nation's food supply, (2) it involved a $12-billion-a-year industry, and (3) it provided a major health benefit by preventing botulism. The Commissioner stated that the task force was to establish FDA's regulatory position, the size of the carcinogenic effect as reported by the MIT study, plausible hypotheses for the cause of the observed effects, the statistical significance of the study, and an assessment of risk associated with the continued use of nitrite.

FDA officials told us that, had the Commissioner decided to have the nitrite study evaluated by the usual method, the evaluation and preparation of a comprehensive document about nitrite's use in food products would have been coordinated by the Bureau of Foods' Division of Food and Color Additives, with involvement by the Divisions of Toxicology, Pathology, Chemistry and Physics, Microbiology, Food Technology, Nutrition, Consumer Studies, and Mathematics. According to the officials, the results of the evaluations would have been forwarded in a report with recommendations from the Associate Director for Compliance through the Director, Bureau of Foods, to the FDA Commissioner. These officials said that FDA believed such a review in this instance would have taken more time than the apparent seriousness of the study's findings would permit.

FDA CONCLUDES NITRITE CAUSES CANCER--LATER REVIEWS QUESTION MIT STUDY'S VALIDITY

On May 16, 1978, the Commissioner's nitrite task force began meeting weekly. The task force toxicologist issued a memorandum on nitrite's carcinogenic potential which

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1/A similar procedure takes place in the Bureau of Foods' Office of Compliance. Analysts in the Division of Food and Color Additives evaluate regulatory aspects of a scientific finding and make recommendations to the Director of the Office of Compliance, who, along with the Associate Director for Science, recommends a course of action to the Director, Bureau of Foods.

summarizes the MIT study and suggests several hypotheses for its results. The memorandum states that a literature review of prior studies on the carcinogenic potential of nitrite showed that such studies focused on effects of nitrite as related to nitrosation. The memorandum notes that these "numerous studies have produced negative results for nitrite-fed control groups" and that their failure to produce positive results similar to those in the MIT study might be explained in that most of the studies did not focus on the lymphoreticular system and that histopathology, hematology, or clinical chemistry work required to identify positive results was not performed. The toxicologist characterized the memorandum as primarily a literature review.

On May 30, 1978, the project officer and the toxicologist visited the MIT laboratory to determine if any of the data in the researcher's final study report shed any new light on the information discussed during the May 2, 1978, briefing. They concluded that no new information in the report would significantly alter FDA's assessment of nitrite's carcinogenic potential. The final report dated May 18, 1978, was received by FDA on June 5, 1978.

The report was sent to the project officer, who sent copies to the Project Advisory Group (PAG) for review. (The project officer is a member of the PAG.) The group decides whether the study's objectives, as set forth in the protocols, were met by the contractor. By memorandum dated July 11, 1978, the PAG concluded that in some instances the report failed to

--describe statistical analyses used,

--show survival times for male and female rats separately,

--include total numbers of animals by sex to allow calculation of tumor incidence by sex, and

--provide photo-micrographs and other documentation of relevant lesions.

In a second memorandum, dated July 27, 1978, the PAG recommended that the report be accepted. The memorandum concluded that:

"In view of the fact that none of the changes suggested in the referenced memorandum [dated July 11, 1978] are substantive so as to change the final tenor of the conclusions, the PAG considers that the report may be accepted as received."

Although these additions and changes were not requested from MIT at this point in the study evaluation, additional data were requested during later scientific evaluation of the study.

Once it concluded that nitrite causes cancer, FDA was faced with a unique situation, because, for the first time, a substance known to reduce the risk of botulism was suspected of being a cancer risk. According to the Commissioner, since nitrite was a very sensitive regulatory issue, he believed it was important that FDA have its regulatory position developed when the study's results were made public. Therefore, concurrent with the task force's scientific evaluation, policy options regarding the regulation of nitrite were also being identified. In a May 22, 1978, memorandum to the Commissioner, his Special Assistant presented four available options--a total ban on the use of nitrite, continued use to prevent botulism, continued use for a limited period to permit further study, and inaction.

The primary document the task force used in developing the agency's regulatory position was a paper outlining the results of the MIT study, the basis for FDA's conclusion that nitrite caused cancer, and the agency's regulatory strategy to ban nitrite's use in food. Some task force members told us that precautions were used to keep their discussions and conclusions, the MIT study, and the position paper secret. These included discouraging discussion of the nitrite problem with persons outside task force and numbering copies of working documents and returning each to FDA's Chief Counsel.

FDA officials who did not serve on the Commissioner's task force told us that the closed atmosphere in which the task force operated prevented an open and adequate review of the study's scientific validity. They indicated that, had the study results been made available for scientific review from the time they were first reported, many of the problems now confronting the agency about the study's validity could have been identified and considered in setting the agency's regulatory direction.

For example, the Associate Director for Science, Bureau of Foods, told us he had been denied access to study data, even though normally such data would be reviewed by several divisions under his administration and the evaluations coordinated in his office. He stated: "I have never experienced before in my government career a situation where the word was most of us were excluded and not to get involved." He added that, as a result, he had been concerned about the quality of scientific review being conducted since "the personnel I observed associated with the review of the * * * data were not sufficiently strong scientifically." He stated that he had expressed to the Acting Director, Bureau of Foods, his "growing dismay and concern that events were proceeding too quickly without an adequate foundation of scientific review."

One scientist who was excluded, the Associate Director for Regulatory Evaluation, Division of Toxicology, said he had been concerned because none of the task force members were experienced in carcinogenicity studies. He said that a scientist with such experience would have detected the flaws in the MIT nitrite study.

According to FDA officials, references to secrecy carry a connotation of wrongdoing that is "unfair and significantly misleading." They pointed out that the work of the task force was known within the Bureau of Foods to many people and that people who did not serve on the task force were kept informed of its progress. They stressed that FDA was concerned about the possibility of premature disclosure and the arousal of public reaction before it had completed a preliminary review of the study's results. The officials stated that the Commissioner believed very strongly that all reasonable efforts should be used to prevent such a premature disclosure and that, when the study results were disclosed to the public, FDA should be able to answer questions from the Congress, the press, and the public about its position and the actions it intended to take.

We do not intend to imply wrongdoing on the part of FDA. We merely want to note that (1) the MIT nitrite study was reviewed by the task force in a closely controlled environment, (2) most scientific review steps in the Bureau of Foods were bypassed, and (3) while FDA personnel who were normally part of the review process were aware that a task force had been formed to review the nitrite issue, most were not involved in the initial evaluation of its scientific, regulatory, and legal aspects.

In a July 21, 1978, memorandum to the Commissioner and the Deputy Commissioner, the Chief Counsel expressed concern about the agency's proposed conclusion that nitrite causes cancer. He stated, "I have read the narrative portion of the * * * [MIT] report and am troubled by several of its statements * * *." Statements in the report which he quoted as causing him concern included:

> "'(3) Despite the somewhat less than convincing case that nitrite is lymphomagenic in Sprague-Dawley rats, one cannot escape the distinct impression that nitrite does affect the lymphoreticular system of the rat.
>
> "'(4) While these observations require some consideration, the data are only suggestive and the biological significance of nitrite associated lesions of the lymphoreticular system is unclear.'"

He noted that:

> "* * * the quoted statements, even taking into account the norms of scientific understatement, cast doubt on the statistical basis for reaching the Delaney conclusion: that nitrite induced cancer when ingested."

He went on to inquire:

> "Are we subjecting the American people to a risk of botulism on the basis of a case that is 'less than convincing' and of data that are merely 'suggestive' and whose biological significance is 'unclear'?"

He suggested that the researcher respond to the above statements.

On July 31, 1978, the Chief Counsel in a memorandum noted that the researcher had been shown the July 21 memorandum and had restated his belief that his findings are quite significant and that in the opinion of an FDA toxicologist, the quoted statements are examples of the researcher's conservatism. The task force proposed that FDA and USDA take an unprecedented regulatory approach--phase out nitrite's use over a period of years.

In a July 26, 1978, memorandum, the Commissioner notified the Secretary of HEW of FDA's plan to phase out the use of nitrite. He discussed the scientific and legal basis for this unprecedented regulatory action and set out FDA's strategy for announcing the planned action to the Congress and other interested parties. (See pp. 33 to 36 for details of the plan.) The Secretary in turn decided that an opinion on the legality of FDA's plan should be requested from the Department of Justice. The Justice Department responded 7 months later that there was no legal basis for a phaseout and that, if nitrite were found to cause cancer, the agencies were to assure its orderly removal from commerce. (See p. 37.)

Issues raised about the study

Since FDA's plan to phase out the use of nitrite was developed, many issues have been raised about the design, conduct, and evaluation of the study that cast doubt on its scientific validity.

Scientific issues began to surface in late July 1978 during preparations for the concurrent release of the regulatory phaseout plan and the MIT study. To help anticipate questions from the media and industry, four Bureau of Foods' scientists participated in a role-playing exercise by taking the roles of agency and industry officials--two scientists for each side. Their discussion revealed potential problems, including (1) failure to use appropriate control groups, (2) potential litter effect caused by too many test animals being selected from each litter, (3) lack of a predictable dose-response, (4) the possibility that nitrosamines caused the reported tumors, and (5) failure to use appropriate statistical methods.

The Acting Director, Bureau of Foods, who participated in the exercise, said that, because of the problems identified, he recommended to the Commissioner that a working group be formed to review the study's scientific validity.

On August 8, 1978, the Interagency Working Group (IAWG) on nitrite was established. The IAWG was to review and evaluate the chemistry, toxicology, and epidemiology of nitrites/nitrates/nitrosamines; identify knowledge gaps; and recommend research to address those gaps. Representatives from FDA, USDA, the National Cancer Institute, and the National Institute of Environmental Health Sciences were appointed to the group. They included experts in toxicology, pathology, chemistry, risk assessment, statistics, and

residue evaluation. The Associate Director for Science, Bureau of Foods, and the Associate Director for Regulatory Evaluation, Division of Toxicology, Bureau of Foods, headed the group. (See app. III for a list of the IAWG's members.)

The record of the first meeting on August 28, 1978, shows that the members were given the following charge:

> "Review nitrites with respect to toxicity and carcinogenicity, assess the second * * * [MIT] study, determine if data indicate that nitrite has a direct effect on carcinogenicity or if it is nitrosamine or otherwise mediated, and determine what additional research is needed."

As the IAWG began its efforts, FDA also forwarded copies of the nitrite study report to scientists outside the agency requesting their scientific peer review. Such an examination of study design, procedure, and analysis serves to either reinforce an experimenter's interpretation of data or point out flaws that undermine his conclusions. The FDA Commissioner stated

> "Scientific peer review tries to establish (as 'proof') the validity of a test of a hypothesis. * * * It puts a seal of reliability on an experimental result, so that it can be used in further theory construction. It is not a complete guarantee of being right -- only history can provide that -- but it is as much of a guarantee as can be made with the work at hand [the MIT nitrite study]."

Scientific peer review of the nitrite study was made difficult because the report was not in a format that would permit a complete analysis. The MIT researcher and an FDA scientist cited incomplete pathology verification and statistical analysis, lack of literature citations, and a failure to clarify data as omissions which hindered the review.

At the time of our audit, 17 scientists had responded to FDA's request for peer review comments. They raised the following issues:

--The study report lacked sufficient animal data and/or inadequately described the study procedure to permit full review (65 percent raised the issue).

--The practice of combining all control and all nitrite-treated groups regardless of nitrite dose or diet in calculating statistical significance raised doubts about the scientific validity of the study (53 percent raised this issue). For example, the vice-president of the American Health Foundation said that comparing data from all control groups with data from all nitrite-treated groups is inappropriate and that the proper treatment for the data would be to consider each group at a given dose level by comparing it to its appropriate control group.

--The statistical significance of the study was disputed (47 percent raised this issue). The Council for Agricultural and Science Technology stated that effects noted in the nitrite study are not statistically significant.

--The control groups had an unusually high incidence of lymphomas (35 percent raised this issue). The Office of Science and Technology Policy, Executive Office of the President, commented that the background incidence of lymphomas in the control group is higher than expected and that this might suggest something unique about the MIT animals or their housing.

--The fact that the number of tumors in the rats did not increase proportionally as the level of nitrite exposure increased was unlike test results for other carcinogens (35 percent raised this issue). The president of the National Academy of Sciences noted that there is no evidence of a graded dose response but rather an absolute effect at very high levels. A scientist with the Eppley Institute for Research in Cancer stated "the lack of a dose-response relation is most disturbing."

--Additional studies are needed (41 percent raised this issue). The senior principal medical officer, Department of Health and Social Security, United Kingdom, concluded that this study would need to be repeated in another strain of rat and another species before a definite answer could be forthcoming.

--Nitrosamines may have caused some or all of the tumors (24 percent raised this issue). Iowa State University scientists commented that there is no evidence available to support the statement that nitrite-caused tumors are distinct from those caused by nitrosamines.

The National Research Council said lymphomas have been strongly associated with nitrosamine exposure.

--Animals in nitrite study group 1, shipped to the researcher on October 23, 1974, became the control animals for nitrite-exposed animals in groups 5, 6, and 7; however, those animals came from a different lot shipped on October 30 (12 percent raised this issue). The Council for Agricultural and Science Technology stated that the study may not give an appropriate indication of the statistical significance of lymphoma, because of an inappropriate control group.

Finally, two reviewers disagreed with the MIT study conclusion that nitrite is a health hazard. The President of the National Academy of Sciences concluded that "the results of that experiment [the MIT nitrite study] are, at most, barely suggestive that nitrite should be viewed as a small public health hazard." A professor at the Eppley Institute for Research in Cancer said, "I doubt whether nitrite consumption in nitrite-preserved meat contributes to human cancer."

Regarding the comments provided by the 17 scientists, the MIT researcher stated (see app. IV):

"There is no study published to date that cannot be taken apart if one wishes to critically evaluate everything. * * * This study conducted at M.I.T. did not propose to answer all questions. It simply put forward the suggestion that a second study using several different permutations of dietary exposure to nitrite might help resolve the previous observation. In that regard, I feel that it did do so. It can be understood readily that the reviewers who examined my report and who are intimately concerned with the meat industry particularly the pork production would be quite adverse to anything that might be said in a report suggesting that nitrite should be eliminated. For this reason much of the comment made about the study has to be taken with some caution."

Some of the same issues raised by the 17 reviewers have also been raised by members of the IWAG on nitrites. The Chairman of this group told us, however, that the accuracy of the MIT pathology diagnoses was his biggest concern. In

September and October 1978, two pathologists on the IAWG reviewed a portion of tissue slides diagnosed by the MIT researcher as lymphomas. One of the pathologists reported, by memorandum dated October 16, 1978, that they were in basic agreement with one another, but in substantial disagreement with the researcher's diagnoses of lymphoma. Since most disagreement was over the type of cancer, the new diagnoses caused a reduction in the original diagnoses by 17 percent in the number of malignant tumors of any kind.

In commenting on the review by the two pathologists, the MIT researcher stated:

> "What we provide as pathologists is an opinion. That is exactly what I provided in the study results and other pathologists may or may not agree with my assessment. It is significant in fact that I have traditionally disagreed with diagnoses provided by the two government pathologists that looked at my material at the outset. It is not surprising then that the diagnoses of these two pathologists disagreed with my own. * * * I have no apologies and no doubt that the implications that my diagnoses delineated are indeed correct and that under the conditions of this study nitrite did affect the reticuloendothelial system in an adverse fashion."

The results of the two pathologists' reviews were presented at the second meeting of the IAWG on October 18, 1978. The minutes of that meeting state:

> "It became apparent that there was a potential for a disagreement among reputable pathologists as to the diagnostic criteria and classifications related to the spectrum of tumors involved with FDA contract 74-181 as reported by * * * [the MIT researcher]. Because accurate and reliable diagnoses are fundamental to any statistical analyses * * * it was decided that a thorough and complete, impartial review by an independent group of expert pathologists recognized on a national and international basis for their expertise should be commenced as soon as possible."

The findings of the two pathologists subsequently led FDA to issue a contract to confirm the pathological diagnoses of the MIT researcher. (See pp. 57 to 59.)

Our review of the minutes of IAWG meetings and our discussions with members and consultants (nonmember scientists whose assistance was requested) indicate that other potentially serious problems being considered by the group include:

--The tendency of animals from the same litter to respond more alike to a test substance than animals from different litters. If not considered in the statistical analysis, the hazard may be overstated. (See ch. 5.)

--Laboratory practices. Deficiencies in executing the experiment led to questions about the validity of the study results. Failure to comply with acceptable laboratory procedures may result in a study of questionable integrity. (See ch. 6.)

--The three feeding groups that had the greatest statistically significant incidence of lymphomas may lack an appropriate control group because of the procedures used in assigning animals to test groups. The appropriateness of the control group used has not been determined. (See ch. 3.)

Finally, two issues raised by the peer review that the IAWG believes are particularly significant are (1) the possibility that the tumors were caused by nitrosamines and (2) the high incidence of spontaneous lymphomas in the control groups.

Nitrosamines are known potent animal carcinogens. In a June 1979 article 1/ the MIT researcher stated "the pattern of tumors suggests that the carcinogenic effect of nitrite was through a mechanism other than formation of nitrosamines." 2/ As additional evidence he said "The feed samples were analyzed on two different occasions for the presence of nitrosamines * * * none were detected." However, FDA scientists have been unable to obtain copies of the feed analyses. The MIT scientist cited as the individual who performed the feed analyses for the nitrite experiment said he had not done such analyses.

1/"Nitrite Promotes Lymphoma Incidence in Rats," Science, v. 204, pp. 1079-1081, June 8, 1979.

2/Nitrosamines cause cancers in different organs throughout the body. The study showed tumors that primarily affected the lymphatic system.

The high incidence of spontaneous lymphomas in the control groups--7.9 percent versus the normal rate of 1 to 2 percent--has troubled scientists associated with the IAWG. A National Cancer Institute (NCI) data base and a literature search of other experiments that used Sprague-Dawley rats by a member of the IAWG establish that the normal incidence of spontaneous lymphoma is much lower than that shown at MIT. Several theories have been advanced to explain this difference, including (1) the condition was misdiagnosed or (2) a bad infection or virus caused the lymphoma.

In response to these concerns, the MIT researcher stated (see app. IV):

> "The high incidence of spontaneous lymphomas in the control groups repeatedly comes up in discussions of the M.I.T. nitrite study. Anyone who wishes to take a look at the data and the literature relative to the incidence of lymphomas in this strain of rats as well as in others will find that it varies enormously. * * * There is no validity to the comment that the control group of animals had an excessively high incidence of lymphoma implying that there was some environmental problem associated with the study."

No meetings of the IAWG were held between October 18, 1978 and the completion of our audit work in December 1979. Members of the group said that their individual projects are in abeyance until the study's pathological diagnoses are confirmed. If the pathology is not confirmed, there may be no problem with nitrite and no need for additional work. If the pathology is confirmed, completion of IAWG efforts to evaluate nitrite's safety is not expected before mid-1980.

FDA contracts for full-scale pathology review

On March 30, 1979, FDA signed a contract with Universities Associated for Research and Education in Pathology, Inc. (UAREP), a nonprofit consortium representing the pathology departments of 15 universities, to review the pathology material and findings reported by the MIT researcher for the nitrite study. The $469,000 contract also provided for a similar review of the relevant control and nitrite-fed animals in the nitrite/morpholine study. The contract's objective is to confirm or deny, by a panel of impartial expert pathologists, the accuracy of MIT's pathology diagnoses regarding

nitrite and cancer and to develop reports describing the findings, opinions, and rationale for the UAREP diagnoses.

The contract requires that, before any slides are reviewed, a committee of expert pathologists nominated by UAREP and approved by FDA must establish review criteria that reflect the state-of-the-art of pathology. Once the diagnostic criteria are established, the tissue slides and gross pathology data are to be completely reexamined by pathology reviewers selected by UAREP. The reexamination will be conducted in three stages--a pretest of slides from about 200 animals from the nitrite/morpholine study and two tests, each involving slides from about 1,200 animals, in a double blind fashion in that the reviewers will know neither what previous diagnosis was made by the researcher nor which group of animals the slides come from.

FDA determined the order in which the slides were to be reviewed to give the earliest possible indication of whether the nitrite and the nitrite/morpholine studies show positive effects. The contract provides that the UAREP reviewers will record their findings as to all malignant and premalignant lesions, 1/ including any abnormal findings that might relate to lesions capable of being misdiagnosed. The committee of experts will evaluate the reviewers' findings, and once it has been established that the criteria have been properly followed and that the diagnoses are acceptable, the findings will be compared to the MIT diagnoses and the results turned over to FDA. FDA will determine the group assignments for each animal and analyze the results with the help of NCI statisticians.

UAREP is required to complete its final report by February 28, 1980.

NITRITE'S EFFECT ON PUBLIC HEALTH UNCERTAIN

Since the first reports of potential carcinogenicity were received by the agency, FDA officials have lowered their assessment of cancer risk resulting from nitrite consumption. This reduced assessment has resulted from changes in both study data and statistical assumptions of agency officials. Also, FDA officials are considering more closely other findings in the MIT study that may require a ban on nitrite.

1/A lesion is any pathological or traumatic discontinuity of tissue or loss of function of a part.

The former FDA Commissioner said that nitrite would have to be banned even if it were not a carcinogen.

Cancer is not the only toxic effect associated in the MIT study with nitrite exposure. (See p. 32.) Even if a finding of carcinogenicity for nitrite is not supportable, questions about other toxic effects may be a sufficient basis for banning the substance. Under the FD&C Act, a food additive may be banned if, after its approval, a substantial unresolved question as to its safety arises. Authority for USDA to ban a poisonous or deleterious substance in food is provided in the Federal Meat Inspection Act and the Poultry Products Inspection Act.

Risk assessment changes

When the final report on the nitrite study was submitted to FDA, the Division of Mathematics, Bureau of Foods, was requested to perform a risk assessment. A risk assessment describes the probability that a particular harm will befall an individual, members of a particular group, or members of society as a whole. Such risk expressions are usually broad statistical measures that take into account the chance of being exposed as well as the chance of adverse effect from exposure. For example, the average American's risk of death in an automobile accident in a given year is about 1 in 4,650.

For chronic hazards--those that do not exert an immediate effect--estimating and expressing risks are much more complicated. Many assumptions are required when making a quantitative estimate of a cancer risk in humans on the basis of animal studies. It is necessary to assume that:

--Humans and experimental animals have the same sensitivity to the cancer-causing substance in the diet.

--The incidence of cancer will be reduced proportionately as the amount of the carcinogen in the diet is reduced. (i.e., a direct relationship between the amount of carcinogen and the incidence of cancer).

--Each exposure to a carcinogen can cause cancer.

The task force position on nitrite was based on a preliminary risk assessment prepared by a Bureau of Foods' statistician. The task force position paper assumed that (1) humans are exposed to one-fourth the amount of nitrite initially added

to cured meat products, 1/ (2) humans and test rats are equally sensitive to nitrite's carcinogenic effects, (3) there is a direct relationship between the incidence of cancer resulting from doses ingested by rats and that resulting from doses to which the average American is exposed in an ordinary diet, and (4) the risks of cancer from nitrite are evenly spread over the U.S. population.

The task force estimated the range of lifetime cancer risk from human exposure to nitrite as

--1 chance in 3,450 to 1 chance in 794 (2.9 and 12.6 per 10,000) for all nitrite consumed in the average American's diet and

--1 chance in 16,700 to 1 chance in 3,700 (0.6 and 2.7 per 10,000) for nitrite added to meat products.

The task force concluded that reducing dietary nitrite levels will decrease the risk of human cancer.

Later, the MIT researcher and another pathologist reviewed the tissue slides. A second set of study results was forwarded to FDA by memorandum dated August 25, 1978, and a third set was dated September 25, 1978. The changes reported showed a reduction of about 14 percent in the incidence of lymphomas when compared to his original submission. The overall incidence of lymphoma changed from 12.5 percent and 7.9 percent to 10.7 percent and 6.3 percent for nitrite-exposed and unexposed animals, respectively.

A more recent risk assessment was prepared at the request of the Director, Bureau of Foods, as part of an effort he initiated on November 3, 1978, "to examine the broader health implications of human exposure to nitrites from all sources." The June 1979 draft of the risk assessment report notes that estimating risk from nitrite is a rough approximation because of gaps and weaknesses in what is known about nitrite/nitrate/nitrosamine exposure and toxicology. The principal findings were:

--The primary sources of nitrate and nitrite ingested in the average diet are vegetables and cured meats; 95 percent of nitrate (nitrate converts to nitrite) comes from vegetables and about 5 percent of nitrite

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1/Some nitrite is destroyed during the processing and cooking of such products.

comes from cured meats (the original FDA estimate was 20 percent).

--An estimated 135 cases of cancer will occur yearly in the United States from exposure to nitrite; of these 6 can be attributed to nitrite in cured meat. This represents a 91-percent decrease in the original FDA estimate of risk. The decrease is attributed to different factors, including (1) use of the MIT researcher's third set of data and (2) changing assumptions.

--An estimated 22 deaths would occur from botulism in the first year after total removal of nitrite from cured meats unless an intensive educational program was instituted.

--Additional research is required in almost every major facet of the nitrite/nitrate/nitrosamine/botulism question.

The Acting Deputy Director, Bureau of Foods, in a letter dated July 26, 1979, to us stated that risk assessment is an inexact tool of science. He said:

> "We wish to point out that when one reads the risk assessments for nitrites, nitrosamines and botulism * * * the various assumptions described in the report must be taken into consideration. The different risks should be considered on a comparative basis and not on an absolute basis. The technique of doing risk assessment to determine the effect of a chemical on a population group is very new and, as yet, an inexact tool of science. Many toxicologists, epidemiologists, and other scientists frequently do not agree as to the method of applying such techniques and there is a wide variation of opinion on whether this technique should be used and how it should be applied. Many of us think that risk assessments give us some indication of comparing hazards among different chemicals but no one should use the numbers as exact values."

FDA believes that the task force discussion of risk assessment was adequate to point out the uncertainties intrinsic to risk assessment.

Other toxic effects

Cancer is not the only toxic effect reported from the MIT nitrite study. Three other effects reported are (1) myocardial effects (enlargement of the heart), (2) immunoblastic cell proliferation (suppression of the immune response), and (3) splenic hyperplasia (abnormal increase of the number of cells in the spleen).

The statistical significance of the last two effects, according to an FDA scientist, depends on the results of the pathological evaluation being made by UAREP. The decision as to the impact these findings have on nitrite's regulation, therefore, will not be made until after UAREP completes its review.

The first effect, however, is not being reviewed as part of the UAREP contract. The co-chairman of the IAWG said that during the MIT study the hearts of male rats increased in size and weight directly in proportion to the levels of nitrite administered. A known effect from nitrite exposure--methemoglobinemia 1/--reduces the blood's effectiveness in carrying oxygen from the lungs to vital organs. The co-chairman hypothesized that, because of the reduced effectiveness of the blood, the heart is forced to work harder to ensure a sufficient oxygen supply to the body. This stress may cause the heart to increase in size and weight.

FDA and USDA legislation requires that, once a determination has been made that a substance is "poisonous or deleterious" which may render it injurious to human health, the substance be prohibited in foods. Consideration of health or other benefits derived from the substance is not appropriate once this scientific determination of hazard is made, and the substance must be banned or its use restricted.

In determining whether the proposed use of a food additive is safe, the FD&C Act (21 U.S.C. 348(c)(5)(C)) requires FDA to consider safety factors generally recognized by qualified experts as appropriate for the use of animal experimentation data. FDA's regulations (21 CFR 170.22) state:

1/Literally, the presence of methemoglobin in the blood. It involves chemical changes in the red blood cells and has caused poisoning in both livestock and humans, especially children.

"Except where evidence is submitted which justifies use of a different safety factor, a safety factor in applying animal experimentation data to man of 100 to 1, will be used; that is, a food additive for use by man will not be granted a tolerance that will exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals."

To establish the level of safe use for a substance, the maximum amount that can be fed to animals without producing adverse effects (the no-effect level) must be determined. FDA officials told us that, based on estimates of nitrite consumed in treated meat and poultry, about 15 ppm would be permissible. According to USDA officials, at least 120 ppm of nitrite must be added to food to be effective against botulism formation.

FDA/USDA REGULATORY ACTION IN SUSPENSE

Upon reviewing FDA's plan to phase out nitrite's use over several years, the Secretary of HEW determined that, before such steps could be initiated, the Department of Justice should review and approve the plan since this approach was unprecedented. The plan was, therefore, put in abeyance pending a Justice Department interpretation of FDA and USDA legislative authorities. In March 1979, the Attorney General replied that neither agency had authority to phase out the use of nitrite; if the substance was shown to, in fact, be a carcinogen, the agencies were to assure its orderly removal from commerce. The administration has introduced legislation to prohibit the banning of nitrite until May 1, 1980, and to provide FDA and USDA with authority to implement a phaseout as soon as safe, feasible alternatives are available.

FDA plan to phase out nitrite

The Commissioner's task force, which, with USDA's concurrence, developed the plan to phase out nitrite's use, also outlined a detailed public notification plan to announce the phaseout. The FDA Commissioner submitted the plan to the HEW Secretary, by a July 26, 1978, memorandum, in which he discussed the scientific and legal basis for the proposed regulatory action on nitrite and set out FDA's strategy for informing the Congress, the public, and other interested parties of the planned action. The Secretary was provided with information about

--the history of nitrite's use and recent FDA/USDA regulatory actions reducing allowable levels in bacon;

--the basis for the MIT study and the results, which showed an excess of cancers of the lymphatic system in the nitrite-fed animals; and

--an exhaustive review of the MIT study within FDA and by the Commissioner personally.

The Commissioner stated that he believed these circumstances were adequate to trigger action under the Delaney Clause to remove nitrite from use. He pointed out that the law wasn't explicit about the speed with which a ban must be instituted, and he concluded that the only rational course was to begin phasing out nitrite's use over several years to the point that there was no nitrite in food. According to him, the plan provided an opportunity for "mid-course correction" should technological advances prove inadequate to prevent a serious botulism risk.

He proposed a detailed public notification campaign to take place around "Day-N." Day-N referred to the day when a press conference was to be held to announce and explain the proposed action and when the MIT study was to be released. It was surrounded by a series of actions to facilitate acceptance of the phaseout strategy, including briefings, both in person and by telephone, of selected senators, congressmen, and their staffs; Federal officials with science policy responsibilities; leading scientists; and consumer, trade, and industry leaders.

A 50-page background paper was also to be released at the press conference. This document, entitled "FDA's and USDA's Action Regarding Nitrite," dated August 1978, was the product of the Commissioner's task force and explained the legal and scientific basis for the proposed phaseout. The paper concludes that:

--Nitrite induces cancer when ingested by laboratory rats and therefore poses a significant cancer risk to humans.

--The findings will be confirmed by further review; an overwhelming scientific consensus is expected.

--FDA and USDA will propose a coherent plan to remove deliberately added nitrite (and nitrate) from the food supply over a period of years.

--The sole reason for the phaseout is to avoid creating a problem with botulism while protecting against cancer.

--The estimated lifetime cancer risk is between 1 in 3,450 and 1 in 794 in the United States for all nitrite consumed in the diet.

Finally, broad scientific dialogue on the merits of the MIT study and its conclusions was anticipated following release of the MIT study report.

In commenting on the rationale for pursuing a ban on nitrite's use as a food additive, FDA officials explained that the regulatory responsibility for protecting the public health required the agency to begin the administrative procedures necessary to remove nitrite from the market before all scientific questions about the MIT study had been answered. They stated that a key factor in the agency's decision to pursue a ban was the amount of time these procedures consume.

FDA officials pointed out that section 409 of the FD&C Act (21 U.S.C. 348) lists a series of administrative and legal procedures that provide an opportunity for public comment on proposed regulatory actions but which take years to complete. They stated that agency officials believed in August 1978 that enough scientific review work had been done to justify beginning the administrative process. They acknowledged that the review did not answer all the questions that could have been or that were later raised, but they stated that it was sufficient to justify commencing the years-long process. They pointed out that peer review of the MIT study was to occur while the process was being followed.

Upon reviewing the FDA/USDA plan, the Secretary of HEW suggested that the nitrite phaseout be temporarily halted and that HEW and USDA ask the Department of Justice about the legality of their approach. In letters dated August 22, 1978, the Acting Secretaries of both agencies requested the Attorney General's opinion on:

--Whether FDA, under the Delaney Clause and the general food safety provisions of the FD&C Act, has the authority to implement a phaseout of nitrite. The letter noted that the phaseout seemed appropriate because (1) a recent study indicated nitrite causes cancer and (2) nitrite prevents botulism.

--Whether USDA should, under the Federal Meat Inspection Act and the Poultry Products Inspection Act, balance the carcinogenic effects of nitrite against its beneficial effects of preventing botulism.

According to the Commissioner, in early August 1978, news of the phaseout plan began to leak to the press. He told us that, when a newspaper reporter called him with the story about the plan, FDA and USDA were forced to issue the August 11, 1978, press release (see p. 1) to inform the public directly about the regulatory dilemma presented by the MIT study's results.

In a September 11, 1978, memorandum, the Commissioner expressed to the Secretary of HEW his philosophy on the need for acting quickly on nitrite even in the absence of complete scientific data. This memorandum was the result of growing concern about the scientific validity of the MIT study. He stated:

> "Because of the Congressionally-mandated emphasis on prevention of harm to the public health, regulators are required to act without waiting for 'complete' scientific evidence to support their action. Regulators are, of course, not free to act on the basis of the slightest of evidence. It is clear, however, from the health regulatory laws and from judicial interpretation of those laws, that regulatory action to protect the public health from a perceived risk is appropriate, even when the perceived risk is based on a mixture of scientific fact, theory and supposition."

The Commissioner also discussed the unlikely possibility that the study might "have some unforeseen defect." He stated:

> "Even in the unlikely event of a successful challenge to the study, the outcome would not be clear: it would appear to the media and the public as such things inevitably appear -- as rather arcane, confusing debates among the cognoscenti. Thus the possibility for real embarrassment even given the worst possible outcome of our evaluation is very slight, simply because outcomes are never that clear in a matter so complex."

Department of Justice
rules the plan illegal

On March 30, 1979, the Attorney General replied to the HEW and USDA inquiries about the proposed phaseout. He stated that the Congress had not given either Department authority to phase out a carcinogen's use and that, if nitrite is, in fact, a carcinogen, the decision to postpone or eliminate a ban must rest with the Congress. The opinion concluded:

> "The Secretaries of HEW and Agriculture have the discretion, upon making a finding that nitrites are carcinogenic, to adopt timetables and procedures to assure the orderly removal of that substance from commerce. It is our opinion that the Secretaries, however, do not have the authority to balance the benefits of nitrites against their potential harm and determine that their continued use will be permitted until such time as a feasible substitute is developed and put in place. Upon a determination by the Secretaries that an additive causes cancer in man or animals, the decision whether the statutory ban shall be postponed or eliminated is reserved to the Congress."

On the same day the Secretaries of HEW and Agriculture held a joint press conference to announce their intention to propose legislation to

--prohibit FDA or USDA from banning before May 1, 1980, the addition of nitrite to any food to prevent botulism even if nitrite is carcinogenic or otherwise toxic and

--give FDA and USDA the authority to phase out nitrite, if it is determined to be carcinogenic, over a period of years, dependent upon development of alternative means of food preservation.

Material prepared to support the proposed legislation noted that the 1-year moratorium was intended to end speculation that the Government will act hastily against nitrite. It would give the agencies time to collect and evaluate information about the health risks and benefits of nitrite and the availability of alternatives. At the end of the proposed moratorium, if studies continue to show that nitrite poses a health hazard, the agencies would propose an orderly phaseout of its use. Once the phaseout is begun, FDA and USDA believe

that all nitrite would be removed as a food additive by April 30, 1982. As part of the phaseout, FDA and USDA would be required to assure that any alternatives to nitrite (1) are safe, (2) provide full protection against botulism, and (3) are commercially feasible.

In 1979 the HEW- and USDA-proposed legislation was introduced in both houses of the Congress (S. 886, H.R. 3364). A legislative proposal has also been introduced requiring a moratorium of 3 years on any action to ban nitrite. Other legislative proposals provide for research for a nitrite substitute and a prohibition on an FDA/USDA ban on nitrite until a satisfactory alternative food preservative is developed, unless available validated evidence proves beyond a reasonable doubt that nitrite as a food preservative has a significant carcinogenic effect on humans. As of December 31, 1979, none of these bills was being actively considered.

CHAPTER 3

NITRITE STUDY CONTRACTOR PERFORMANCE

NOT ADEQUATELY MONITORED

FDA monitors contractor performance to ensure compliance with contract provisions. The agency's operating procedures provide for onsite visits to contractor facilities as one of several monitoring methods. Although FDA has recognized that onsite visits are important in assessing a contractor's technical performance, the agency did not make any onsite visits to the MIT laboratories until after the animal testing phase--a critical phase of the study.

FDA's contract with MIT required that the contractor submit quarterly progress reports, and FDA's operating procedures require that the agency prepare a written evaluation of each report. Of 14 required quarterly progress reports, 2 were not submitted and 4 were submitted late. Reports for 2 quarters were combined with reports for 2 other quarters into 6-month reports. There is no documentation in the contract file to show why this was permitted. FDA did not followup with the contractor when reports were late and did not make a prompt written evaluation of the reports that were submitted.

FDA officials stated that the project officer maintained close communication with the MIT researcher for the duration of the contract through correspondence, telephone calls, visits, and briefings.

SITE VISITS NOT EFFECTIVELY USED

The Memorandum of Need (MON) for the nitrite study states that the study's technical aspects would be monitored through periodic onsite visits. An MON--the official requisition document used in awarding FDA research contracts--contains such information as project title, objectives, scope of work, duration, reporting requirements, and cost. Site visits are made to monitor first hand the study's technical progress throughout the life of the contract.

The nitrite study project officer who was responsible for making site visits did not visit MIT until January 1977--about 30 months after the study began. By that time,

the animal testing phase was nearly completed. During the animal testing phase, the animals are assigned to study groups, placed on their respective diets, and maintained at those feeding levels until they die or are killed. Proper conduct of this phase is critical to the credibility of the study results. During the visit, the project officer discussed study progress with the researcher, but he did not visit the laboratories because they were closed.

Also in January 1977, FDA made a Good Laboratory Practices (GLP) inspection at the MIT facility and cited deviations from acceptable laboratory practices that raised questions about the validity of study data. (See ch. 6.) As a result of this inspection, the project officer and an FDA pathologist made a second site visit in June 1977. This visit was made to assess the adequacy of pathology procedures being used to determine whether they were "sufficient to safeguard from major error." MIT's pathology procedures were reported to be adequate.

A final onsite visit was made on May 30, 1978, by the project officer and an FDA toxicologist to review the final study report, which had not yet been transmitted to FDA, and compare it with information provided in an oral briefing by the researcher on May 2, 1978. They reported to the Acting Director of the Bureau of Foods that the final report contained no new information that would significantly alter the toxicologist's (May 19, 1978) assessment of nitrite's potential to cause cancer.

Some guidance on site visits is available in HEW's guide for project officers, "The Negotiated Contracting Process." This guide states that the project officer is responsible for making site visits to contractor facilities, if required, to check contractor performance, and that visits should include an evaluation of

--actual performance versus scheduled and reported performance;

--changes in the contractor's technical performance which may affect financial status, personnel or labor difficulties, overextension of facilities, etc.; and

--the number of employees charged to cost-reimbursement contracts compared with those actually performing work.

However, we believe additional guidance is needed to specify when visits should be made during contracted studies.

QUARTERLY PROGRESS REPORTS NOT SUBMITTED AND EVALUATED AS REQUIRED

FDA's Staff Manual Guide (FDA 2610.1) states

> "To promote good administration of agency needs placed under contract, each MON shall provide for the submission of progress reports at appropriate intervals."

The guide further states that, when the progress reports are received by FDA:

> "Each contractor's report (quarterly, annual, final or any other required report) shall be evaluated in writing by the project officer, assisted by the PAG to the extent considered necessary." (Emphasis added.)

As the FDA official charged with overall management of a contract, the contracting officer's responsibilities include ensuring that contract progress reports are submitted by the contractor and evaluated by the project officer. The project officer is responsible and accountable to the contracting officer for the technical sufficiency of the work performed. He is assisted by three or more persons nominated by the Bureau sponsoring the contract to serve in an advisory and review capacity on technical matters. These individuals, with the project officer as chairman, serve as the PAG.

The MON for the nitrite study was prepared by the study's PAG after consultation with the MIT researchers who would conduct the study. It states that the primary method for monitoring the technical aspects of the contract would be "close review of the data submitted in the quarterly reports."

The contract, which became effective on June 28, 1974, required that technical progress reports be submitted within 15 days after the end of each quarter during the life of the contract. The contract states that the progress reports were to include

--a quantitative description of overall progress;

--an indication of any problems that may impede performance, and proposed corrective action; and

--a discussion of the work to be done during the next reporting period.

During the course of the MIT contract from June 28, 1974, to March 31, 1978, the contractor was required to submit 14 progress reports. However, as the following table shows, two were not submitted, two were combined with reports for 2 other quarters into 6-month reports, and four others were submitted late by as much as 25 days. Those that were received were not promptly evaluated in writing, and one had no written evaluation.

MIT Nitrite Study Progress Report Submission and Evaluation Dates

Quarterly reporting period number	Date report due	Date report submitted	Date of written evaluation	Period covered by the progress report
1	10/13/74	(a)	-	-
2	1/12/75	b/1/15/75	6/28/77	7/1/74 - 1/12/75
3	4/12/75	(a)	-	-
4	7/13/75	6/15/75	6/28/77	1/12/75 - 6/15/75
5	10/13/75	b/11/4/75	6/28/77	7/1/75 - 9/30/75
6	1/12/76	b/2/6/76	6/28/77	10/1/75 - 1/1/76
7	4/12/76	3/23/76	6/28/77	1/2/76 - 3/20/76
8	7/13/76	6/28/76	6/28/77	3/20/76 - 6/15/76
9	10/13/76	b/10/22/76	6/28/77	6/16/76 - 10/15/76
10	1/12/77	12/22/76	6/28/77	10/16/76 - 12/20/76
11	4/12/77	3/30/77	6/28/77	12/21/76 - 3/25/77
12	7/13/77	7/7/77	(c)	3/25/77 - 6/30/77
13	10/13/77	(d)	-	-
14	1/12/78	(d)	-	-

a/Report for this quarter not submitted as required, but combined with the report for the next quarter and submitted as a 6-month report.

b/Report submitted late.

c/Report not evaluated in writing.

d/Report not submitted.

The contracting officer for the nitrite study paid little attention to the quarterly reports submitted until January 1977, when an FDA laboratory practices inspection questioned the integrity of the study. That inspection of the MIT laboratory and nitrite study disclosed many deviations from acceptable laboratory practices. (See ch. 6.)

In an April 4, 1977, memorandum, an FDA contract specialist responsible to the contracting officer advised the project officer that:

> "I have reviewed this contract file and have found no written evaluation of reports submitted. Would you please send me a memo summarizing your evaluation of reports submitted from the inception of the contract through December 20, 1976. Subsequent to that date, an evaluation for each report submitted will be requested."

Almost 3 months later, on June 28, 1977, the project officer responded that the progress reports through June 15, 15, 1976, were satisfactory and acceptable; however, those submitted for June 16, 1976, through March 25, 1977, were not. He stated:

> "I have discussed the matter of these reports with * * * [the researcher] and he is aware that it is necessary for him to furnish an up-to-date report covering especially the pathology findings. This will be forthcoming in the report which is due for the quarter ending this month."

When the next progress report was submitted by the contractor to FDA (covering March 25 to June 30, 1977), it was transmitted to the project officer by a memorandum from the contracting officer directing that "This report should be evaluated in accordance with FDA Staff Manual Guide 2610.1" (i.e., in writing). There is no evidence that the project officer complied with the request. The contract specialist gave us neither a written evaluation of the report nor evidence that FDA attempted to determine why such an evaluation was not made. As a result, we could find no evidence that the deficiencies identified by the project officer in the reports covering June 1976 to March 1977 were satisfactorily corrected, or that the

report covering March 25 to June 30, 1977, was acceptable. No progress reports were submitted covering July 1977 to June 1978, when FDA received the final study report. FDA advised us that during this period the final report being prepared.

The contracting officer for the nitrite study did not know why FDA did not follow up with the contractor to obtain the missing progress reports or whether any steps were taken to ensure timely report submissions.

According to the project officer, he sent copies of the contractor's progress reports to members of the PAG and sometimes discussed the reports with them by phone. However, he did not notify the contracting officer until 7 months later that the progress reports covering June 16, 1976, through March 25, 1977, were not acceptable. He explained that:

> "* * * progress reports on long-term toxicity studies, especially of a weak carcinogen like nitrite, are of little value. All they tell you is how far along the researcher is in the study. Any conclusions must await the final report."

The MIT researcher told us that, in his view (see app. IV):

> "* * * the reports were adequate to keep the FDA up-to-date with what was going on in the study and furthermore that there were no progress reports submitted * * * because we had over a 1,000 [sic] animals to submit to autopsy and histologic evaluation and therefore there was very little to report other than a one sentence statement that indicated that was what was being done. Therefore despite regulations we were within proper guidelines in submitting information to the FDA. This has been very accurately alluded to by the quote of the project officer * * *."

In commenting on our observations about the submission and evaluation of quarterly progress reports, FDA officials said:

"Prior to January 1977, it was not our practice to enforce a requirement for written evaluation of progress reports. Receipt and internal distribution of reports was tracked, and acceptance and approval of the progress report was assumed unless the Project Officer otherwise notified the Contracting Officer. In January 1977, the Negotiated Contracts Branch began a more critical review of all contract reporting requirements based upon an HEW initiative to improve contract administration throughout the Department. This effort also coincided with the submission of the Good Laboratory Practice inspection results which pointed out certain deficiencies in the contractor's laboratory."

The importance of a thorough, timely review of all quarterly progress reports is exemplified by the fact that the nitrite researcher's procedures in assigning animals to study groups is one of the issues now being raised which question the study's validity. Those procedures were explained in the first progress report submitted to FDA on January 15, 1975.

About 500 animals were purchased to form or provide offspring for the study groups. Because of the size of the study, the animals were bred and shipped in four different lots. These shipments were made on September 18 and 25, and October 23 and 30, 1974. As each shipment was received, the researcher assigned the animals to study groups sequentially, for example, study groups 1, 2, 3, and 4 were made up entirely of animals shipped on October 23, while study groups 5, 6, 7, and 8 were made up entirely of animals shipped on October 30.

According to the study protocol, group 1 animals, not exposed to nitrite, would serve as controls for animals in groups 2 through 7. This assumed that all animals assigned to groups 1 through 7 would be bred and shipped at the same time, and would provide a concurrent control for groups 2 through 7. As the animals were received, however, group 1 animals, shipped on October 23, became the controls for animals in groups 5, 6, and 7, which were shipped October 30. Thus control group 1 is not concurrent with treated groups 5 through 7 since they were not assigned from the same shipment.

The researcher in his progress report submitted to FDA on January 15, 1975, reproduced copies of animal shipping invoices which indicated that the animals in groups 1 through 7 came from two shipments made about 1 week apart, and handwritten notes on the invoices indicated the study group to which the animals had been assigned.

Lack of a concurrent control group affects the credibility of the nitrite study's results for the three groups determined to have the greatest statistically significant incidence of tumors--groups 5, 6, and 7. During FDA's role-playing exercise in preparing for public release of the final study report, the toxicologist on the Commissioner's task force said:

> "* * * in terms of its random selection -- unfortunately, as far as I'm concerned, that makes it very difficult to take study groups 5, 6, 7, 8 and, in fact, include them."

With respect to the source of the random selection problem, he continued, "I assume that someone wasn't paying attention to what was going on in the design * * * [of the study]."

CONCLUSIONS

Although FDA has recognized the importance of site visits in monitoring contractor performance, it has not issued guidelines defining when such visits should be conducted; therefore, project officers are at liberty to schedule them as they see fit. FDA should develop guidelines that give criteria on when site visits should be made. Guidelines defining at what points in a study FDA considers site visits to be the most useful would help provide more effective, consistent contract administration. While we recognize the need for flexibility, at least one visit during the animal feeding phase of a long-term study would seem desirable to effectively monitor factors such as those identified in HEW's guide.

Since progress reports are to provide a means of monitoring contractor performance to ensure compliance with contract requirements and the project officer's review provides an assessment of technical performance needed to evaluate research work in progress, reports should be submitted and evaluated promptly so that deviations can be quickly identified and corrected.

The MIT study contract required the researcher to submit quarterly progress reports, and FDA officials should have followed up when reports were not submitted as required. Furthermore, the researcher's progress reports should have been evaluated in writing throughout the contract, instead of after the January 1977 GLP inspection, which raised questions about the credibility of study results--some 30 months after the study began. Finally, FDA officials should have required revisions to or followed up on progress reports judged unacceptable and should have made a written evaluation of the last progress report submitted by the contractor.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary direct the FDA Commissioner to establish guidelines on when site visits should be made during long-term toxicity studies.

FDA RESPONSE AND OUR EVALUATION

FDA officials agreed to establish more formal FDA guidelines on conducting site visits for negotiated contracts. They stated that FDA Staff Manual Guide 2610.1 would be amended to require that each MON state how often site visits are planned and to give project officers additional guidance about areas to cover in site visits. The officials do not believe that all studies require the same freqency of site visits or that all site visits should be conducted in the same way. Their guidelines, therefore, are going to allow some flexibility in site visits based upon the requirements and conditions of specific contracts.

In a draft of this report, we suggested that the Secretary of HEW direct the FDA Commissioner to evaluate the extent to which quarterly progress reports are not being submitted in accordance with requirements of FDA contracts or not reviewed in accordance with FDA's Staff Manual Guide. We suggested that, if warranted, the Secretary should direct the Commissioner to ensure that

--progress reports are submitted as required and

--progress reports are evaluated in writing, that the evaluation is timely, and that any deficiencies noted are corrected.

According to FDA officials, the Secretary of HEW initiated a program in January 1977 to correct major contract deficiencies in the Department and that, as a result, FDA evaluated the extent to which contract progress reports were not being properly submitted and reviewed. They said that, at that time, FDA implemented a practice of both written and oral followup on delinquent reports and is now routinely following up to ensure prompt receipt and evaluation of reports. They indicated that, as of December 1977, HEW's procurement procedures state that contracts requiring progress or other reports must state that, unless reports are submitted promptly, payment will be withheld. The FDA officials believe this approach ensures that most progress reports will be submitted as required and provides a means for penalizing the few contractors who do not meet the terms of the contract. They added that FDA has issued a Procurement Instruction which establishes a formal procedure whereby samples of contracts are periodically reviewed for compliance with the contract requirements and procurement regulations. They said that corrective action is taken on deficiencies noted.

Because our review was limited to the nitrite study contract, we cannot comment on the effectiveness of the program cited by FDA officials. However, during our review we did note the following:

--The project officer notified the contracting officer in June 1977 that progress reports for June 1976 to March 1977 were not acceptable. There is no evidence that the contracting officer followed up with the researcher to ensure that the reports were satisfactorily corrected.

--The project officer did not evaluate the progress report for the March 1977 to June 1977 contract period in writing as required. There is no evidence that the contracting officer acted to ensure that the progress report was evaluated.

--The researcher did not submit progress reports 13 and 14 (due 10/13/77 and 1/12/78, respectively). There is no evidence that the contracting officer took any followup action to ensure that the reports were submitted.

We recognize it takes time to implement new procedures. However, the above examples point out that, as much as 1 year after HEW initiated its program to correct deficiencies, appropriate followup action had not been taken regarding the MIT contract.

CHAPTER 4

NEED TO ENSURE THE ACCURACY OF PATHOLOGICAL DIAGNOSES FOR FDA-SPONSORED STUDIES

FDA's review of long-term study results does not usually include a reexamination of the animal tissue slides which, along with notes from the physical (gross) examination of the animal, are the basis for the researcher's pathological diagnoses. FDA did not reexamine animal tissue slides for the nitrite study until questions about the validity of the researcher's diagnoses were raised by IAWG pathologists. Their review of a sample of slides from animals diagnosed by the MIT researcher as having lymphoma led to the award of a contract for an independent reexamination of all slides from animals in the nitrite study. The contract also provides for reexamining some animal tissue slides from the nitrite/morpholine study which implicated nitrite as a possible cancer-causing substance. Accurate pathological diagnoses are essential since conclusions drawn from them may have major regulatory impact.

Pathology diagnoses provide the information necessary for comparing tumor incidences, types, and latency periods for treated and control animals, a process essential for determining the cancer-causing potential of a test substance. The diagnoses are made by a pathologist who examines the animals as they die or are killed and assesses the gross and microscopic changes that have taken place during the study.

The gross examination includes an inspection of external and internal organs and tissues. It pinpoints tumors and abnormal changes in an organ's size or proliferation of its tissues for later microscopic examination and classification. After the gross examination, representative tissue sections are mounted on slides and stained for microscopic examination. The pathologist who reviews the slides examines the cellular structure for any abnormalities. The microscopic examination enables the pathologist to establish the diagnosis and determine the extent of damage to the tissues examined. The findings of the gross and microscopic examinations are summarized in a pathology report.

FDA STUDY EVALUATIONS DO NOT ROUTINELY TEST THE ACCURACY OF PATHOLOGY DIAGNOSES

FDA has no written procedures guiding scientific evaluations of contract study results. Bureau of Foods officials told us that the division sponsoring the study decides how to evaluate it. Both the Commissioner and the Bureau Director told us that the Bureau's evaluation of study results includes a reexamination of the animal tissue slides. The Director of the Bureau's Division of Pathology told us, however, that this is not routinely done because the Bureau has too few pathologists to make such reviews. He believes, however, that the Division of Pathology should reexamine the pathology from all studies making positive findings of importance. In the case of nitrite, such a review was initiated after the IAWG became involved in assessing the study's validity.

According to a Bureau of Foods' toxicologist, when he evaluates the pathology from a study, he compares the report of the gross examination with that from the microscopic examination to determine whether the gross appearance of the animal is consistent with the diagnosis made from the microscopic examination of its tissues; however, he does not review the animal tissue slides used in the microscopic examination.

In a published article, 1/ the Acting Chief of the Tumor Pathology Branch, National Cancer Institute Carcinogenesis Testing Program, and others point out that

> "Pathology findings rely upon judgment and interpretation rather than precise and quantitative measurements. A quality assurance program attempts to provide standards which may serve as a guide to pathologists and technicians to achieve the necessary objectivity."

1/Ward, J.M., Goodman, D.G., Griesemer, R.A., Hardisty, J.F., Schueler, R.L., Squire, R.A., and Strandberg, J.D., "Quality Assurance for Pathology in Rodent Carcinogenesis Tests," Journal of Environmental Pathology and Toxicology, vol. 2, no. 2, pp. 371-378, 1978.

The article outlines NCI's quality assurance program in reviewing study results, including its review of slides by NCI pathologists who have extensive experience in identifying lesions in the strains of rodents used. These pathologists review slides from a statistical sample of animals having tumors and related lesions, and organs affected by the test substance, and write a quality assessment report. An NCI Pathology Working Group--a team of pathologists associated with NCI's Testing Program--evaluates examples of induced tumors and lesions and any obvious discrepancies noted in the quality assessment report. In controversial cases, the NCI Working Group may determine the diagnoses by consensus.

The Chairman of the Cancer Assessment Committee believes that FDA should not accept contract reports concerning bioassay-type studies unless samples of pathological diagnoses have been confirmed to ensure the validity of the study diagnoses.

VALIDITY OF MIT PATHOLOGY DIAGNOSES IN DOUBT

The MIT researcher has revised his pathological diagnoses twice since submitting his final report. Government pathologists reviewing a sample of his diagnoses questioned their accuracy. As a result, FDA has contracted with an independent consortium of university-affiliated pathologists to review all animal tissue slides from the nitrite study to determine the validity of the researcher's diagnoses.

MIT researcher submitted revised diagnoses after final study report issued

On May 30, 1978, after the MIT researcher's oral briefing, the project officer and a Bureau of Foods toxicologist visited MIT to look at the draft of the final study report. While at MIT, the toxicologist looked at the pathology reports, but not at the slides. The toxicologist told us that, upon his return from MIT, he suggested to the Commissioner's task force that the slides from the nitrite study be reviewed. He said that his comparison of the gross and microscopic reports, coupled with the researcher's conservative reputation (i.e., always having to be very certain of his diagnosis), caused him to be concerned that the actual incidence of lymphoma was probably higher than reported by the researcher.

The researcher's final report, dated May 18, 1978, and submitted to the agency on June 1, 1978, supported the information provided to FDA during his May 2 briefing. The researcher later revised his pathological diagnoses twice.

In explaining the basis for the revised diagnoses, the researcher told us that he had been working under self-imposed pressure to complete the pathology evaluations since it had already taken him over a year longer than he expected to complete the study. After the final report was submitted, he said, he had more time and began to review the slides with another pathologist at MIT. The researcher said that, before this, no other pathologist had made a detailed review of positive slides. He said that a pathologist at Peter Bent Brigham Hospital in Boston had previously looked at several slides to confirm the researcher's diagnosis of a tissue change not normally seen in rats. However, this had been an informal and limited review.

On August 10, 1978, the MIT researcher advised FDA by telephone that his reassessment of tissue slides showed a decrease in the number of lymphoma previously reported in all animal study groups but two. On August 25 he submitted this information to FDA in writing.

Again, on September 25 the researcher revised his pathological diagnoses. At this time, he advised FDA that malignant tumors previously categorized as "of undetermined origin" were "most likely lymphosarcomas" and should be included in the totals for lymphomas.

A comparison of the incidence of lymphoma reported to FDA in the May 18 final study report and the August and September revisions is shown in the table on the following page.

Data on Incidence of Lymphoma in MIT Nitrite Study as Reported by the Researcher

Group number (note a)	Vehicle/ diet base (note b)	Nitrite dose (ppm)	Number of animals in group	Number of animals with lymphoma 5-18-78	Incidence of lymphoma (note c) (percent)	Number of animals with lymphoma 8-25-78	Incidence of lymphoma (note c) (percent)	Number of animals with lymphoma 9-25-7c	Incidence of lymphoma (note c) (percent)
1	/Agar Gel	0	136	7	5.1	5	3.7	5	3.7
2	Food/Agar Gel	250	136	12	8.8	10	7.4	11	8.1
3	Food/Agar Gel	500	136	11	8.1	11	8.1	11	8.1
4	Food/Agar Gel	1,000	136	14	10.3	11	8.1	11	8.1
5	Food/Agar Gel	2,000	136	16	11.8	14	10.3	15	11.0
6	Water/Agar Gel	1,000	136	21	15.4	16	11.8	17	12.5
7	Water/Agar Gel	2,000	134	19	14.2	14	10.4	15	11.2
9	/Rat Chow	0	132	11	8.3	9	6.8	9	6.8
10	Food/Rat Chow	1,000	134	17	12.7	14	10.4	14	10.4
11	Food/Rat Chow	2,000	132	11	8.3	12	9.1	12	9.1
13	/Dry Casein	0	136	12	8.8	10	7.4	12	8.8
14	Food/Dry Casein	1,000	136	21	15.4	18	13.2	20	14.7
d/15	/Agar Gel	0	33	3	9.1	1	3.0	1	3.0
d/16	Food/Agar Gel	1,000	34	9	26.5	6	17.6	6	17.6
e/17	/Agar Gel	0	136	12	8.8	6	4.4	9	6.6
e/18	Food/Agar Gel	1,000	131	22	16.8	16	12.2	16	12.2
				218		173		184	

a/Groups 8 and 12 have been omitted from this table since their only purpose in the study was to demonstrate susceptibility of the strain of rats used in the study to the inducement of lymphoma by a known carcinogen--urethane.

b/The vehicle is the method by which nitrite was administered to the treated animals.

c/Rounded to the nearest 0.1 percent.

d/Animals in groups 15 and 16 were the mothers of animals in groups 1 and 4.

e/In contrast to animals in groups 1 to 14, whose exposure to their assigned group diets began in utero, animals in groups 17 and 18 were not exposed to their assigned group diets until they were weaned.

Government pathologists differ with researcher's diagnoses

After reviewing the MIT nitrite study report and consulting with officials from NCI and the Center for Disease Control, on August 25, 1978, the Assistant Secretary for Health suggested to the FDA Commissioner that arrangements be made for "an independent review of the pathological findings" if this had not already been done. Similarly, members of the IAWG on Nitrite Research attending the group's first meeting on August 28 believed that the pathological diagnoses should be independently reexamined. The minutes of the meeting gave the rationale for the review:

> "If the NCI pathologists agree with * * * [the researcher] on most counts they would have confidence in his interpretations. Once it is determined that the diagnoses are reasonable, their significance will be assessed."

As a first step, the IAWG proposed that the project officer obtain all slides for animals diagnosed as having lymphomas and/or immunoblastic proliferations in groups where the statistical significance of the findings appeared to be the greatest. IAWG pathologists would review a sample of these diagnoses.

In accordance with the IAWG's proposal, slides were obtained and the group's pathologists--one from FDA and one from NCI--reviewed slides from about 25 percent of the rats diagnosed by the researcher as having "lymphoma." On September 28, 1978, the two pathologists independently conducted a "blind review" (i.e., they did not know from which group each rat originated) of a sample of slides indicated in the May 18, 1978, final nitrite study report as having "lymphoma."

Diagnoses from all groups were sampled, except for groups 15 and 16 (mothers of rats in groups 1 and 4), which were reviewed completely, and groups 8 and 12 (the urethane-treated animals), which were not reviewed at all. The FDA pathologist reviewed slides from 35 animals, and the NCI pathologist reviewed slides from 29. Slides from 21 of the animals selected were common to both. On October 4, 1978, the NCI pathologist reviewed slides from another 25 animals--9 of which had been reviewed by the FDA pathologist on September 28. In all, slides from 59 of the animals

diagnosed by the researcher as having lymphoma were reviewed by the FDA pathologist or the NCI pathologist, and slides from 30 of the 59 animals were reviewed by both. The two pathologists' diagnoses agreed on most of the 30 slides.

The FDA pathologist's memorandum summarizing his review of slides from the 35 animals states that he was unable to confirm the researcher's diagnoses of malignant lymphoma in 29 of the animals. Of those 29, however, he diagnosed malignancies other than lymphoma in 23. 1/ In the other six animals, he found either benign or nontumorous conditions. Based on his review, he concluded:

> "Although the present review covers only about 16% of all animals diagnosed malignant lymphoma, the differences in diagnosis are so pronounced it would appear highly probable that the differences will be sustained in a total review of approximately 217 malignant lymphomas."

The NCI pathologist agreed with the researcher's diagnosis for only 2 of the 29 animals in his initial review on September 28. He diagnosed malignancies other than lymphoma in 16 of the 29 animals and found nonmalignant conditions in the other 11. Reporting on his review, he stated that:

1/These 23 malignancies did not occur at a single tissue/organ site. Therefore, a finding of 23 malignancies other than lymphoma is not necessarily of the same significance as a finding of 23 lymphoma. The finding may be more or less significant depending upon the organ/tissue sites at which the tumors occur and the spontaneous tumor rates at those sites. The significance of the tumor rate at a particular organ/tissue site is assessed by comparing the number of tumors observed in treated and untreated animals at that site. A relatively small increase in tumors at a site having a low spontaneous tumor rate may be very significant, while a larger increase in tumors at a site with a high spontaneous tumor rate may not be significant.

"* * * a review of these 29 cases provided evidence that the pathologist(s) responsible for the histopathologic diagnoses on the necropsy forms and in the MIT Final Report were not familiar with typical rodent lesions and/or lacked expertise in histopathology."

On the basis of the NCI pathologist's October 4 review of slides from 25 animals diagnosed as having lymphoma, he concurred in the researcher's lymphoma diagnosis in only 5 animals. Of the other 20 animals the researcher diagnosed as having lymphoma, the NCI pathologist found malignancies other than lymphoma in 12 animals and nonmalignant conditions in 8 animals.

In response to the review and statements by the two pathologists, the MIT researcher stated:

"Whether or not either are accurate, I can only commend the FDA pathologist for summary and his fair but appropriate conditional evaluation. However, one can only condemn the kinds of comments that the NCI pathologist made * * * in which he not only concludes that he is right in his diagnoses and that the two of us, * * * [a consulting pathologist], who is a board certified medical pathologist and practicing in the Boston hospitals and I, who am an A.C.V.P. [Amercian College of Veterinary Pathologists] board certified pathologist are not only unfamiliar with typical rodent lesions which we have looked at for the past 20 years but lack expertise in histopathology in general. It was not my impression that the FDA was asking for anything more than a diagnosis of the lesions observed and not a personal attack upon the pathologist who made that report. These kinds of comments of course are consistent with those who are unfamiliar with the nature of the problem and the biological behavior of reticuloendothelial tumors in rodents."

FDA awards contract to examine slides from nitrite and nitrite/morpholine studies

Based on the conclusions of the two IAWG pathologists, the group determined in its October 18, 1978, meeting that

a thorough, impartial reexamination of the slides by an independent group of expert pathologists was needed. Consistent with the group's decision, its Chairman, Co-chairman, and the FDA pathologist prepared a Justification for Non-Competitive Procurement. According to the October 19, 1978, justification:

> "In order to establish public confidence that the data generated by * * * [the researcher] and his associates are accurate and reliable, the best available pathology experts should conduct a major re-examination of the histopathology in a manner designed to assure the FDA and the public that no significant biases occur either from the professional viewpoint or from the viewpoint of a conflict of interest, financial or otherwise."

On March 30, 1979, FDA awarded a contract to evaluate the slides from the nitrite and nitrite/morpholine studies to UAREP. (See p. 27.) A final assessment of the validity of the researcher's pathological diagnoses cannot be made until UAREP's examination of the slides is completed; however, a June 15, 1979, progress report from the contractor referring to the pretest of tissues from the nitrite/morpholine study states that:

> "(a) The Nitromorpholine Study is not adequate as a pretest because * * * [the researcher] sectioned very few tissues, often failed to section tumors and made very incomplete histologic records.
>
> "(b) The Nitromorpholine Study shows poor agreement between * * * [the researcher] and UAREP's first pathologist. In tumor diagnosis there was agreement in less than 1/2 the diagnoses. In the case of lymphoma, * * * [the researcher] appears to have made the diagnosis about three times as often as UAREP.
>
> "(c) There was good agreement (over 95%) between UAREP's first pathologist and the consensus group."

In comments on the slide review by the two IAWG pathologists and the UAREP slide evaluation, the MIT researcher stated (see app. IV),

"* * * I can only point out that my experience in diagnosing typical rodent lesions are in excess of the experience that the two government pathologists have had and I am hopeful that the UAREP report will help in resolving the question."

Work under the contract is expected to be completed in late February 1980.

CONCLUSIONS

Determination from a study that a substance causes cancer is usually based upon a comparison of tumor incidences, tumor types, and the lengths of time for tumor development in treated and control animals. Pathology, the science of diagnosing these factors, is subject to judgmental decisions. In studies involving weak carcinogens, a few inaccurate pathology evaluations may result in incorrect conclusions. An accurate pathological evaluation is vital because conclusions drawn from the evaluation may shape major regulatory decisions. Therefore, for all FDA-sponsored studies on which regulatory action is contemplated, FDA should ensure the accuracy of pathological diagnoses by verifying tissue slide diagnoses and examining the researcher's records.

RECOMMENDATION TO THE SECRETARY OF HEW

We recommend that the Secretary direct the FDA Commissioner to develop a system for ensuring the accuracy of pathological diagnoses for FDA-sponsored studies on which regulatory action is contemplated and to consider the need for verifying tissue slide diagnoses as part of that process.

FDA RESPONSE

FDA officials generally agreed with the need to require verification of pathological diagnoses for FDA-sponsored studies. According to them, the cost of uniformly requiring separate verification of all pathology slides from all studies would be prohibitive and probably not justified from the perspective of the taxpayer. For that reason they do not intend to adopt a policy of verifying all pathology slides, but will explore the merits of having samplings from each contract verified. They pointed out, however, that undertaking verification could reduce other work that can

be done either by contract or in-house and that the extent of verification will be limited by the relatively small number of trained scientists qualified to evaluate the pathology of tissues prepared from small animal/rodent experiments.

FDA officials further stated that FDA currently does verify pathology results when there are internal inconsistencies (e.g., gross observations and clinical biochemistries) that are not consistent with the pathology; when certain pathology descriptions are ambiguous or do not agree with overall conclusions; when results are at odds with other available data on the substance under study or chemically similar substances that have been studied; or when data from other sources (short range-finding tests, human data, etc.) suggest that there are inconsistent findings. They pointed out that in the nitrite case FDA has undertaken a 100-percent verification of the pathology based upon anomalies in the final report revealed during the scientific evaluation of the study.

CHAPTER 5

GUIDELINES FOR STUDY DESIGN, DATA RECORDING AND REPORTING, AND STATISTICAL EVALUATION NEEDED

Deficiencies in the design and the recording and reporting of data for the MIT study may have caused FDA to overstate the risk associated with nitrite. Moreover, procedures used by the researcher and FDA to evaluate the statistical significance of the MIT study results may have biased the findings.

FDA does not have guidelines for design and data collection and reporting for long-term toxicity studies. Nor does FDA have guidelines for making statistical evaluation of study results. Such guidelines would help ensure that study designs are adequate in light of current scientific thought, that the data necessary for evaluation of study results are collected and reported, and that the evaluation is performed consistently, in order to minimize bias or the appearance of bias.

GUIDELINES FOR THE DESIGN AND DATA COLLECTION AND REPORTING OF LONG-TERM TOXICITY STUDIES LACKING

FDA does not have guidelines for the design of, or the data collection and reporting for, long-term toxicity studies. The design and data requirements of each study are planned by a Project Advisory Group on an ad hoc basis. Since the membership of the PAG varies from study to study, important aspects of each plan may differ, and there is no assurance that the study's design will be adequate in light of current scientific thought or that all data required for statistical analysis of the study results will be collected and reported. Recognizing design problems involving food additive safety studies, Bureau of Foods scientists noted in November 1978 that:

> "A major difficulty in the preparation of a safety profile for a food additive, is the lack of common, consistent, and clearly defined testing guidelines for the design and conduct of required toxicological studies. Another difficulty is the lack of orderly

recording and reporting of the critical information required for assessment of effects observed in toxicological tests."

Bureau officials believe that guidelines embodying standards that could be used to evaluate the quality and adequacy of food safety studies could eliminate these difficulties.

Study design deficiencies may reduce the statistical significance of study results

The design of both the nitrite and nitrite/morpholine studies failed to consider the possibility that animals from the same litter tend to respond similarly to a test substance (litter effects) or the impact this could have on the interpretation of the studies. If the study data are characterized by litter effects, FDA's failure to consider them in the statistical analysis of study results could cause an overstatement of the risk associated with nitrite added to food.

Litter effects, which have been recognized since the late 1960s, are characteristic of data generated when a study includes more than one animal from the same litter. Litter effects may be due to such factors as genetic backgrounds, prenatal exposure through the placenta, and exposure through mother's milk during lactation. Researchers point out that, when a study uses more than one animal per litter, litter effects seem to be present as the rule, rather than as the exception--particularly if a carcinogenic response to a test substance is induced or enhanced through prenatal exposure to the test substance.

Except for groups 15 and 16 (mothers) and groups 17 and 18, each group of nitrite study animals was composed of the litters from 34 pregnant animals who were placed on assigned group diets about 5 days before giving birth. The study protocol specifies selecting two males and two females from each of the 34 litters, totaling 136 rats per group. The protocol for the nitrite/morpholine study, like that for the nitrite study, required animals to initially become exposed to the test substance in utero, but called for selecting eight animals per litter rather than four.

The Head of Chemical Statistics, Health and Welfare Canada, who is evaluating the MIT study for the Canadian government, told us that the potential for litter effects

is present in the nitrite and the nitrite/morpholine studies. He said that, if there are litter effects in these studies, the effective sample size could be somewhat less than the number of animals per group. For example, if each member of a litter responds to a test substance the same way that all other members of the litter respond, then the number of animals for statistical purposes would equal the number of litters. On the other hand, if each member of a litter responds to a test substance in a way that is totally different from the way all other members of that litter respond, then the number of animals for statistical purposes would equal the number of animals in the group. In reality, however, neither of these extremes is likely to exist. Rather, the effective sample size would be somewhere between these extremes. He pointed out that, if there are litter effects in a study, the probability of detecting carcinogenic effects decreases as the number of animals selected per litter increases. He said that, if existing litter effects are not considered in the statistical analysis of study results, any risk identified with a test substance could be overstated.

Lack of specificity in nitrite protocol hampered study evaluation

The nitrite and the nitrite/morpholine study contracts did not include specific instructions concerning what data the researchers should collect during the studies or which categories of data should be submitted to the agency with the final study reports. These determinations were left to the MIT researchers. Consequently, data needed to answer specific questions about the validity of the study results were not available at the conclusion of the study because the researcher had not recorded the information during the study. In other cases, some data that FDA scientists needed to evaluate the studies were submitted late. Complete recording and reporting of critical information is necessary to evaluate toxicity study results.

Certain critical information was not recorded during the nitrite study. For example, a toxicologist on the Commissioner's Task Force said the agency cannot answer questions about apparent differences between the four lots of animal shipments because no records were kept on how the animals were randomized. He said that this could mean that, rather than being considered as one large study, the

nitrite study would have to be viewed as four separate studies. Furthermore, one of those studies might have to be discounted since animals from one shipment were assigned only to groups 5 through 8. No animals from that shipment were assigned to the untreated group, which was used as the control for nitrite-fed groups 5 through 7.

The Director of the Division of Mathematics, Bureau of Foods, said that the researcher's nitrite study data tended to be reported in summary form and was much less detailed than data usually submitted to FDA on the safety of a food additive. He said that, although FDA intended to make its own analysis of the MIT researcher's data when the final nitrite study report was submitted, its analysis was delayed because

--some data needed for the analysis were not included in the final report (e.g., length of time individual animals lived, identities of litter mates, and response data on males versus females) and

--data originally submitted on the incidence of lymphoma were changed twice, resulting in an overall decrease in the reported incidence of lymphoma.

STATISTICAL EVALUATION MAY HAVE OVERSTATED NITRITE RISK

FDA does not have guidelines for statistically evaluating study results. Some scientists on the IAWG and others have criticized the statistical procedures used by the MIT researcher and FDA to evaluate the nitrite study data. Some of the questioned procedures relate to:

--Comparing combined data from all animals fed nitrites with combined data from all animals not fed nitrites, rather than comparing data from each test group with its appropriate control.

--Using an inappropriate control group to determine the effects noted in some nitrite-fed animals.

--Failing to adjust study results for the differing lifespans of the animals, which may have affected their chances of developing tumors (i.e., some animals may have developed tumors because they lived longer and had, therefore, a greater opportunity to develop them).

Long-term toxicity studies generally (1) involve feeding a substance to test animals of both sexes over their lifetimes and (2) produce animal data that provides a basis for evaluating the changes that occurred during the study. The scientists reviewing the study evaluate the carcinogenicity of the test substance by examining the reported animal survival and tumor patterns. Statistical evaluation methods allow scientists to interpret the data by quantifying the strength of the experimental evidence.

Bureau of Foods scientists reviewing study results determine how the data are analyzed, and these determinations may differ with each scientist. As a result, the statistical treatment of study data may vary. In studies involving strong carcinogens, the procedures may affect the strength of the experimental evidence, but are not likely to affect the overall determination of carcinogenicity. For weak carcinogens, however, using inappropriate procedures may lead to an erroneous determination about carcinogenicity.

In the absence of proper evaluation procedures, bias may be introduced into the analysis. According to an FDA statistician, if an analysis begins with a bias, the statistical analysis can be made to support that bias. Even if the analysis is not characterized by intentional bias, there may nonetheless be an appearance of bias. For example, in an August 1, 1979, report, "Case History of FDA Actions on MIT Nitrite Study," the Congressional Research Service stated that FDA documents and statements it reviewed imply that the agency's scientific review of the MIT nitrite study was a "formalistic process of validating results, rather than the unbiased scrutiny it is intended as."

CONCLUSIONS

The design, recording of data, and statistical evaluation of the MIT study could have greatly influenced the conclusions drawn from it. The study design did not consider the impact litter effect could have on interpretation of the study results. Consequently, FDA's statistical analyses of the MIT study, which provided the basis for preliminary assessments of the nitrite risk, may have resulted in an overstatement of the risk. Certain questions about the validity of the study cannot be answered because the information needed was not recorded during the study. Deficiencies in FDA's statistical evaluation, including the use of combined data and inappropriate animal controls, may have

biased the nitrite study analysis toward a finding of carcinogenicity. Because of the regulatory impact that often results from analyses of long-term toxicity studies and to eliminate bias or the appearance of bias in the study evaluation, guidelines are needed to ensure that study evaluations are performed consistently.

To minimize such problems in future FDA-sponsored studies, FDA should develop formal guidelines concerning design, data collection and reporting, and statistical evaluation of long-term toxicity studies.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the FDA Commissioner to (1) develop guidelines for design and data collection and reporting of long-term toxicity studies and (2) establish standards and methods for statistically evaluating such studies.

FDA RESPONSE AND OUR EVALUATION

FDA officials stated that the scientific community has struggled for years toward an amenable solution to the very difficult and complicated problems of study design and statistical evaluation and pointed out the difficulty in developing a single set of guidelines that would receive universal approval by the scientific community.

FDA officials agreed that guidelines can be helpful in designing long-term toxicity studies and noted that, by regulation, they rely on three published documents: The "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959), "Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides" (1970), and the "Guidelines for Carcinogen Bioassay in Small Rodents" (1976).

FDA officials also said that, in March 1979, the agency published for comment a document entitled "Scientific Bases for Identifying Potential Carcinogens and Estimating Their Risks," dealing with proposed criteria and procedures for evaluating assays for carcinogenic residues in food-producing animals. When the document is published in final form, it is to also provide guidance on designing and evaluating long-term toxicity studies intended to determine the carcinogenicity

of chemicals. In addition, according to FDA officials, the ongoing Cyclic Review of Food Additives and Generally Recognized As Safe Substances has developed information relating to study design and evaluation of toxicological studies that will serve as guidelines when they are published as procedural regulations. They recognize the continuing need to update such guidelines through a comprehensive review process.

FDA officials said that limited guidelines for statistical evaluation are contained in these documents and that, as a result, statistical techniques not cited in these documents may sometimes be used. Whether a statistical procedure is appropriate in a particular situation can involve substantive biological issues and may be controversial. According to the officials, these issues are not amenable to resolution through the use of guidelines.

Although we recognize that designing long-term toxicity studies and establishing standards and methods for statistical evaluation are difficult and complicated subjects, we believe that more guidance should be made available to FDA scientists and statisticians. During our discussions with Bureau of Foods scientists involved in long-term toxicity study design, none mentioned the guidelines that FDA officials later cited as relevant. Bureau statisticians said they were free to use any procedure that, in their professional opinion, was appropriate for the study under evaluation.

CHAPTER 6

FDA LABORATORY INSPECTION IDENTIFIES SERIOUS PROBLEMS WITH NITRITE STUDY

In January 1977, FDA inspected the researcher's laboratory at MIT and found several deficiencies. The inspection was based on proposed Good Laboratory Practices regulations that became final in December 1978. Deficiencies that raise important questions about the validity of the study results relate to

--contamination of the laboratory environment,

--a feeding mixup in which a negative control group received nitrite-treated feed, and

--failure to follow the study protocol.

These matters have been referred to the IAWG on nitrite for further assessment. The group's work is not expected to be completed until mid-1980.

GLP INSPECTION OF MIT STUDIES

In early 1976, FDA discovered that some studies used to support the approval of new human and animal drugs, food additives, and biological products had been conducted in a shoddy and sloppy manner and that the reporting of some results was fraudulent. As a result, FDA initiated a Bio-Research Monitoring Program in part to evaluate nonclinical (animal) toxicology laboratories.

On November 19, 1976, FDA published proposed GLP regulations for nonclinical toxicology laboratories in the "Federal Register." (Final regulations were published Dec. 22, 1978.) The regulations called for inspecting the physical condition and operation of the specific laboratory and evaluating the studies conducted there. These regulations outlined proper procedures for conducting nonclinical studies, including standards for animal facilities, animal care practices, qualifications of personnel, recording and handling of data, administration of the test and control substances, maintenance of records, and reporting of results.

Before the final GLP regulations were issued, FDA tested the regulations by devising a pilot inspection program. The program was designed to

--improve the proposed GLP regulations where necessary,

--gain experience useful in making later investigations,

--show that FDA intended to aggressively inspect the animal laboratories, and

--take administrative or regulatory action based on deficiencies found that might affect the validity of the studies inspected.

Inspections were made by teams composed of at least one headquarters scientist and one field office inspector. Because this was a new program, all team members participated in a 2-week training course at the National Center for Toxicological Research, Jefferson, Arkansas, specifically designed for the GLP program.

During the pilot program FDA teams inspected 39 nonclinical laboratories. Each FDA bureau participating in the pilot program--Food, Drugs, Biologics, and Veterinary Medicine--selected laboratories and studies to be inspected. The Bureau of Foods selected studies that were submitted to support the safety of food and color additives during the 5-year period 1971-76. Laboratories were selected on a stratified random sampling basis by laboratory type (university, contractor, sponsor) and level of activity (those involved in three or fewer studies and those involved in four or more studies in the 5-year period). MIT was the only laboratory specifically selected by the Bureau of Foods, since results from three MIT studies--nitrite, nitrite/morpholine, lactose--were of concern to the Bureau during this period. MIT was one of three laboratories found to have deficiencies that FDA considered serious.

A team of FDA inspectors visited the MIT researcher's laboratory on January 11-14, 17-21, and 26, 1977. Using the proposed GLP regulations as guidelines, they observed animal care, handling, and facilities; diet preparation and feeding; and necropsies 1/ for the ongoing nitrite study

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1/The post-mortem examination of test animals.

and reviewed histological slides, necropsy records, and research notebooks for the nitrite study and the completed nitrite/morpholine study.

FDA's Establishment Inspection Report cites the following deficiencies:

1. An animal caretaker was observed feeding the wrong diet to a group of rats. He was feeding a test diet containing nitrite to a control group that was to receive a nitrite-free diet.

2. A vitamin supplement was administered to test animals without apparent authorization.

3. Test and control diets were mixed in a common container without washing between mixes.

4. Animals were changed from one study group to another without justification or inclusion of that fact in the final report (nitrite/morpholine study).

5. For the nitrite/morpholine study, differences were noted between the final report summary and the raw data summary of the number of rats started on the experiment. In some instances the final report lists a larger number than the raw data.

6. MIT had no quality assurance unit. Such a unit is responsible for assuring conformance of the facilities, equipment, personnel, methods, and controls to the GLP regulations; the quality and integrity of the data obtained from the laboratory; and adherence to protocols and standard operating procedures.

7. MIT had no written standard operating procedures for laboratory tests, data storage and retrieval, test system observations, and the receipt, handling, and administration of test control substances.

8. Handling of test and control substances did not conform to the regulations in that:

   (a) Diets were prepared in a common preparation room that had no dust control system, and no measures were taken to prevent cross-contamination.

(b) The positive control substance, urethane (a potent, highly volatile carcinogen), was stored on top of a cabinet in one of the rooms housing test animals.

9. Study protocols were not observed in that:

   (a) Not all tissues requiring examination were examined by a pathologist.

   (b) Changes in protocols were not documented or signed by the study director.

10. The animal room environment was not monitored for air quality, and drinking water was not periodically analyzed for contaminants.

11. Test and control substances undergo decay--a change in chemical composition which decreases their concentration over a period of time. Test and control substances were not tested for stability, either before beginning the study or before feeding the animals.

The deviations cited in the inspection report were discussed with the researcher. He stated that, although he could not justify mistakes and errors, he believed that, because his laboratory is a university research laboratory and not a commercial testing laboratory, some of the GLP regulations should not apply. The researcher told the inspectors that some of the deviations would be easily corrected and that he would address his views on the applicability of GLP regulations to a university research laboratory in written comments.

GLP deviations raise serious questions about the validity of study data

The Establishment Inspection Report containing the checklist, narrative, and summary was received in the Bureau of Foods on March 23, 1977. A Bureau of Foods' GLP monitoring unit, composed of two toxicologists and one person with a regulatory background, made a detailed scientific review of the inspection report.

In its March 30, 1977, report, the monitoring unit noted that five GLP deviations were cause for critical concern. The unit stated that, on the basis of these deficiencies:

"* * * coupled with the observation of rampant lack of adequate control on the studies, we conclude that the studies observed are of questionable integrity."

The monitoring unit also concluded that the studies had "serious deviations from acceptable scientific procedures" and could not be used to demonstrate safety. FDA's current policy, as stated in the discussion of the GLP regulations in the Federal Register, provides that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard.

The monitoring unit submitted its findings with several recommendations to a Bureau of Foods' GLP review committee, made up of one toxicologist and two regulatory representatives, which reviewed them for policy application. First, the monitoring unit recommended that MIT should be advised that (1) based upon the Establishment Inspection Report, the nitrite and nitrite/morpholine studies were not conducted in accordance with acceptable experimental procedures and (2) corrections must be made to preclude such practices from continuing. Secondly, an in-depth investigation should be made of the earlier MIT study of the safety of lactose. (See p. 69.) Finally, all future FDA-funded toxicology studies should be inspected using the GLP guidelines to ensure consistency in the conduct of the work.

With regard to the latter, the Acting FDA Commissioner, by memorandum dated September 7, 1979, instructed the agency to incorporate compliance with GLP regulations as a provision of all future contracts that deal with toxicological safety testing. He instructed that, if a laboratory has received a GLP inspection less than 1 year before the contract was let, a second inspection is unnecessary unless requested by one of the agency's bureaus.

With regard to the first two recommendations, the chairman of the review committee, in a memorandum dated April 4, 1977, advised the Director, Bio-Research Monitoring Staff, who is responsible for developing and implementing an FDA-wide program for monitoring all aspects of nonclinical testing, that "Our review of the subject EIR [Establishment Inspection Report] reveals significant deviations from acceptable experimental procedures." The chairman recommended that a letter be sent to the researcher

advising him of the committee's findings and requesting information on corrective measures to preclude future occurrences of the type observed during the inspection. He further recommended that a "for cause" inspection (an inspection initiated at the request of an agency unit because of questions arising from submitted data) be conducted at MIT on the lactose study.

According to an April 4, 1977, memorandum by the contracting officer, the Bureau of Foods' Extramural Review Committee, which is responsible for reviewing FDA-funded contracts, believed that the GLP inspection raised serious doubts concerning the validity of the study and recommended that the nitrite contract be terminated. Specifically, the committee was concerned that the feeding mixup would jeopardize the study results. According to a committee staff memorandum that discussed the April 20, 1977, meeting, however, the Director, Division of Toxicology, believed that the contract study should be completed since he thought that the pathology data from the study would be valuable. The difference of opinion between the committee and the Division Director was submitted to the Bureau's Acting Director, who decided to continue the contract for another 5 months.

In a May 11, 1977, letter to the researcher, the Associate Commissioner for Compliance discussed the five critical deviations from the GLP regulations and their effect on the validity of the nitrite and nitrite/morpholine studies. The letter stated:

> "Until we are assured that corrections have been instituted to preclude deviations from acceptable scientific procedures we cannot rely upon data from other studies you may have under way or contemplate for the future.
>
> "In the case of the work done under Contract No. 74-181 [nitrite study] the investigatory findings give us reason to question the data at this time. We will have to discuss the matter at some length in view of these discrepancies. If the study can be completed, we will review the data generated by this contract to see what conclusions can be drawn."

The researcher, by letter dated July 11, 1977, responded to the Associate Commissioner. He denied the feeding mixup had occurred, and with regard to the other four points, he explained that:

--Administration of a vitamin supplement to the diet of test animals without apparent authorization was done in a few cases because of a skin condition. Research notebooks show that (1) the supplement was authorized, (2) the animals were carefully chosen, and (3) the treatment and followup were adequately documented.

--Although mixing both test and control diets in a common container without washing between mixes was reported, the standard operating procedure was to mix first the control diet, then the test diet in ascending order of concentrations. All utensils were cleaned between mixing when it was considered necessary. Standard operating procedures assumed no chemical carryover to the next mix. Analyses show no contamination.

--Changing positive control group animals (group 12) from the positive diet to an untreated diet was properly documented. The action was taken because of a high mortality rate, which dictated discontinuing urethane in the diet.

--The unexplained differences in the final nitrite/morpholine report summary and the interim report data sheets on the number of rats started on the experiment (a smaller number is shown in the final report) was caused by missing animals, illegible numbers on cages, and two necropsy reports with the same number. Any animal with questionable identification was deleted.

The Bureau of Foods' GLP monitoring unit reviewed the researcher's response and, in a September 14, 1977, memorandum to the GLP Review Committee, concluded that circumstances existed that generally were sufficient safeguards to prevent a compromise of the nitrite study. Concerning the nitrite/morpholine study, the unit stated that, "based on the unexplained discrepancy concerning the number of rats actually started on the experiment, we conclude that the study is still questionable." Consequently, the monitoring unit recommended that a second letter be sent to the researcher.

In a September 19, 1977, letter the Acting Director, Bureau of Foods, advised the researcher that the explanations provided in his July 11, 1977, letter were satisfactory, except regarding the number of rats started on the nitrite/morpholine study. He requested additional information on the actual number of animals used in that study.

The FDA Boston district office did not agree that the researcher's explanations for the GLP deviations were satisfactory. The district office, by letter dated October 12, 1977, advised the Bureau of Foods' Acting Director that, although the researcher contended there was no feeding mixup, "control rats were observed eating the test diet." Regarding the other deficiencies, the district office advised the Acting Director that the district inspector's position is that:

--The administration of a vitamin supplement was not authorized in writing.

--Utensils used for the nitrite study were in a community kitchen and were not washed before the diet was mixed. Other investigators used the same utensils for their research.

--Quarterly reports submitted by the researcher did not show that a positive control group (group 12) had been switched to an untreated diet.

The researcher, in a letter dated October 18, 1977, provided additional information on the number of animals used in the nitrite/morpholine study. The FDA records we reviewed did not indicate any comments or response to this letter.

The Bureau of Foods' normal practice is to make a separate scientific and policy analysis for all laboratory responses to a GLP inspection. FDA made a scientific analysis of the July 11, 1977, response. However, we found no documented evidence that policy analyses were made of the researcher's July 11 and October 18, 1977, letters, nor did we find that a scientific analysis was made of the October 18, 1977, letter.

The Acting Director, Bureau of Foods, who had the ultimate responsibility in this matter, told us that he did not recall why the normal reviews had not been completed

before advising the researcher that his explanations were satisfactory.

GLP FINDINGS TO BE REVIEWED BY INTERAGENCY WORKING GROUP

The IAWG on nitrites, formed on August 8, 1978, to review and evaluate nitrites with respect to carcinogenicity and toxicity, is assessing whether the GLP inspection findings affect the validity of the study's conclusion. In May 1979, the chairman of the group told us that problems raised by the GLP inspection had not been resolved to the group's satisfaction. Two problems that the group identified as being potentially significant are urethane contamination and cross-contamination of treated and untreated feed.

Urethane contamination

Urethane, a potent, highly volatile carcinogen was used as a positive control to compare the results of exposing animals to a substance known to cause lymphoma with the results of exposure to nitrite. Treated feed with 2,000 ppm urethane was given to two of the study groups.

The FDA inspectors reported that the urethane bottle was kept on top of a cabinet in one of the rooms where animals were housed. The Director of the Bureau of Foods' Division of Chemistry told us that his experience had shown that urethane was so highly volatile it contaminated everything in the surrounding area. The Co-chairman of the IAWG told us that a urethane contamination rate equal to 1 percent of the urethane dose given to the positive control animals could have occurred and could have caused the nitrite study's result.

Cross-contamination of feed

The possibility that test animals in negative control groups actually ate treated or contaminated food was raised by the GLP inspection findings. The inspectors noted that:

--Mixing of all treated and untreated feed occurred in a common preparation room that had no dust control system, and no measures were taken to prevent cross-contamination.

--Containers and utensils were not washed between mixing batches of food.

--Other toxicants may have been mixed in the same room.

A USDA scientist who is a member of the IAWG has been asked to review this part of the inspection report. He is convinced that cross-contamination occurred during the nitrite study. He stated that, based on USDA's experience with commercial animal feed rooms:

--Dry feed is like powder and will spread completely over the room in which it is mixed.

--A 2- to 4-percent cross-contamination of feed is normal when one mixer is used to prepare all diets and the mixer is cleaned by washing.

--The type of mixing equipment used in a commercial feed lot and a laboratory is similar.

The questions to be decided are (1) how much cross-contamination actually occurred and (2) what level is significant enough to affect study results? These questions have not been resolved. The USDA scientist acknowledged that he does not plan to do any work on this problem until the UAREP pathology review has been completed and analyzed.

The IAWG minutes of meetings dated August 28, 1978, state that their questions relating to the management of the nitrite study are:

--Whether the feeding mixup in which treated feed was given to a control group occurred at other times.

--Whether cross-contamination occurred; given that the inspection showed (1) mixing of all treated and control feed was in the same room, (2) containers were not washed between mixing batches of feed, (3) other toxicants may have been mixed in the same room, and (4) a pest strip was in the animal room.

--Whether the feed and water were analyzed for nitrite levels actually fed to the test animals.

As to the seriousness of the problems identified by the GLP inspection, the MIT researcher stated:

> "The checkoff list that the Compliance Branch used was designed to be used in studies that are now being initiated. No such regulations were in effect in 1971 or in 1974 when both of these studies were designed and conducted. There was in fact, no contamination of the laboratory environment, a feeding-mix-up did not jeopardize the validity of the study and I am in agreement that the interagency working group should further examine the question to resolve the matter in their own minds, whether or not I agree with them."

These questions will not be resolved until the analysis of the UAREP report is completed.

CHAPTER 7

SCOPE OF REVIEW

We reviewed laws, regulations, and practices relating to FDA's analyses of the nitrite and the nitrite/morpholine contracts; inspected FDA records concerning the planning, administration, and monitoring of these contracts; and reviewed FDA efforts to analyze the nitrite study results and to formulate a policy on nitrite regulation. We also examined USDA's role in these matters.

We reviewed the nitrite and nitrite/morpholine study reports as well as other nitrite-related research, reports, and publications prepared by FDA, USDA, and other experts concerned with the scientific and health issues related to the nitrite/nitrate/nitrosamine problem. In addition, we studied both House and Senate hearings on the nitrite study report and Congressional Research Service issue papers.

From October 1978 through December 1979, we interviewed FDA and USDA officials; scientists from FDA, USDA, NCI, the National Institute for Environmental Health Sciences, the Frederick Cancer Research Center, and the Canadian government; and other interested parties. We also spoke with the FDA regional office personnel in Boston, Massachusetts, who performed and analyzed the GLP inspection and the MIT researcher in Cambridge, Massachusetts, who conducted the nitrite study.

NITRITE USES, PURPOSES, LEGAL STATUS, AND DATES OF APPROVAL

Use	Purpose	Legal status	Dates of approval
Meat	Preservative, curing agent, color fixative	Prior Sanction	1925, 1941, 1945
Fish (sable, shad, smoked chub, salmon)	Preservative, color fixative	Approved food additive	9/23/61 7/31/63 11/5/64 8/26/69
Poultry	Preservative	Unaproved food additive	-
Home cures	Preservative, color fixative	Approved food additive	3/3/62
Canned pet food	Color fixative	Approved food additive	9/23/61
Smoked cured tunafish	Color fixative	Approved food additive	9/23/61
Cod roe (note a)	Curing agent	Approved food additive	7/26/63
Imported cheese	Antimicrobial agent	Unapproved food additive	-
Indirect uses	Various	Approved food additives	Various

a/Nitrate rather than nitrite is approved for use in cod roe.

APPENDIX II

DATA ON INCIDENCE OF LYMPHOMA IN MIT NITRITE

STUDY AS REPORTED BY THE RESEARCHER

Group number	Vehicle/ diet base (note a)	Nitrite dose (ppm)	Number of animals in group	Number of animals with lymphoma 9-25-78	Incidence of lymphoma (note b)
					(percent)
1	/Agar Gel	0	136	5	3.7
2	Food/Agar Gel	250	136	11	8.1
3	Food/Agar Gel	500	136	11	8.1
4	Food/Agar Gel	1,000	136	11	8.1
5	Food/Agar Gel	2,000	136	15	11.0
6	Water/Agar Gel	1,000	136	17	12.5
7	Water/Agar Gel	2,000	134	15	11.2
8	Food/Agar Gel	c/0	136	37	27.2
9	/Rat Chow	0	132	9	6.8
10	Food/Rat Chow	1,000	134	14	10.4
11	Food/Rat Chow	2,000	132	12	9.1
12	Food/Rat Chow	c/0	136	14	10.3
13	/Dry Casein	0	136	12	8.8
14	Food/Dry Casein	1,000	136	20	14.7
d/15	/Agar Gel	0	33	1	3.0
d/16	Food/Agar Gel	1,000	34	6	17.6
e/17	/Agar Gel	0	136	9	6.6
e/18	Food/Agar Gel	1,000	131	16	12.2
			2,226	235	

a/The vehicle is the method by which nitrite or urethane was administered to the treated animals.

b/Rounded to the nearest 0.1 percent.

c/Groups 8 and 12 were fed a known carcinogen--urethane at 2,000 ppm. They are the positive control groups.

d/Animals in groups 15 and 16 were the mothers of animals in groups 1 and 4.

e/In contrast to animals in groups 1 through 14, whose exposure to their assigned group diets began in utero, animals in groups 17 and 18 were not exposed to their assigned group diets until they were weaned.

MEMBERS AND AFFILIATIONS OF INTERAGENCY WORKING GROUP ON NITRITE

Chairman

Associate Director for Science,
Bureau of Foods, FDA

Co-Chairman

Associate Director
for Regulatory Evaluation,
Division of Toxicology,
Bureau of Foods, FDA

Members

Assistant Director for Risk Assessment, National Institute of Environmental Health Sciences, NIH

Chief, Epidemiology Unit, Bureau of Foods, FDA

Coordinator in Vitro, Division of Cancer Cause and Prevention, National Cancer Institute, NIH

Associate Executive Director, National Institute of Environmental Health Sciences, NIH

Head, Mathematical Statistics and Applied Mathematics Section, National Cancer Institute, NIH

Staff Scientist, National Program Staff, Science and Education Administration, USDA

Scientific Coordinator for Environmental Cancer, National Cancer Institute, NIH

Acting Director, Residue Evaluation and Surveillance Division, Food Safety and Quality Service, USDA

Mathematical Statistician, Division of Mathematics, Bureau of Foods, FDA

Veterinary Pathologist, Tumor Pathology Branch, Division of Cancer Cause and Prevention, National Cancer Institute, NIH

Director, Division of Pathology, Bureau of Foods, FDA

Director, Division of Mathematics, Bureau of Foods, FDA

APPENDIX IV

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Graduate Programs in Food Science and Technology
Nutritional Biochemistry and Metabolism
Biochemical Engineering
Toxicology
Neural and Endocrine Regulation
Human and Clinical Nutrition

December 4, 1979

Philip A. Bernstein
Acting Director
United States General Accounting
Office
Washington, D.C. 20548

Dear Mr. Bernstein:

I appreciate the opportunity to look over the draft of the proposed report conducted by your staff relative to regulatory agencies and their activities concerning nitrite, in particular the studies done here at M.I.T. Since I am leaving the country today, I am having to dictate this letter and it will be transcribed and forwarded to you in order to reach you before December 7.

The cover statement is fair and reasonable and I am in general agreement with it. There is a need to strengthen procedures used in government contracts to ensure validity of data prior to issuing any formal report.

Page 1, fourth paragraph regarding reviews of the nitrite study by scientists inside and outside the government and questions that have been raised in turn raises some questions on my part. Anyone who critically reads the report that I submitted to the FDA as well as the lengthy explanation of the alleged irregularities discovered by FDA inspectors will see that only one of the alleged discrepancies had any substantive implications in any way. All of the others were satisfactorily resolved both to my satisfaction and to the satisfaction of the FDA representatives. The one question regarding the feeding of the diet containing nitrite to the control group was also satisfactorily resolved and I feel comfortable with the resolution of that question. Nitrite was not fed to control animals and the various levels that were administered either in the diet or the water were accurate. This was shown very conclusively by the analyses that were conducted during the conduct of the study.

APPENDIX IV

Page ii, the diagnosis of pathologic lesions in animals and man has traditionally and historically been a subject for debate because it is a subjective assessment. What we provide as pathologists is an opinion. That is exactly what I provided in the study results and other pathologists may or may not agree with my assessment. It is significant in fact that I have traditionally disagreed with diagnoses provided by the two government pathologists that looked at my material at the outset. It is not surprising then that the diagnoses of these two pathologists disagreed with my own. Furthermore, I was in complete agreement with the FDA in setting up an impartial review which is now underway. One should not be encouraged to think that the UAREP will in any sense agree unanimously with my diagnoses. In the final analysis however, I have no apologies and no doubt that the implications that my diagnoses delineated are indeed correct and that under the conditions of this study nitrite did affect the reticuloendothelial system in an adverse fashion.

Page iv, in regard to the laboratory inspection identifying serious problems, this I disagree with very strongly. The check-off list that the Compliance Branch used was designed to be used in studies that are now being initiated. No such regulations were in effect in 1971 or in 1974 when both of these studies were designed and conducted. There was in fact, no contamination of the laboratory environment, a feeding-mix-up did not jeopardize the validity of the study and I am in agreement that the inter-agency working group should further examine the question to resolve the matter in their own minds,whether or not I agree with them.

Page 7, The question of nitrosamines and the nitrosation of dietary amines by nitrite in the diet is one that is far from resolved. There can be no question in anyone's mind however that nitrosation does occur, that nitrosamines are indeed carcinogenic for a large number of animal species and probably man, and that a responsible regulatory agency will take this into account when assessing the addition of nitrite to foods consumed by a broad segment of the population. In that regard, please refer to the story about "Murder by Cancer" regarding an incidence of Stephen Roy Harper who prosecuters say committed the first murder by cancer and who has recently been sentenced to the electric chair. This is indeed a sobering thought in my view.

Pages 10-12, is an accurate accounting of some segments of the study including the original one with nitrite and morpholine.

Page 20, the statement by the Chief Counsel about his concerns relating to statements made by me in the final report are of interest. These comments which represent basically my feelings about the study results are accurate and should be kept in mind by anyone who is attempting to evaluate this study and my assessment of the results.

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Page 22. The comments of the 17 scientists responding to FDA's request for peer reviews are worthy of note as are those individuals who made the comments. There is no study published to date that cannot be taken apart if one wishes to critically evaluate everything. If it were possible to design and conduct a study that answered every question then there would be no further reason to spend billions of dollars investigating carcinogens in the environment today. This study conducted at M.I.T. did not propose to answer all questions. It simply put forward the suggestion that a second study using several different permutations of dietary exposure to nitrite might help resolve the previous observation. In that regard, I feel that it did do so. It can be understood readily that the reviewers who examined my report and who are intimately concerned with the meat industry particularly the pork production would be quite adverse to anything that might be said in a report suggesting that nitrite should be eliminated. For this reason much of the comment made about the study has to be taken with some caution.

Page 24. The question of the accuracy of diagnoses of the lesions by me and by the two pathologists who reviewed my study is again a reflection of difference of opinion and in my view an honest difference of opinion. But as I referred to earlier I have often disagreed with the diagnoses of these two pathologists.

Page 26. The top of the page regarding Good Laboratory Practices and the assignment of animals to the various groups refer to practices that were common in my laboratory and in virtually all of the others around the country and which were acceptable to the FDA and my own colleages at the time. Again there is a reference to the fact that the tumors may have been caused by nitrosamines and this I do not deny. However, as opposed to the statement on page 26 that no nitrosamines were detected,this is true. The person doing the feed analyses for me at that time was also analyzing samples from other studies that were ongoing as well as from tissue samples from animals. The two that were accomplished during this period were in with all of the others and I am sure that he did not have the identification of the samples that were analyzed. The samples were analyzed on two occasions and no nitrosamines were found although the methods used at that time were considerably less sensitive than the methods used today.

Page 27. The high incidence of spontaneous lymphomas in the control groups repeatedly comes up in discussions of the M.I.T. nitrite study. Anyone who wishes to take a look at the data and the literature relative to the incidence of lymphomas in this strain of rats as well as in others will find that it varies enormously. In fact, 6 or 7% lymphomas in this strain of rat is the usual case. Furthermore, as has been published by

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the NCI itself, lymphomas occur in the Fischer rat at an incidence rate of 10-12%,therefore there is no validity to the comment that the control group of animals had an excessively high incidence of lymphoma implying that there was some environmental problem associated with the study.

Page 32. Under, "other toxic effects" it should be pointed out that although cancer is the one endpoint that everyone today seems to be looking for there are many other kinds of pathology that are equally as bad because they will also result in the demise of the animal. The myocardial damage that was observed in the M.I.T. study is of some significance. The immunoblastic cell proliferation is also significant and splenic hyperplasia which no one can doubt if they take the time to examine the organ weight studies is of considerable concern. While I am cognizant of the usefulness of statistical evaluations I am much more concerned about the biologic significance of lesions such as those that were found in my study.

Pages 43-44. Refer to alleged discrepancies or deficiencies in quarterly reports. I submit that the reports were adequate to keep the FDA up-to-date with what was going on in the study and furthermore that there were no progress reports submitted between April of 1977 to June 1978 because we had over a 1,000 animals to submit to autopsy and histologic evaluation and therefore there was very little to report other than a one sentence statement that indicated that was what was being done. Therefore despite regulations we were within proper guidelines in submitting information to the FDA. This has been very accurately alluded to by the quote of the project officer on page 44.

Pages 45-46. The matter of assignment of groups and of control groups to the various treatments again exemplifies a lack of understanding of the inherent problems in setting up large groups of animals and the lack of any serious valid criticisms of the way the animals were assigned. The assignment of the various animals to the groups in my opinion was a correct one and I stand by it.

Pages 56 and 57. Regarding the review by the FDA pathologist and the NCI pathologist I can only point out that my experience in diagnosing typical rodent lesions are in excess of the experience that the two government pathologists have had and I am hopeful that the UAREP report will help in resolving the question. In any case, there is very little likelihood that the matter will be resolved to everyone's satisfaction but perhaps the entire nitrite issue has focused attention on an area that requires considerable thought and debate. It is imperative that studies be done correctly and that appropriate guidelines be set for them.

APPENDIX IV

Finally, I would be remise if I did not comment on the statements on pages 56 and 57 of your draft report relative to the memorandum of the FDA pathologist's report and the NCI pathologist's report. Whether or not either are accurate, I can only commend the FDA pathologist for summary and his fair but appropriate conditional evaluation. However, one can only condemn the kinds of comments that the NCI pathologist made stated in the middle of page 57 of the report in which he not only concludes that he is right in his diagnoses and that the two of us, Dr. Adrianne Rogers, who is a board certified medical pathologist and practicing in the Boston hospitals and I, who am an A.C.V.P. board certified pathologist are not only unfamiliar with typical rodent lesions which we have looked at for the past 20 years but lack expertise in histopathology in general. It was not my impression that the FDA was asking for anything more than a diagnosis of the lesions observed and not a personal attack upon the pathologist who made that report. These kinds of comments of course are consistent with those who are unfamiliar with the nature of the problem and the biological behavior of reticuloendothelial tumors in rodents.

I once more wish to express my appreciation for examining the report and hope that the report and the decisions that flow from it will help to clarify some of the complex areas that we are all concerned with and have to face up to.

Sincerely,

Paul M. Newberne,
Professor of
Nutritional Pathology

PMN:lfs

GAO note: Page references have been changed to correspond to the final report.

APPENDIX V

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Biochemical Engineering
Toxicology
Neural and Endocrine Regulation
Human and Clinical Nutrition

December 20, 1979

Philip A. Bernstein
Acting Director
Human Resources Division
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Bernstein: Re: M.I.T. Nitrite Study

After re-reading my comments about the GAO report on the nitrite study conducted here at M.I.T. it became obvious that an important element was missing from my comments and, apparently, from the GAO report. In the interest of fairness and completeness I am forwarding these additional comments and hope that they can be sent along to all recipients of the report. In addition to my comments forwarded to you in a letter dated December 4, 1979, I add the following:

In the context of the GAO report on the M.I.T. nitrite study it must be recognized that the appropriateness of any scientific activity or data can be equitably judged only by comparison with valid appraisals of the state-of-the-art of that discipline existing at the time the activity was planned and/or the data were developed. Ten years ago the multidisciplinary field of carcinogenicity testing in animals was almost totally lacking in either established or proposed scientific guidelines. This need was recognized, and a response attempted, in May 1973 (1). The considerable level of

APPENDIX V

Mr. Bernstein, GAO report

disagreement existing among scientific experts is readily apparent in the reference cited (see also reference 2). Additional efforts toward reaching a concensus on controversial issues occurred in 1976 (reference 3) and, after extensive revision, culminated in FDA Good Laboratory Practice guidelines, which became effective in June of this year (1979). Thus, a definition of "scientifically acceptable procedures," as promulgated by the U.S. Food and Drug Administration, now exists for the first time. That document does not, however, address the question of how to resolve differences in diagnostic interpretation by pathologists. A procedure adopted and applied profession-wide has yet to be established. In the absence of an established procedure, it is essential to list each diagnosis and the contributing pathologist's identity in any document purporting to compare such diagnoses and to draw conclusions therefrom. To do otherwise is scientifically unacceptable, and may constitute an unwarranted imputation of that professional's reputation.

References

1) Carcinogenesis Testing of Chemicals; F. Golberg, editor; Proceedings of a Conference held May 23-25, 1973. CRC Press; 1973.
2) The Testing of Chemicals For Carcinogenicity, Mutagenicity, and Teratogenicity; Ministry of Health and Welfare Canada; September, 1973.
3) Federal Register 41:51206; November 19, 1976.
4) Federal Register 43:59986; December 22, 1978.

Sincerely,

Paul M. Newberne,
Professor of
Nutritional Pathology

PMN:lfs

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