DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 510 and 558

[Docket Nos. 76N-0172 and 76N-0232]

Nitrofurans; Withdrawal of Approval of New Animal Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; final decision following a formal evidentiary public hearing.

SUMMARY: The Commissioner of Food and Drugs is issuing his final decision on the proposal to withdraw approval of the new animal drug applications (NADAs) for two nitrofuran animal drugs: furazolidone (NADAs 11-698, 9-073, 12-061, 9-393, 13-805) and nitrofurazone (NADAs 6-395, 8-142, 9-415, 8-989, 10-741). The drugs are labeled and approved for antiprotozoal use for a wide variety of conditions in poultry and swine.

The Commissioner has determined that nitrofurazone and furazolidone are not shown to be safe under the conditions of use for which they were approved under 21 U.S.C. 360b(e)(1)(B).[1] Additionally, the Commissioner finds that furazolidone and its metabolites have by substantial new evidence been shown to induce cancer in man or animals within the meaning of 21 U.S.C. 360b(d)(1)(I). Thus, he is withdrawing approval for the drugs and is revoking the regulations codifying the approval of these applications in 21 CFR 510.515, 558.4, 558.15, and 558.262, and 558.370. Also, he is affirming with modifications the initial decision of the Administrative Law Judge, who made similar findings.

EFFECTIVE DATE: September 23, 1991.

ADDRESSES: The transcript of the hearing, evidence submitted, and all other documents cited in this decision may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Robert L. Spencer, Division of Regulations Policy (HFC-220), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3480.

SUPPLEMENTARY INFORMATION: The purpose of this proceeding is to determine whether the Food and Drug Administration (FDA) should withdraw approval of the NADAs for use in food-producing animals. The effect of this decision is that these two drugs may no longer be marketed in the United States, nor may they be exported except as allowed by law.

I. Introduction

The history of this hearing is set forth in the initial decision (I.D.) and in the notice of hearing (49 FR 34965, September 4, 1984). That entire history will not be repeated here. Briefly, this consolidated proceeding involves two animal drugs that have been used in this country since the 1940's, in the case of one of the drugs, and since the 1950's, in the case of the other drug. The two drugs, furazolidone and nitrofurazone, are part of a chemical class referred to as nitrofurans. In the 1960's, evidence first surfaced that furazolidone caused tumors in laboratory animals. As evidence began to mount, FDA issued a notice of opportunity for hearing on March 31, 1971 (36 FR 5927), proposing to withdraw the NADAs for nitrofurazone on the grounds that it was no longer shown to be safe. A similar notice for furazolidone was issued on August 4, 1971 (36 FR 14343).

Since that time, the sponsors of these drugs (Hess and Clark and SmithKline, sponsors) have brought new data before the agency, which has reviewed the data. A full evidentiary hearing has been held to determine whether the NADAs of these two drugs should be withdrawn on the grounds that the drugs are no longer shown to be safe, and, in the case of furazolidone, whether its NADA should be withdrawn under the Delaney anticancer clause as well.

The Administrative Law Judge (ALJ) issued his I.D. on November 12, 1986, finding that the NADAs should be withdrawn. The ALJ found that furazolidone was an animal carcinogen that should be withdrawn under both the Delaney clause (21 U.S.C. 360b(d)(1)(I), as incorporated in 21 U.S.C. 360b(e)(1)(B)) and the general safety clause (21 U.S.C. 360b(e)(1)(B)). He also found that nitrofurazone, including its metabolites, is an animal tumorigen, and, therefore, a suspect carcinogen that should be withdrawn under the general safety clause. The ALJ also found that the sponsors had failed to provide a reliable method of residue detection for either drug and that the residues of neither drug have been shown to be safe. In addition, he determined that the concentrations of residues of furazolidone were not shown to be below the level of carcinogenic or toxicological concern.

Since the issuance of the I.D., the sponsors have filed briefs and exceptions totalling over 350 pages that take exception to virtually every ultimate and supporting conclusion of the ALJ, and that raise several legal and procedural exceptions as well.[2] Following the filing of exceptions, on August 25, 1987, the Center for Veterinary Medicine (Center) moved to reopen the evidentiary record in order to receive National Toxicology Program (NTP) draft reports of bioassays involving nitrofurazone, one of the drugs at issue here, and nitrofurantoin, another nitrofuran but one not directly at issue here.[3] See GF-1700. On September 21, 1987, the two sponsors of the NADAs also filed motions requesting that these materials be admitted in the record, and in addition requesting that the case be remanded to the ALJ for further testimony regarding the issues raised by the NTP reports.

By an order dated November 2, 1987, then Commissioner Frank Young granted the motions by all parties to reopen the record to admit the draft NTP reports. In response to the sponsors' motion to remand the matter for further testimony, Dr. Young permitted a limited remand to the ALJ. Under the terms of the remand, each party was allowed to submit written testimony concerning the NTP reports from one expert witness who had already testified in the proceeding. The remand order also allowed 1 day of cross-examination to be conducted before the ALJ. Finally, the order allowed each party to submit a supplemental brief following the hearing on the NTP reports. Each party filed its expert's supplemental testimony on January 6, 1988. The hearing on remand was held on February 3, 1988, and supplemental briefs were filed on March 8, 1988. Since that time, the record in this hearing has been officially closed.

After fully reviewing the evidence in the administrative record and the exceptions to the I.D. raised by the sponsors, I find that there is clearly enough evidence in the record to justify the ALJ's conclusion that furazolidone and nitrofurazone are no longer shown to be safe.

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[1] Section 360b(e)(1)(B) contains a reference to "subparagraph (H) of paragraph (1) of subsection (d) * * *." Because, in Pub. L. 100-670, Congress redesignated subparagraph (H) as subparagraph (I), the reference should read "subparagraph (I) of paragraph (1) of subsection (d) * * *." For purposes of this final decision, FDA is interpreting the act as if Congress had made this necessary conforming change.

[2] The exceptions filed by the sponsors in this proceeding exceeded in volume those filed in any other hearing before FDA. Many exceptions were frivolous or trivial.

[3] The final version of this report has been published, but it does not differ from the draft as to any conclusions pertinent to this hearing.

I also find overwhelming evidence in the record to support the ALJ's conclusion that the sponsors have failed to provide a reliable means for detecting residues of these drugs and their breakdown products in animal tissue. Such a detection method is necessary to enable FDA to ensure that no dangerous residues enter the human food supply.

On the basis of the administrative record, I find that I am unable to ensure that foods derived from animals treated with these drugs will contain no more than safe levels of residues of furazolidone, nitrofurazone, and their breakdown products (metabolites). Therefore, I am by this notice withdrawing all NADAs for furazolidone and nitrofurazone.

In doing so, pursuant to 21 CFR 12.130(d), I am adopting the I.D. as issued with some modifications as stated below. As to exceptions filed by the parties, I am herein addressing only those that I consider significant. I am not required by law or regulation to address *every* exception made—only those raising "significant" issues. *Simpson* v. *Young*, 854 F.2d 1429, 1434 (D.C. Cir., 1988); 21 CFR 12.120(b) and 12.130(c). Where I do not specifically address an exception of Hess and Clark (H&C) or SmithKline (SK), their exceptions are overruled for reasons stated in the Center's Reply to Exceptions.

I am expressly not ruling on any exception filed by the Center because I believe that doing so is not essential to a decision on the issues in this proceeding. As a result, my failure to address a particular exception by the Center should not be construed as either an affirmance or an overruling of that exception.

II. Initial Findings

1. I reaffirm the statement of the allocation and formulation of the burden of proof in the Commissioner's diethylstilbestrol (DES) decision (44 FR 54852), September 21, 1979) and apply that to this proceeding. Under both the Delaney and general safety clauses, approval may be withdrawn if "new evidence," evaluated together with previously existing evidence, shows that the drug is not shown to be safe. "New evidence" includes any evidence not available at the time the application was approved, tests by new methods, and tests by methods not originally considered applicable. There does not appear to be an issue about the "newness" of the evidence upon which the Center relies. The evidence concerning the nitrofurans was not available at the time they were originally approved.

The proponent of withdrawal, the Center, has the burden of making the first showing (i.e., that the drug is no longer shown to be safe). *Hess and Clark, Division of Rhodia, Inc.* v. *Food and Drug Administration*, 495 F.2d 975, 992 (D.C. Cir. 1974).[4] In *Hess and Clark I*, the court found that FDA has "an initial burden of coming forward with some evidence of the relationship between the residue and safety to warrant shifting to the manufacturer the burden of showing safety." Id. at 993. In the Commissioner's DES decision, Commissioner Kennedy adopted the following formulation of the Center's threshold burden:

> "* * * [the Center] must provide a reasonable basis from which serious questions about the ultimate safety of DES and the residues that may result from its use may be inferred."

44 FR 54861.

Once the limited threshold burden has been satisfied, of course, the burden passes to the sponsors to demonstrate safety. *Id.*

There does not appear to be a significant difference between the parties on the subject of the burden of proof. In any case, I find that the ALJ applied the correct standard.

2. I find that cost/benefit considerations are irrelevant under both the Delaney clause and the general safety clause. I agree with the Center's view that *American Textiles Manufacturers Institute* v. *Donovan*, 452 U.S. 490 (1981) is ample authority for the proposition that clauses like the Federal Food, Drug, and Cosmetic Act's (the act) general safety clause do not permit, much less invite, cost/benefit analysis.[5] The sponsors do not seriously argue that such an analysis would be applicable where the Delaney clause applies.

3. The sponsors argue that the rodent studies that indicted nitrofurans as carcinogens did not satisfy good laboratory practice (GLP) standards and, thus, cannot satisfy even the Center's limited threshold burden of proof. I disagree. No one argues that these studies were very good studies by today's standards. However, despite their faults, as explained below, the data that they generated constitute substantial evidence of carcinogenicity—evidence which is sufficient to satisfy the Center's threshold burden.

I should note that FDA's GLP regulations were not even proposed until several years after the nitrofuran bioassays were completed. Even more important, by the terms of the preamble to the GLP regulations, "valid data and information in an otherwise unacceptable study which are adverse to the product * * * may serve as the basis for regulatory action. This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard." (November 19, 1976, 41 FR 51206 and 51212). To the same effect, see FDA's similar statement in the preamble to the final rule (43 FR 59990).

The report of the NTP ad hoc panel on chemical carcinogenesis testing and evaluation (HF-104) cannot be cited to the contrary: "All studies must serve as an adequate basis for regulatory decisions even though they have protocol deficiencies in number of animals per group, number of dose levels, absent clinical observations, etc." HF-104, 12-4. The panel added that "our intent is *not* to imply that previous studies would or should be judged inadequate on the basis of modern criteria [emphasis added]." Id. at 13.

4. I need not and do not address the question of whether hormonally mediated carcinogens are subject to the Delaney clause. This is because the sponsors have not proven that any compound that is the subject of this hearing is a hormonally mediated carcinogen. See, e.g., Denial of Petition for Listing of FD&C Red No. 3 (February 1, 1990, 55 FR 3520, 3537, and 3541). See also *infra*, pp. 37 ff. In addition, as discussed elsewhere (i.e., see pp. 48 ff), I find that none of the compounds that are the subject of this hearing has been shown to be safe within the meaning of the general safety clause. 21 U.S.C. 360b(e)(1)(B).

5. I agree with the Center (main brief at 82, n. 67) that 10^{-6} is an appropriate risk standard by which to judge nitrofurans and their metabolites. The sponsors, while not directly attacking this standard, did suggest that FDA has in the past allowed greater levels of risk, but they have cited no FDA-approved new animal drug for which higher levels of risk from residue were found.

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[4] There are two *Hess and Clark* cases: *Hess and Clark, Division of Rhodia, Inc.* v. *Food and Drug Administration*, 495 F.2d 975 (D.C. Cir. 1974) (hereafter *Hess and Clark I*); and *Rhone-Poulenc, Inc., Hess and Clark Division* v. *Food and Drug Administration*, 636 F.2d 750 (D.C. Cir. 1980) (hereafter, *Hess and Clark II*).

[5] In the Commissioner's DES decision, 44 FR at 54883, FDA said: "The law is clear that FDA may not consider socio-economic benefits in the determination of the safety to human beings of a new animal drug, and I am not prepared to conclude that it permits consideration of human health benefits."

III. "New Evidence That Furazolidone Causes Cancer in Man or Animals"

I will proceed now to consider in some detail the adequacy of the Center's "new evidence that furazolidone causes cancer in man or animals."

A. Evidence of Carcinogenicity—The Four Norwich Studies

The Center's new evidence that furazolidone causes cancer consists of four animal bioassays performed under the auspices of Norwich-Eaton, the original furazolidone NADA sponsor, in 1973 and 1974. GF–195a, GF–195b, GF–196, and GF–197 (collectively referred to as "the Norwich studies"). These studies are summarized in the I.D. at pp. 19–23. In addition to the Norwich studies, the Center relies on mutagenicity studies to demonstrate that furazolidone is a mutagen. If furazolidone is demonstrated to be a mutagen, that fact would lend support to the contention that furazolidone is a carcinogen.

The sponsors contend that the Norwich bioassays are not reliable indicators of cancer for a host of reasons. The most important deficiencies cited by the sponsors include the allegation that the maximum tolerated dose (MTD) was exceeded in several of the tests, so that tumors attributed to the carcinogenic affect of furazolidone were, in fact, the result of toxic stress. The sponsors also contend that the incidence of neoplasms in treated test animals was not statistically significant or was within the historical range for spontaneous tumor generation in the test animals. The sponsors further argue that positive indications of carcinogenicity were based on improper groupings of benign and malignant tumors, or of different tumor types. The sponsors also fault the Norwich studies for failing to comply with GLP regulations that were adopted by FDA after these studies were completed. Among the GLP deficiencies cited by the sponsors were illness in the test animals or impurities in the test substance, which should invalidate the results of the Swiss Mouse Study, according to the sponsors.

To the extent that the Norwich studies do indicate that furazolidone causes benign or malignant tumors, the sponsors argue that furazolidone does not act as a "direct" carcinogen. Rather, they contend, the evidence demonstrates that furazolidone causes cancer only in doses high enough to distort hormone levels in the test animals. It is the change in hormone levels, the argument runs, that actually "causes" cancer in the test animals. The sponsors also claim that the Norwich test data demonstrate that, at low enough levels, the ingestion of furazolidone will have no carcinogenic effect. The sponsors also claim that, because humans and rodents have different hormones, it is unlikely that ingestion of furazolidone-treated animals could cause cancer in humans.

Regarding the mutagenicity tests, the sponsors' strongest argument is that furazolidone was only weakly mutagenic or was shown to be mutagenic only under conditions that are unlikely to be duplicated in mammals. Thus, they argue, these mutagenicity studies are not a reliable indicator of furazolidone's carcinogenic potential.

After a thorough review of the evidence and the arguments in the record, I find, for the reasons stated below, that the Norwich bioassays, while imperfect, satisfy the Center's initial burden of adducing new evidence raising questions about the safety and carcinogenicity of furazolidone that are sufficiently serious to require the manufacturers to demonstrate furazolidone's safety.

I also find that the mutagenicity tests, when considered together with the Norwich studies, add further evidence that furazolidone is, at the very least, a suspect carcinogen, and at worst, is a proven animal carcinogen. I also find that the Norwich studies and the mutagenicity tests, considered together, are inconsistent with the sponsors' claims of a hormonal theory of cancer induction.

1. Maximum Tolerated Dose

I agree with the sponsors that the MTD was exceeded in certain dosage groups of two of the studies. Specifically, I find that the MTD was exceeded in the high- and mid-dose groups in the Sprague-Dawley High Dose Study (GF–195b) and in the high-dose group in the Fischer 344 Rat Study (GF–196). HF–310, p. 21; HF–309, p. 9; GF–1617.1, pp. 9–10; GF–1623.1, p. 21a. The MTD may also have been exceeded in the mid-dose group in the Fischer study (GF–196). HF–309, p. 9; HF–310, p. 21; GF–1617.1, pp. 9–10; Transcript ("Tr.") III, pp. 39, 45–6, 50.

However, in the low-dose Sprague-Dawley Study (GF–195a), I find that the MTD was not exceeded in any test group. HF–310, p. 14; GF–1617.1, p. 9. The sponsors do not contend otherwise. As to the Swiss Mouse Study, the fact that there were no early deaths in males is evidence that the MTD was not exceeded in males. G–1617.1, p. 12. The MTD may have been exceeded in females. However, the weight gain noted in treated animals was comparable to that noted in control animals, suggesting that the toxicity was not due to overdosing. G–1617.1, p. 12; GF–1623.1, p. 22. Even if the MTD was exceeded in the mid- and high-dose females, the results would just confirm the effect seen in lower doses. The results in these mid- and high-dose animals, although not demonstrating relevant carcinogenicity, will not have shown safety either. GF–1623.1, pp. 21–2.

Moreover, neither SK nor H&C argues that the MTD was exceeded in the low-dose group of test animals in either the High-Dose Sprague-Dawley Study (GF–195b) or the Fischer Rat Study (GF–196). I agree that the MTD was not exceeded, based on evidence in the record demonstrating that the test animals in the low-dose groups in both the High-Dose Sprague-Dawley Study and the Fischer Rat Study did not suffer a weight decrement exceeding 10 percent and did not exhibit other characteristics usually associated with toxic dosing. GF–1623.1; Bryan, Tr. XII–67–8; GF–1617.1, pp. 9–10.

After reviewing the evidence concerning every group of test animals whose dosage did not exceed the MTD, I find that, in every case, the animals dosed with furazolidone developed neoplasms that exceeded the controls' rate of neoplasms, and that the difference was statistically significant in most cases.

Specifically, I find that mammary tumors in female rats in the Low-Dose Sprague-Dawley Study (GF–195a) exhibited a statistically significant dose response that is indicative of the carcinogenicity of furazolidone. GF–1615.1, p. 11. I also find that, in the Swiss Mouse Study (GF–197), statistically significant dose-response trends were exhibited respecting bronchial adenocarcinomas or adenomas in both sexes and for lymphosarcomas in males. GF–1613.1, p. 8; GF–1615.1, p. 10.

In the Fischer Rat Study, I find that the incidence of mammary tumors exhibited by rats in the low-dose group was statistically significant when compared to the controls. GF–1617.1, p. 10. I also find that the low-dose Fischer rats exhibited not only increases in mammary tumors but also decreased onset time, increased multiplicity and increased malignancy, all of which indicate that furazolidone is a carcinogen at doses below the MTD. GF–1617.1, pp. 9–10; GF–1623.1, pp. 21–2.

In the High-Dose Sprague-Dawley Study (GF–195b), I find that, even in the low-dose group, whose dose did not exceed the MTD, the evidence demonstrates that 41 out of the 50 treated rats developed mammary

tumors, while only 29 out of 50 control rats developed mammary tumors. GF-195b, p. 32; GF-1623.1, p. 22. Where so large a number of low-dose females developed mammary neoplasms in comparison with the controls, I doubt that acute toxic stress, rather than furazolidone, is the cause. The toxic stress argument is also inconsistent with the clear dose-response relationships generated by this study. GF-1623.1, pp. 11-12; GF-1612.1, pp. 6-7, 10; GF-1617.1, pp. 6, 9, 11; HF-309, p. 16; Tr. X, p. 93; Tr. IV, p. 153.

The fact that test animals in the low-dose groups in the Norwich studies developed neoplasms at rates higher than the controls did demonstrate that findings of carcinogenicity in these studies cannot be dismissed as a byproduct of overdosing. In addition, the types of tumors and neoplasms developed by rodents in groups where the MTD was exceeded do not differ in type or locus from those found in groups where the MTD was not exceeded. GF-1617.1, pp. 9-12; GF-1623.1, pp. 21-2. This continuity of tumor type across dosage groups suggests that not all the neoplasms observed in animals whose doses exceeded the MTD can be attributed to acute toxic stress. See GF-1617.1, p. 11. While I would not rely solely on test data from dosage groups where the MTD was exceeded, I find that the similarity of tumor types between dosage groups above and below the MTD provides additional support for the finding that furazolidone itself, rather than any overdosing, caused neoplasms in the test animals that are indicative of carcinogenicity.

2. Statistical and Biological Significance

The sponsors challenge findings in the I.D. that the incidence of neoplasms in treated test animals are statistically and biologically significant. Statistical significance is concerned with the probability that a given test result occurred by chance, rather than because of the effect that the test is designed to study. Biological significance is concerned with whether the animal harboring a lesion will ultimately become diseased as a result of the lesion. GF-1612.1, p. 2.

The ALJ found that statistical analysis of the tumor data from the four Norwich studies was insufficient to evaluate the effects of furazolidone, and that an evaluation of their biological significance was necessary. I.D., p. 42. The ALJ found the Norwich data to provide ample evidence of biological significance. I.D., pp. 42-6. The sponsors challenge findings of biological significance, arguing that mammary tumors occur spontaneously at a high rate in Sprague-Dawley and Fischer 344 rats (HF-309, pp. 5, 22; HF-310, pp. 15, 18, 26; Tr. III, pp. 57-8). The sponsors also assert that important factors that can affect the incidence, multiplicity, and onset time of mammary tumors—such as age, diet, environment, physical stress, hormonal status, and immunologic competence—were not adequately controlled in the Norwich studies. The sponsors further assert that the mammary tumors found in treated test animals were in fact the result of hormonal disruption and generalized physiological stress in aging animals caused by toxic doses of furazolidone that far exceeded the MTD. HF-309, pp. 22-3; HF-310, pp. 3, 18, 22.

For the reasons stated below, I find that the incidence of neoplasms in test groups whose dosage did not exceed the MTD was, for the most part, statistically significant. Since toxic stress cannot explain away these tumors, which were the same types of tumors found in the higher dose groups, I find that the Norwich bioassays provide ample evidence that furazolidone is an animal carcinogen. Moreover, the increased multiplicity of tumors, decreased onset time, and increased malignancy of tumors in all groups of test animals fed furazolidone are additional evidence that the tumor findings generated by these studies are biologically significant—i.e., that the findings are indicative of the actual or potential carcinogenicity of furazolidone. See p. 20, *supra*.

While I agree with the sponsors that age, hormonal status, physical stress and immunologic competence may have some effect on cancer rate, I am concerned that these factors cannot be controlled in either the target animal population that is fed furazolidone or in the human population that eats food products derived from these animals. Therefore, I reject the sponsors' invitation to ignore test findings raising safety questions where these factors were not controlled.

Accordingly, where, as here, four different animal bioassays involving two different species of rat and one species of mouse all demonstrate that treated test animals have an increased rate of neoplasms even at doses below the MTD, I find this to be biologically significant evidence that the test substance is an animal carcinogen. The bioassays are treated individually below.

a. *The Low-Dose Sprague-Dawley Study.*—Regarding the Low-Dose Sprague-Dawley Rat Study (GF-195a), the sponsors assert that the incidence of mammary tumors in treated females was not statistically significant. G-195a, p. 9; GF-1631.1, p. 9; GF-1616.1, p. 11; HF-310, p. 28. However, the sponsors failed to consider time-to-tumor information or to adjust for differential mortality among dose groups. GF-1623.1, pp. 10-11; GF-1612.1, p. 10; GF-195a, p. 6; HF-310, p. 28; HF-309, p. 16; GF-1617.1, p. 9; GF-1615.1, p. 11; GF-1280, p. 17. Proper statistical analyses of tumor data adjust for different mortality among dose groups. See HF-104, pp. 210-14. Also, the sponsors failed to test for dose-response trends, which make more efficient use of the data and are generally more sensitive in detecting effects than are individual comparisons of each dosage group with the control group. GF-1613.1, p. 2; HF-104, pp. 209-10.

In reviewing the results of the Low-Dose Sprague-Dawley Rat Study, I find a statistically significant increase in mammary neoplasms in females with increasing doses of furazolidone, with $P=0.006$ when using a trend test and incorporating corrections for differential mortality among the dose groups. GF-1615.1, p. 11; GF-1280, p. 17. I find that the statistical analyses conducted by the Center are valid and in accord with analyses conducted by the NTP (HF-104). I also find that the results in the Low-Dose Sprague-Dawley Study are biologically significant. In addition to showing a statistically significant increase in mammary tumors in dosed females, the test results show increased multiplicity of mammary tumors in female rats as the dosage of furazolidone increased. GF-195a, p. 6. When the multiplicity is expressed as a percentage, the rate is monotonic (i.e., goes in one direction only), ascending, dose-related, and significant. GF-1623.1, pp. 11-12; Tr. IV, p. 153.

A witness for the sponsors testified that the NTP rejects multiplicity of mammary neoplasms in rats as an indication of carcinogenic potential. Tr. XV, pp. 72-3; GF-195a, p. 56. I find that, to the contrary, the NTP draft reports on nitrofurazone (GF-1700, p. 11) and nitrofurantoin (GF-1701, p. 7) list "multiplicity in site-specific neoplasia" as one of the several "key factors" to be considered when evaluating bioassay test data for findings of carcinogenicity. The same witness observed that the incidence of rats in the study with single mammary tumors went down as the dosage of furazolidone increased. Tr. XV, pp. 72-3; GF-195a, p. 56. This statement is misleading. The test results in the Low-Dose Sprague-Dawley study demonstrate that the proportion of animals with mammary tumors increased with dose and that the

proportion of animals with multiple mammary tumors increased with dose. GF–195a, pp. 6, 56; Tr. IX–47; IV–150–3. Obviously, all that has happened is that the proportion of animals in the study with the more severe condition—multiple mammary tumors—has increased with dose, decreasing the proportion of animals with the less severe condition of only a single mammary tumor.

In addition, Norwich, the original study sponsor, conceded that two of the three doses in the study significantly increased tumor multiplicity and "caused significantly earlier onset time of mammary neoplasms and caused significantly decreased survival rates when compared to control female rats." GF–195a, pp. 9–10, 50. The sponsors assert that the decrease in mean time-to-palpable-tumor was only marginally significant in the mid- and high-dose females and was not significant in the low-dose group. However, I find that, after adjusting for the differences in tumor onset times between control and treated animals, there was an increased evidence of benign and malignant mammary gland neoplasms in treated females. GF–1623.1, pp. 10–11; GF–1612.1, p. 10. These were biologically significant. GF–1623.1, pp. 11–12; Tr. XII–55–6; HF–104, p. 167. Also, I find that when the decrease in onset time in the mid-dose and high-dose groups is considered in conjunction with the statistically significant increases in mammary tumors and with the dose-related increase in multiplicity, it provides additional evidence of the carcinogenicity of furazolidone. GF–1612.1, p. 8; GF–1617.1, p. 5; GF–1623.1, pp. 11–12; HF–104, pp. 167, 200–14; Tr. IV, p. 153.

I also find that males in the mid-dose and high-dose groups in the Low-Dose Sprague-Dawley Rat Study exhibited an increase in thyroid follicular adenomas that increased with dose level. GF–195a, p. 24. There is no evidence in the record that a statistical analysis was conducted on these data. Notwithstanding the lack of statistical analysis, the dose-related increase in thyroid follicular adenomas in the mid- and high-dose males is still noteworthy. The same tumor was found in dosed males in the High-Dose Sprague-Dawley Study (GF–195b, pp. 28, 36–64; GF–1623.1, p. 11; GF–1612.1, p. 10; Tr. IX–135; Tr. X–41–2 and in the Fischer Rat Study GF–196, pp. 4, 9–11, 26–7, 34–64; GF–1623.1, p. 10; GF–1612.1, p. 11; HF–309, p. 8; HF–310, pp. 21, 23). I find that: (1) the increased incidence of thyroid follicular adenomas in male rats in three different studies; and (2) the findings of mammary adenomas in females in all four studies combine to provide significant evidence that furazolidone is an animal carcinogen.

b. *The High-Dose Sprague-Dawley Rat Study.* The sponsors' main attack on this study is that the dosage levels exceeded the MTD and that the tumors seen in this study were the result of acute toxic stress. However, although the MTD was exceeded in the high- and mid-dose groups, this finding does not explain away the results generated by this study.

First, I note that, in the low-dose group alone, where the dose did not exceed the MTD, 41 out of the 50 treated female rats developed mammary tumors, while only 29 out of 50 female control rats developed such tumors. GF–195b, p. 24. Unfortunately, I can find no evidence in the record that this comparison was analyzed for statistical significance.

However, when a statistical analysis was performed using only the low- and mid-level dose groups in this study, the incidence of mammary tumors was found to be statistically significant after adjusting for differential mortality. GF–1613.1, pp. 3, 4, 6, 9. Because the same types of tumors were observed in the mid-dose group as in the low-dose group, it is clear that not all the tumors in the mid-dose group can be explained away as the result of overdosing. GF–1617.1, pp. 6, 9; GF–1623.1, p. 11; GF–1612.1, p. 10. Therefore, I find that the statistical significance of the incidence of mammary tumors in treated female rats in the low- and mid-dose groups in the High-Dose Sprague-Dawley Study is evidence of the carcinogenic property of furazolidone.

The evidence demonstrates a statistically significant increase in thyroid follicular adenomas in treated male rats, with $P=0.0003$ when using a trend test and incorporating corrections for differential mortality among the dose groups. GF–195b, pp. 28, 36–64; GF–1615.1, p. 6; Tr. IX, p. 135; Tr. X, pp. 41–2. Because this calculation includes dosage groups that exceeded the MTD, I would not base a finding of furazolidone's carcinogenicity on this fact alone. However, when this fact is considered together with other relevant evidence in the record, I find that it is further evidence of the carcinogenic potential of furazolidone. The fact that treated male rats in all three of the Norwich studies that used rats developed the identical tumor, including rats in the Low-Dose Sprague-Dawley Study, suggests that this finding is not the result of overdosing. GF–195a, p. 24; GF–195b, pp. 28, 36–64; GF–196, pp. 4, 9–11, 26–7, 34–64; GF–1623.1, pp. 10–11.

The High-Dose Sprague-Dawley Study contained much the same evidence of biological significance as did the Fischer Rat Study and the Low-Dose Sprague-Dawley Study. For example, the High-Dose Sprague-Dawley showed a dose-related increase in multiplicity of mammary tumors and a decreased onset time in treated females. GF–195b, pp. 3, 8, 14–15, 26, 32–3, 36–64; GF–1623.1, p. 11, GF–1617.1, p. 9; HF–309, p. 16. I find substantial credible evidence in the record that both of these factors are biologically significant evidence of carcinogenicity. GF–1623.1, pp. 11–12; HF–104, pp. 167, 210–214; GF 1615.1, p. 4; GF–1612.1, pp. 6–7; Tr. IV, p. 153; Tr. X, p. 93.

In addition to this evidence, the data also showed a statistically significant increase in neural astrocytomas in males, both in all dosage groups and in just the two lower dosage groups, when the data were adjusted for differential mortality rates among the groups. GF–195b, pp. 28, 36–64; GF–1623.1, p. 11; GF–1612.1, p. 10; GF–1613.1, pp. 3–4, 6–9; HF–309, p. 16; HF–310, pp. 19–20. While I would not base a judgment of furazolidone's carcinogenic potential on this fact alone, I find that, when weighed with the other evidence in the record, the increased incidence of neural astrocytomas in males is additional evidence pointing to the ultimate finding of carcinogenicity. Tr. IV–121; Tr. X–36–38, 44.

When all of the above evidence is considered, i.e., the dose-related, statistically significant generation of the tumors reported in this study; the large increase in tumors in the low-dose group; the additional factors evidencing biological significance; and the similarity of these findings with similar studies, as a whole, the evidence from this study is inconsistent with the sponsors' assertions that the tumors reported in this study were the result of overdosing.

c. *The Fischer Rat Study.* In the Fischer Rat Study (GF–196), as noted earlier, even if we limit our review to the low-dose group, which received a dose of furazolidone that was below the MTD, a statistically significant increase in mammary neoplasms in treated animals was demonstrated. GF–1617.1, pp. 9–10.

The sponsors complain that benign and malignant tumors should not have been grouped together for the purposes of analysis. While I disagree with the sponsors for reasons that will be detailed in a separate section, I note that, even without combining benign and malignant tumors, mammary adenocarcinomas (malignant tumors)

alone exhibited a statistically significant dose-related increase in the three dosage groups in this study. GF–1615.1, p. 10. I find that the two factors listed above—the statistically significant increase in mammary adenocarcinomas in females in the low-dose group (which were not dosed above the MTD, GF–1617.1, p. 9) and the statistically significant increase in malignant mammary neoplasms in all dosage groups—are biologically significant evidence that furazolidone is an animal carcinogen. GF–1617.1, pp. 6, 9–10.

In addition several other indicators of furazolidone's carcinogenicity were found in the Fischer Rat Study. When all three dosage groups were considered, test animals fed furazolidone exhibited increases in mammary neoplasms with decreased onset time, increased multiplicity, and increased malignancy. GF–1617.1, pp. 9–10; GF–1623.1, pp. 21–2. While the sponsors complain that data from the mid- and high-dose groups should not be considered because the dose exceeded the MTD, I find that the continuity of tumor type as the dosage increased allows us to consider these findings as additional indications that furazolidone is an animal carcinogen.

As noted earlier, I also find it biologically significant that males in this study developed the same type of tumor—adrenal follicular adenomas—as did the male rats in the Low-Dose Sprague-Dawley Study (in which no dosage group exceeded the MTD) and the High-Dose Sprague-Dawley Study. GF–1623.1, pp. 10, 14–15; GF–1617.1, p. 10; GF–1612.1, p. 11; HF–309, p. 8; HF–310, pp. 21, 23; GF–196, pp. 4, 9–11, 26–7, 34–64. Moreover, furazolidone demonstrated a dose response as to these tumors in this study. GF–1615.1, p. 9; GF–1280, p. 11; GF–1613.1, p. 9. I find this to be additional evidence that furazolidone is an animal carcinogen.

d. *The Swiss Mouse Study.* The sponsors argue that the data in the Swiss Mouse Study (GF–197) are not biologically significant because, after the treatment period ended, the mid- and high-dose females and the high-dose males suffered a high mortality rate that is indicative of severe toxic stress. The sponsors argue that, whether this high mortality was due to environmental factors, intercurrent infection, or doses exceeding the MTD, the study is too flawed to provide evidence on the issue of whether furazolidone causes lung cancer.

I disagree. First, statistically significant dose-response trends for bronchial adenocarcinomas and/or adenomas in both sexes and for lymphosarcomas in males were reported. GF–1613.1, p. 8; GF–1615.1, p. 10. If the tumors were produced by environmental factors or from doses exceeding the MTD, I would not expect to find the clear dose-response relationship that this study evidences. In addition, I agree with the Center that the Swiss Mouse Study may actually understate the incidence of tumors expected from a lifetime exposure to furazolidone. GF–1623.1, pp. 23–4; GF–1617.1, pp. 7–8. This understatement may have occurred because test animals should be exposed to the test substance for 24 months in the standard bioassay (HF–104, p. 188). In the Swiss Mouse Study, by contrast, the test animals were dosed for only 13 months (GF–197, p. 5; HF–309, p. 19) but nevertheless produced positive results. Thus, I find that the data are at least as likely to understate the carcinogenic effect of furazolidone as they are to overstate it.

3. Combination of Tumor Type

The sponsors assert that benign tumors should not be considered in assessing the carcinogenicity of furazolidone, and that benign tumors should not be grouped together with malignant tumors for the purpose of statistical analysis. The sponsors also complain that different types of skin tumors were improperly grouped together for the purposes of analysis.

Benign neoplasms are considered to be indicative of cancer because benign and malignant tumors often arise in the same tissue and may represent a spectrum of tumor development and progression. GF–1623.1, pp. 13–14. In the Fischer Study (GF–196) and in the Low-Dose and High-Dose Sprague-Dawley studies (GF–196a and GF–196b, respectively), benign and malignant mammary tumors were grouped together because benign mammary tumors can progress to malignancy, because they arise in common tissue (mammary epithelium), and because of differences in diagnosis from one pathologist to another. GF–1623.1, pp. 13, 16; Tr. III, p. 84. I find that the grouping of benign and malignant mammary tumors was proper in these circumstances.

I also note that, while the sponsors rely on a finding of the International Agency for Research on Cancer that only malignant neoplasms provide evidence of cancer (see HF–104, p. 279), the NTP, an arm of the Department of Health and Human Services that was set up to conduct toxicology studies, does consider the increase in benign tumors and an increase in a combination of benign and malignant tumors, under appropriate conditions, when evaluating carcinogenicity. HF–104, pp. 226–229, 232; GF–1700, p. 11; GF–1701, p. 7.

I find that, based on the common organ and tissue site and the known tendency of mammary neoplasms to progress to cancer, the consideration of benign mammary neoplasms and their combination with malignant mammary tumors for the purpose of analysis were appropriate in the Norwich studies. I also find that there is no credible or sufficient evidence in the record to the effect that any known tumorigen causes only benign tumors. I also find that, because the decision to withdraw the NADAs for furazolidone rests on the general safety clause as well as the Delaney clause, the evidence in the record that furazolidone causes an increased incidence of benign mammary neoplasms in treated test animals which received doses below the MTD is evidence that, when considered in conjunction with evidence of mutagenicity, supports the conclusion that furazolidone is no longer shown to be safe.

I further find that the combination of various types of skin tumors for the purposes of analysis was proper to determine that carcinogenicity or tumorigenicity of furazolidone. Combining skin carcinomas and epitheliomas is acceptable under the NTP guidelines (HF–104, p. 232). These types of tumors gave statistically significant dose-response relationships in Fisher 344 rats. GF–1613.1, p. 8. While I would not base a finding of furazolidone's carcinogenicity or tumorigenicity on skin tumor data alone, I find that it is additional relevant evidence that, when considered with the other evidence in the record, helps demonstrate the carcinogenic and tumorigenic properties of furazolidone.

In summary, I find that the four Norwich studies, taken as a whole, provide enough evidence of furazolidone's carcinogenic potential to meet the Center's burden of demonstrating new evidence raising questions about the safety of furazolidone that are sufficiently serious to require the sponsors to demonstrate furazolidone's safety, which they have not done. In each of the four studies, the tumor types were biologically significant because each of them has the potential to affect adversely the health of the animal in which they were observed. Moreover, feeding furazolidone to rodents significantly increased the incidence of each type of tumor, and, where mammary neoplasms occurred, it increased their multiplicity and decreased the time to tumor when compared to rodents that were not fed furazolidone. GF–1623.1, pp. 11–2.

4. Historical Range of Tumor Development

The sponsors claim that the rates of mammary, skin and thyroid tumors observed in treated animals in the rodent studies were within the range of historical variation in spontaneous incidence for these tumors. HF–310, p. 22; HF–309, pp. 22, 25. However, the evidence of record does not support the sponsors' claim. I find that the incidence of mammary tumors in the control female Fischer rats of 20 percent (10/49) is below the historical range reported in the record of 31 percent to 46 percent. GF–1413.1, p. 1451; HF–257, p. 10. The incidence of mammary tumors in the low-dose group alone is 28/50, or 56 percent. GF–196, p. 26. I therefore find that the incidence of mammary tumors in treated females in the low-dose group alone in the Fischer Rat Study exceeds the historical range, providing additional evidence of furazolidone's carcinogenic properties.

The record also contains several reasons why tumor incidence may vary from study to study. HF–310, p. 22. This is the reason why valid scientific test protocols require that concurrent control animals be compared with a test group of treated subjects. This concept of concurrently controlled studies is basic to scientific investigation, and FDA cannot allow historical data to contradict concurrently controlled studies.

5. Hormonal Induction

The sponsors argue that, to the extent that furazolidone and nitrofurazone cause tumors, they do so through a hormonal mechanism which occurs only at dose levels over a threshold and, therefore, are not subject to the Delaney clause because the threshold is above any likely human consumption levels.

Based on the record, I draw three scientific conclusions that militate strongly against the argument that furazolidone's tumorigenicity is based solely or even primarily on a hormonal mechanism. First, the increase in non-endocrine tumors discussed in GF–1623.1, GF–1613.1, p. 8, and GF–1615.1, p. 10 is important in showing that a genotoxic (i.e., damaging to deoxyribonucleic acid, thus causing mutations or cancer) mechanism is almost certainly responsible.

Second, the positive results of mutagenicity tests on furazolidone contradict the hypothesis that hormonal induction is the sole mechanism by which the substance induces cancer. GF–709; GF–710; GF–829; GF–833; GF–834; GF–849; GF–850; GF–1620.1, p. 9.

Third, the failure to demonstrate increased plasma progesterone levels in orally dosed animals means that the target organs for carcinogenic action were not exposed to increased progesterone levels. GF–1018, table 8; HF–310, pp. 4–11. Thus, the hormone hypothesis is clearly refuted by the sponsors' own data.

Against these facts, the sponsors cite what they believe is evidence to the contrary. I will consider their contentions.

The sponsors contend that the Low-Dose Sprague-Dawley Rat Study (GF–195a) demonstrates that furazolidone, unlike direct acting carcinogens, causes tumors only at dose levels that cause hormonal disruption. HF–309, p. 29. However, as stated above the rats in this study did develop tumors, demonstrating a dose response, including tumors at doses below those that would cause "hormonal disruption." Thus, the sponsors' entire argument about a hormonal mechanism based on this study has a false premise.

The sponsors cite as "compelling evidence" supporting their hormonal theory (H&C exceptions, p. 114) studies showing that ovariectomy has been shown essentially to eliminate the occurrence of mammary tumors in furazolidone-treated rats, while significant numbers of tumors occurred in nonovariectomized rats.

However, ovariectomy of rats also reduces the incidence of mammary tumors induced by known carcinogens such as 3-methylchloranthrene (3MC) and *N*-nitrosomethylurea. GF–1417; GF–1616.1, p. 12. Both of these compounds are known to be potent genotoxic and carcinogenic substances. GF–1616.1, p. 12. Ovariectomy also reduced the control incidence of mammary tumors from 20 percent to 0 percent in female rats. GF–430, p. 13. Therefore, the diminution of tumors after ovariectomy is not evidence of the absence of a genotoxic mechanism.

The sponsors suggest that furazolidone blocks the synthesis of corticosterone, leading to enhanced production of progesterone and other corticosteroids, which in turn results in mammary hyperplasia. HF–310, pp. 3–11. This the sponsors consider to be further evidence of the existence of a hormonal mechanism.

On the contrary, a feeding study of the effect of furazolidone on plasma steroid levels, GF–1018, Table 8, showed that there was no increase in the plasma levels of progesterone at the highest dosage level. Thus, the thesis that increased progesterone levels caused by furazolidone are responsible for mammary tumors gains no support. The sponsors attempt to explain away the fact of decreased plasma progesterone levels at the high furazolidone dose by invoking a complex "adrenal adaption" theory, but their "evidence" acknowledges that "weather [adrenal adaption] could lead to mammary tumor formation remains obscure." GF–1011, p. 8. Hence, the sponsors have adduced no evidence for this theory.

I find that the data support the proposition that furazolidone can act as a direct carcinogen: in intact rats, no plasma progesterone increases were seen (GF–1018, Table 8); no change in progesterone-sensitive organs was seen (GF–195b); and mammary tumors were induced. GF–195b, pp. 32–3.

The sponsors also argue that the patterns of tumorigenesis in the four Norwich studies are "characteristic" of hormonal disruption (SX–187, pp. 6–7; Tr. IX–20A; HF–309, pp. 8–9), but their theory fails to explain the statistically significant increase in nonendocrine tumors found in these studies. See *supra*, pp. 19 and 30 and GF–1613.1, p. 8; GF–1615, p. 10; GF–1623.

Further, the sponsors argue that the hormonal mechanism in the rat is not duplicated in human physiology because the function of corticosterone in the rat is performed by cortisol in humans. Because of this difference, they say, the hormonal derangements caused by blocking the synthesis of corticosterone in the rat is less likely to occur in humans. Tr. X–63, 73. According to the sponsors, the evidence shows the rat to be a poor model for predicting the effects of furazolidone in humans because corticosterone is not the primary messenger regulating human hormonal balance. HF–309, pp. 3–4, 6–8, 15–9; HF–310, pp. 4–11, 27–30.

However, my examination of the evidence has revealed that the hormonal mechanism of tumor induction is not unique to the rate but has a physiological analog in man. Tr. X–61–65; Tr. IV–108–111. Hence, the difference between cortisol and corticosterone does not constitute a reason why furazolidone would not have a similar effect in humans.

To conclude, whether or not hormonal changes may occur as a result of acute treatment with furazolidone, as argued by the sponsors, such a mechanism cannot be invoked as the only tumor-inducing mechanism given the evidence of the presence of (1) nonendocrine tumors (GF–1613.1, p. 8, GF–1615.1, p. 10, GF–1623), (2) mutagenic activity (GF–849; GF–850), and (3) the failure of furazolidone to elevate plasma progesterone in any long-term feeding study. GF–1011, pp. 7–8; GF–1018, p. 18.

In fact, the sponsors have not proven that the tumors in the Norwich studies were induced solely by hormonal imbalance. Hence, I reject the sponsors' argument that furazolidone tumors were hormonally medicated.

B. Residue Detection

Having determined that furazolidone is an animal carcinogen at worst, and a tumorigen and suspected carcinogen at best, I now must determine whether residues of furazolidone would remain in animal food products after furazolidone had been given to the animal under the current labeling instructions and whether those residues raise concerns about safety. This determination is necessary under the DES proviso to the Delaney clause (21 U.S.C. 360b(d)(1)(I)(ii)) and is also necessary under the general safety clause. Section 360b(d)(2)(A) states that, in assessing the safety of a drug, I must consider "the probable consumption of such drug, and of any substance formed in or on food because of the use of such drug * * *."

The sponsors have attempted to demonstrate that, under the method of analysis they have proposed, no residues of furazolidone are found in test animals that are 0.5 ppm or greater. H&C exceptions at 132 ff. The sponsors further assert that only furazolidone, and not its metabolites, is covered by the Delaney clause. The argument is based on FDA's regulatory treatment of other chemicals. SK exceptions at 30–33. According to the sponsors, the phrase, "such drug," as used in the "DES Proviso" to the Delaney clause, 21 U.S.C. 360b(d)(1)(I)), refers only to the new animal drug which is the subject of the NADA and which has been shown to induce cancer under the Delaney clause. The sponsors contend that the term, "such drug," does not include the metabolites or degradation products of the drug and charge that the ALJ erred in his interpretation of the Delaney clause by stating, on pages 8, 9, and 13 of the I.D., that the residue includes both the parent drug and its metabolites. SK exceptions at 30 ff. The sponsors further argue that, to the extent the metabolites of furazolidone are in question, the metabolites are incapable of harming consumers of food products that may contain these metabolites. H&C exceptions at 127 ff.

After reviewing the evidence and the relevant portions of the statute, I must disagree with the sponsors on every point. First, I find credible evidence in the record that residues of furazolidone as high as 3.62 ppm were recovered in animals fed furazolidone under conditions of use specified in the label (GF–1618.1, pp. 5, 7; GF–883; GF–884; GF–1078, p. 39; GF–1007, p. 33). These residue levels far exceed the 0.5 ppm level claimed by the sponsors to be of no carcinogenic concern. SX–182, p. 7; HF–307, pp. 5–6; SX–183, p. 15; Tr. X–17–19.

I also find that both the general safety clause and the Delaney clause require the agency to consider the effect that the consumption of drug residues, including metabolites, will have on human consumers. As noted above, the general safety clause, 21 U.S.C. 360b(d)(2)(A), specifically requires the agency to consider this factor when reviewing an original application for an NADA. When the agency considers whether to withdraw an NADA for safety reasons under section 360b(e)(1) of the act, the agency certainly may consider the safety factors mandated by Congress in section 360b(d). See DES Commissioner's Decision, 44 FR 54852. To hold otherwise would be inconsistent with the clear intent of Congress in passing safety legislation intended to protect the American public from ingesting potentially harmful drug residues in food products.

These sponsors' arguments that nitrofurans' metabolites are not of carcinogenic concern are both contrary to principles acknowledged by the parties (Combined Critique of Center for Veterinary Medicine's Allegations of Facts, ¶¶ 208–9) and the law of this proceeding (49 FR 34971 and 34973, September 4, 1984).[6]

More importantly, interpreting the Delaney clause so as not to defeat its purpose requires that FDA find that the clause comprehends metabolites as well as parent drugs. The Center reminds us (Replies to Exceptions, pp. 26–7) that animal drugs may (1) be less carcinogenic than their metabolites, (2) leave no trace of parent compound in the edible tissue of the treated animals, and (3) cause no adverse effects to the treated animals. Hence, the sponsors' interpretation would compel FDA to conclude that dangerous human carcinogens could not be banned under the Delaney Clause. I reject this interpretation.

H&C claims that the court in *Hess and Clark I* accepted its interpretation of the term "residue." However, the language to which H&C refers, 495 F.2d at 991, was, in context, a reference to H&C's argument that the residues were actually attributable to the impurity, "pseudo-DES," not DES residues themselves. Neither is H&C's reliance on *Scott* v. *FDA*, 728 F.2d 322 (6th Cir. 1984) apt. There, the court found that a food additive containing a carcinogenic impurity is not subject to the Delaney clause if the additive, when tested as a whole, does not cause cancer. Here, furazolidone and its metabolites have been shown to cause cancer.

Alleged examples of FDA actions contrary to this position do not form a basis for a contrary conclusion. The sponsors have cited no published FDA document, much less a binding policy statement, in which FDA concluded that the Delaney clause does not apply to metabolites. Nor have they cited a single chemical regulated in a contrary manner.

For the reasons stated above, I find that the Delaney clause does apply to carcinogenic metabolite residues. Therefore, it becomes clear that the sponsors' proposed method of residue detection fails to meet the standards derived from the statute. The sponsors concede that their chosen method of residue detection—the Winterlin method—does not measure total residues, but only residues of the parent compound. HF–260; SX–183, pp. 4–5; Tr. X–11. The Winterlin method of analysis would still be acceptable if the sponsors had provided data demonstrating that the depletion of the measured entity (the "marker") from the measured animal tissue (the "target tissue") bore a known relationship to the depletion of all drug residues of toxicological or carcinogenic concern (December 31, 1987, 52 FR 49582 and 49583); GF–1610.1, p. 4. However, the sponsors have failed to do so. Hence, they have failed to adduce an acceptable method of residue detection that would permit FDA to determine that furazolidone residues remaining in treated animals would be safe to consumers.

The sponsors claim that the evidence demonstrates that none of the metabolites of furazolidone remaining in treated animals would be harmful to consumers. SX–180, p. 3; SX–181, pp. 3–4; SX–182, p. 4. For example, the sponsors claim that the presence of the 5-nitro group in nitrofuran compounds is essential for any mutagenic or carcinogenic activity resulting from its partial reduction into reactive intermediates. SX–182; SX–181; SX–182; HF–308; SF–36.

However, my review shows that the evidence indicates that metabolites of furazolidone without the 5-nitro group do have some mutagenic activity. Aminofuran and acetamidofuran, for example, tested both with and without

[6] "* * * in the absence of information to the contrary, all drug-related residues including metabolites are presumed to be potential carcinogens, and must be taken into account in determining if there is 'no residue.' " 49 FR 34973.

activation, are mutagenic. HF-97, Table 10. Thus, I find that nitroreduction does not necessarily preclude subsequent toxicity.

The evidence shows that there are a number of different metabolic pathways for the breakdown of furazolidone. GF-1621.3. Depending on the pathway, metabolites that still retain the furan ring with the 5-nitro group may be formed. Further, metabolites having the 5-nitro group were detected in the urine of animals treated with furazolidone. GF-712; GF-751. These metabolites included the "415" metabolite, of which the sponsors provide only unsupported speculation concerning nonmutagenicity, but which does not seem to have been investigated. HF-307, p. 18. Hence, I find that this metabolite has not been proven safe.

I also find that at least two metabolites of furazolidone are mutagenic. The sponsors have cited SF 36 to demonstrate to the contrary. However, after examining SF 36 (pp. 9-10), I find that two of the acknowledged metabolites of furazolidone—specifically, aminofuran and acetamidofuran—are mutagenic. For the reasons stated at p. 57, *infra*, I find that mutagenicity is an indication of carcinogenicity as well as a separate health hazard.

The sponsors contend that all the metabolites in the tissues after the required 5-day withdrawal period are harmless because the free metabolites are water soluble and excreted. Tr. XI-72. They claim that the remaining residues are in the form of adducts, which are covalently bound forms of metabolites that are not reactive, and, therefore, are not of carcinogenic concern. SX-182; pp. 4, 6-7, 10; SX-180, pp. 3, 10; SX-181, pp. 4-5, 7-10; HF-307, pp. 8-10, 12-14. However, my examination of the evidence contradicts this position, indicating that not all of the drug is excreted, and that there are significant amounts of extractable residue of furazolidone present in animal tissue, even 14 days after drug withdrawal. GF-556; GF-1618.1, p. 11; GF-1079, pp. 1, 14. This implies that there are unbound residues in the tissue or that the bound residues are unstable. Protein adducts may pose a toxicological hazard if they are not stable, according to the evidence. GF-1459, pp. 2-3; GF-1545, p. 45. Since the nature of these residues and their toxicity were not evaluated, they cannot be regarded as safe.

The sponsors cite further evidence to show that, even if the potential adducts were consumed in treated tissue by humans, and subsequently hydrolyzed, no threat would be posed to human health or safety. HF-307, p. 10. However, after reviewing the evidence, I find that hydrolysis in the human digestive system can free adducts, including semicarbizide, which has been shown to be carcinogenic. Tr. XI-30, 92-4. Residues of furazolidone are clearly bioavailable. HF-76. Inasmuch as the identity of all of these residues is not known, toxicity and carcinogenicity of these compounds cannot be determined, and they cannot be considered safe. GF-1618.

I also find that not all the metabolites of furazolidone are known, and that their safety, given what we know of the other metabolites of furazolidone, cannot be assumed. HF-310, p. 14; GF-1617.1, pp. 9, 12; GF-1623.1, p. 22. On the basis of the factual evidence in the record, I find that the Winterlin method of analysis is an unacceptable method of residue detection until the sponsors can demonstrate that the marker—the measured substance—bears a known relationship to the depletion of the total drug residue.

Contrary to the sponsors' assertions, the evidence fails to demonstrate that furazolidone's metabolites pose no health risk to the human consumers. Given all the other evidence in the record demonstrating that furazolidone is a carcinogen and that its metabolites are mutagens, I find that, contrary to the sponsors' assertions, the metabolites of furazolidone pose a potential health risk to human consumers. Because the sponsors have failed to adduce a method of detecting furazolidone's total residues that measures, even indirectly, the depletion of these residues from treated animals, I cannot determine that, under the methods of use specified in the labeling, no residues of carcinogenic or toxicological concern remain in the animal or food products derived from them.

Accordingly, I find that the NADAs for furazolidone should be withdrawn under both the Delaney clause and the general safety clause, because I have no reliable method of detecting drug residues that pose a safety threat to human consumers who eat animal products that may contain furazolidone residues. Whereas the act requires me to consider such residues, it is up to the sponsors to show that there is a reliable method to identify and determine the safety of such residues. They have not done so.

C. Mutagenicity

I find that furazolidone is a mutagen. Tr. XII-12-3, 96; SF-36. Mutagenicity is a scientifically recognized indication of potential carcinogenicity. HF 104, p. 22. I agree with Center witness Dr. Rosenkranz that both furazolidone and nitrofurazone "have been documented as mutagenic in systems which are highly predictive of cancer-causing ability." GF-1620.1, p. 013, ¶ 26. Also, the genetic damage brought about by a mutagen is a risk to health by itself, quite apart from its relation to carcinogenicity, as former Commissioner Jere Goyen found in his Cyclamate decision (September 16, 1980, 45 FR 61507). Finally, I find that, insofar as mutagenicity is concerned, the sponsors have demonstrated no safe dose of these two nitrofurans. See Tr. XI-33.

The sponsors claim that, where furazolidone and/or its metabolites are shown to be mutagenic, they are only weakly so and, further, that a weak mutagen is unlikely to be a carcinogen. H&C exceptions at 130; SK exceptions at 98. However, I note that nitrofurantoin, one of the chemicals the sponsors contended was a weak mutagen but not a carcinogen, has since been proven to be an animal carcinogen in a study submitted for the record by both parties. See GF-1701. Therefore, based on the evidence in the record, I find substantial credible evidence that several of the known metabolites of furazolidone are mutagens that must be treated as carcinogens.

III. Nitrofurazone

A. New Evidence That Nitrofurazone Is Not Shown To Be Safe

The ALJ found, on the basis of the evidentiary record before him, that nitrofurazone is an animal tumorigen, and, therefore, is not shown to be safe under the general safety clause. The ALJ further found that no reliable detection method has been demonstrated to detect nitrofurazone-derived residues in edible animal tissue and that the residues of nitrofurazone were not shown to be safe. He concluded that the evidence before him raised serious scientific questions about the safety of nitrofurazone and resulting residues. I.D., p. 75.

Since the issuance of the I.D., the record has been reopened to receive a draft NTP report that finds, on the basis of state-of-the-art bioassays, that there is clear evidence that nitrofurazone is an animal carcinogen. GF-1700. Therefore, this study both strengthens and validates the prior evidence of record, which indicated that nitrofurazone is a suspect carcinogen.

In the face of overwhelming record evidence that nitrofurazone is a

carcinogen and a tumorigen,[7] I find that new evidence demonstrates that nitrofurazone is no longer shown to be safe under the general safety clause. Thus, the Center has carried its threshold burden with respect to nitrofurazone.

B. Residue Detection

The sponsors have offered the same method of residue detection for nitrofurazone that they offered for furazolidone, namely, the Winterlin method. This method is inadequate to detect nitrofurazone-derived residues for the same reason that it is inadequate to detect furazolidone-derived residues. The Winterlin method does not detect residues of any of the metabolites of nitrofurazone, but only of the parent drug itself. HF–260; SX–183, pp. 4–5; Tr. X–11. This omission would not be fatal if the sponsors had demonstrated that the depletion of the parent compound from edible animal tissue bears a known relationship to the depletion of all nitrofurazone residues that are potentially unsafe. However, the sponsors have produced no such evidence. In light of this evidentiary omission, I am unable to determine the probable consumption of the parent drug or "of any substance formed in or on food" (21 U.S.C. 360b(d)(2)) as the result of the use of nitrofurazone in food-producing animals.

I agree with the Center that no concentration of the residue of a drug shown to be a carcinogen, be it in a parent drug or in its metabolites, can be shown to be of no carcinogenic concern. See citations from the Center's main brief at 82–87; Id. at 76. I find that the calculation of an acceptable daily intake (ADI) is inappropriate for a carcinogen. Tr. XV–15–6. Even if such a calculation might be appropriate for a carcinogen, I would have to find that one is not appropriate for these nitrofurans because the ADI approach is based upon observation of a no-observed-effect level, which was not determined in the Low-Dose Sprague-Dawley rat study. See citations found in the Center's main brief at 89.

IV. Other Exceptions

SK excepts to the failure of the ALJ to note that nitrofuraldehyde and 5-nitro-furoics retain the 5-nitro group. SK Exceptions at 61. I grant this exception but find that this has no larger implication with respect to other conclusions in the I.D. However, I reject SK's contention that these compounds have low potential for biological activity because of their low mutagenicity and rapid oxidation or reduction and elimination from the animal's body. First, the relationship between mutagenicity and carcinogenicity is qualitative and not quantitative HF–104. Therefore, low mutagenicity does not necessarily indicate negligible carcinogenicity or noncarcinogenicity. As to the rapidity of oxidation or reduction and elimination from the animal's body, I find that there is of record no persuasive evidence that oxidation or reduction rates have any relationship to the toxicological effects of the nitrofurans.

2. I grant SK's exception (Exceptions at 62) to the wording of the I.D. at 51, lines 13–6, concerning whether 4-ipomeanol or 1-aminopyrine are metabolites of furazolidone. The significance of these compounds is that: (1) They are furans without the 5-nitro group, and are thus toxic; and (2) amino-aromatic compounds can be activated to reactive intermediates. Tr. IX–102–3. Granting this exception does not require any further amendment to the I.D.

3. As to evidentiary rulings, I affirm the rulings of the ALJ for the reasons he stated with one exception. I agree with SK that the ALJ erroneously struck portions of the testimony of two witnesses, Doctors Shriner and Olive, on grounds that their testimony was insufficiently supported by citations. Under the Federal Rules of Evidence, all relevant evidence is admissible, except as otherwise provided by law, the Constitution, or the rules of evidence. Federal Rules of Evidence, Rule 402. According to Rule 401, "relevant evidence," means "evidence having any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." In my view, the testimony of Doctors Shriner and Olive, if believed, would have at least had some tendency to establish SK's contentions in this proceeding. Further, under FDA's procedural regulations (21 CFR 12.94) evidence is not made excludable simply because it contains either no citations or insufficient citations. Therefore, I rule that the ALJ erred in excluding the subject testimony. The Center's objections should have been overruled as objections that went to the weight to be accorded the testimony, not to its admissibility.

Having overruled the ALJ on this admissibility question, I nevertheless find that the testimony of the two witnesses is entitled to very little weight as a result of the deficiencies complained of in the Center's objection. That is, these witnesses' views are entitled to little weight because they were not accompanied by adequate citations to evidence of record or to any other supporting literature. For this reason, although I have considered the testimony of Doctors Shriner and Olive, I give it insufficient weight to cause it to change my mind on any fact in issue in this proceeding. Though error, the exclusion was harmless error.

V. Conclusions and Order

The foregoing opinion in its entirety constitutes my findings of fact and conclusions of law. Based on the foregoing discussion, findings, and conclusions, I affirm the ALJ's initial decision as corrected and supplemented by this decision.

Specifically, I conclude that:

(1) New evidence shows that there is a reasonable basis from which serious scientific questions may be inferred about the safety of furazolidone and nitrofurazone and the residues that result from their use.

(2) Neither nitrofurazone nor furazolidone nor their metabolites have been shown to be safe under the conditions of use upon the basis of which the applications were approved within the meaning of 21 U.S.C. 360b(e)(1)(B).

(3) No reliable detection method has been demonstrated to be able to detect nitrofurazone-related residues in edible tissues when conditions of use approved in the NADAs are followed.

(4) The residues of nitrofurazone and furazolidone have not been shown to be safe.

(5) The Winterlin method of detection is incapable of measuring the metabolites of furazolidone. No other method of detection has been demonstrated to be able to measure these metabolites. Hence, no reliable method of detection has been demonstrated which is fully adequate to detect furazolidone-related residues in edible tissues when conditions of use approved in the NADAs are followed.

(6) A practical method of detection capable of detecting both the parent drug, furazolidone, and its metabolites does not exist. Therefore, it is impossible to quantify and qualify the nature of the residues of furazolidone.

(7) Furazolidone and its metabolites have been shown by substantial new evidence to induce cancer in man or animals as prohibited by 21 U.S.C. 360b(d)(1)(I).

(8) A determination of the concentration of drug residues

[7] There is ample evidence of record that tumorigens (inducers of benign tumors) can also be carcinogens (inducers of malignant tumors). GF–1700, p. 7; Tr. III–77–81; Tr. X–112.

consisting of the parent drug, furazolidone, and its metabolites that is of no carcinogenic concern has not been adequately established.

(9) Under the conditions of use specified in the labeling, the actual concentration of drug residues of furazolidone has not been shown to be at or below the level of no carcinogenic concern.

Therefore, I order that the approval of all NADAs for nitrofurazone and furazolidone listed in this document be hereby withdrawn pursuant to 21 U.S.C. 360b(d)(i)(I) and 360b(e)(1)(B). In addition, I order the removal of 21 CFR 558.262 and 558.370. I also order deletions of all references to furazolidone and nitrofurazone contained in 21 CFR 510.515, 558.4, and 558.15.

List of Subjects

21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 558

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 510 and 558 are amended as follows:

PART 510—NEW ANIMAL DRUGS

1. The authority citation for 21 CFR part 510 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 512, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 360b, 371, 376).

§ 510.515 [Amended]

2. Section 510.515 *Animal feeds bearing or containing new animal drugs subject to the provisions of section 512(n) of the act* is amended by removing paragraphs (a)(4) and (a)(5); by removing paragraphs (b)(11), (b)(15), (b)(17)(ii) and reserving them; and in the table in paragraph (c) by removing the entries for "8.", "9.", and "10.", and redesignating entries 11 through 14 as 8 through 11.

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

3. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: Secs. 512, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b, 371).

§ 558.4 [Amended]

4. Section 558.4 *Medicated feed applications* is amended in the Category II table in paragraph (d) by removing the entries for "Furazolidone" and "Nitrofurazone."

§ 558.15 [Amended]

5. Section 558.15 *Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals* is amended in the tables in paragraphs (g)(1) and (g)(2) by removing the entries for "Hess & Clark and SmithKline Animal Health Products."

§ 558.262 [Removed]

6. Section 558.262 *Furazolidone* is removed from subpart B.

§ 558.370 [Removed]

7. Section 558.370 *Nitrofurazone* is removed from subpart B.

Dated: August 16, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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