

*Effect
Bassett
Cummings
Dwyer* FSA

Mr. William Stokes
Petitions Control Branch

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

February 21, 1967

Dr. G. K. Whitmore
Division of Toxicological Evaluation
Petitions Review Branch

File: PPT 7F0558

Notran (2,6-dichloro-4-nitroaniline) 0.05 ppm in or on almond waste
0.5 ppm in or on almond husks

PESTICIDE PETITION NO. 77-0558

Opjohn Company
Farmington, Michigan
(AF 12-868)

Toxicity data provided for Notran Pesticide Petition No. 7-421 (June 22, 1964 memo), Pesticide Petition No. 490 (June 9, 1966 memo) and Pesticide Petition No. 474 (October 6, 1966 memo) demonstrated 100 ppm no effect diets in 2 year dog and rat studies, 100 ppm no effect diet in a 3 generation rat reproduction study, similar rat and human metabolism, no effects in human males consuming 10 mg/day/3 months, and a no effect in a, "Senes", rabbit test for teratogenicity.

These data support the safety of the requested negligible residue tolerance of 0.05 ppm in or on almond waste.

FEI defers to SWI relative to the safety of livestock consuming 0.5 ppm of Notran in or on almond husks.

Enclosures

- cy memo 6-9-66
- cy memo 6-22-66
- cy memo 10-6-66

UNIT:RBImmerthal

cc: PDA
HTE
LIS (Mr. Jacobson)
PP Nos. 77-0558 - 7-421
490 & 474

GWhitmore:ops 2-21-67

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FSA

January 12, 1967

Pesticide Petition No. 7F0558

Dr. Ross R. Herr
Pesticide Regulatory Affairs
Plant Health Products
The Upjohn Company
Kalamazoo, Michigan 49001

Dear Dr. Herr:

We have your letter of January 9, 1967, transmitting a pesticide petition proposing the establishment of tolerances of 0.05 part per million on almond meats and 0.5 part per million on almond husks for residues of the fungicide 2,6-dichloro-4-nitroaniline. We also have the accompanying check for \$600.

This petition has been designated Pesticide Petition No. 7F0558.

Since two tolerance levels are proposed in this petition the necessary fee is \$900. We will hold this petition pending receipt of an additional deposit of \$300.

Sincerely yours,

Drew M. Baker, Jr.
Petitions Control Branch
Bureau of Science

cc: Pesticides Regulation Division
ARS, USDA

cc: PCB FSA DTE FB

DMBaker:rh 1/12/67

NOTE: Two tolerance levels proposed for different parts of the same raw agricultural commodity requires fee as if two different raw agricultural commodities. See precedents in Pesticide Petitions 329 and 378.

DMBaker, Jr.

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Pesticide Petition No. 7P0558

January 20, 1967

Dr. Ross E. Berr
Pesticide Regulatory Affairs
Plant Health Products
The Upjohn Company
Kalamazoo, Michigan 49001

Dear Dr. Berr:

We have your letter of January 17, 1967, and the accompanying check for \$300 to complete the necessary deposit for Pesticide Petition No. 7P0558. Accordingly, this petition is being filed today.

Further action awaits completion of scientific review and evaluation.

Sincerely yours,

Drew H. Baker, Jr.
Petitions Control Branch
Bureau of Science

cc: Pesticides Regulation Division
ARS, USDA

cc: PRD, ARS, USDA (Mr. Bowen)

cc: PCB FSA DTE FB

DMBaker:man 1/20/67

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FSA/Pest. Br.
JAN 23 1967

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MEMORANDUM OF CONFERENCE

January 26, 1967

PRESENT: Dr. Alan J. Lewis) Upjohn Company
 Dr. Kent M. Beckman) Kalamazoo, Michigan
 Dr. Ross R. Herr) 49001
 Dr. Richard L. Johnson) (AF 12-868)

Dr. G. Whitmore) Division of Toxicological
 Dr. O. G. Fitzhugh) Evaluation

Mr. Drew M. Baker) Petitions Control Branch

SUBJECT: Botran (2,6-dichloro-4-nitroaniline)

Mr. Baker's letter of January 10, 1967, to Dr. Herr was the reason for the conference. The letter said that the maximum acceptable daily intake for Botran had been reached and that we will be unable to consider the establishment of additional tolerances for residues which will result in a toxicologically significant increase in the total dietary intake of Botran.

The visitors asked on what basis we concluded that the maximum acceptable daily intake of Botran had been reached. We said on the basis of a hundred-fold safety factor, that is, the no-effect level was 100 ppm, so a daily intake of 1.5 mg/day was acceptable since we considered the average intake of food was 1.5kg/day. We said our calculations indicated an intake of 1.44 mg/day based upon all crops for which tolerance are established having residues at the tolerance levels. The visitors presented their calculations showing a yearly intake of 403.4 mg based upon all crops for which tolerances are established having residues at the tolerance levels. We said 403.4 mg/year is equivalent to 1.15 mg/day. They said the difference between their figure of 1.15 and our figure of 1.44 was probably due to the fact that they had not included canned foods in their calculation because they believe that Botran residues are completely destroyed during the canning process. They said they had included frozen foods in their calculation although they believe that freezing will destroy about half the Botran residues.

We said Mr. Baker's letter does not rule out consideration of tolerances for negligible residues of Botran. However, we want a report from Dr. Curtis at SPAL on his experiments that show some damage to the eyes of dogs being fed Botran. They said they have an appointment with Dr. Curtis next week.

Drew M. Baker, Jr.

cc: PCB FSA DTE PP 7F0558 & 6F0474

DMBAKER:mmm 1/27/67

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MEMORANDUM OF CONFERENCE
January 26, 1967

PRESENT:

Mr. E. L. Johnston	-	
Mr. A. J. Louis	-	Upjohn Company
Mr. Kent M. Beckman	-	Kalamazoo, Michigan
Mr. A. E. Herr	-	(AT 12-866)
Mr. Drew Baker	-	Petitions Control Branch
Dr. G. C. Fitzhugh	-	Division of Toxicological
Dr. G. E. Whitmore	-	Evaluation

SUBJECT: Botran

The visitors inquired about the Petitions Control Branch letter stating additional toxicological significant residue tolerances for Botran could not be established. They presented a table of calculations, based on USDA food intake information, showing possible maximum intake could be 0.94 mg/day from established residue tolerances. Their calculations did not include canned food items. DTE's calculations, including canned food items, showed a possible intake of 1.44 mg/day (1300 gram daily intake). The visitors stated canning destroyed Botran; therefore, they felt consideration of canned item residues weren't germane. They were asked to furnish data supporting Botran absence in canned items.

The SPAL experience with Botran related eye lesions was discussed. DTE stated this experience would have to be examined and related to other data relative to a possible influence upon the demonstrated 100 ppm, no-effect levels. The Upjohn people are visiting SPAL the week of January 30 for a discussion with the investigators about their findings.

The petition for allowed residue tolerances, 77-0538, was discussed relative to the toxicological significance of the requested 0.05 negligible residue tolerance request. DTE concluded that a negligible residue on such a minor food item would not add toxicological significant residues, therefore, they could see no reason for it not being established.

G. E. Whitmore, DTE

INIT:EBHumenthal

cc: DTE
PCBGSHitmore:dps 1-30-67
ED init: OGF 1-27-67

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FEB 20 1967

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Elbert
Bessie
Winnipeg

File:
PP 77-0538

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(AF 12-868)

Pesticide Petition No. 7F0558

February 17, 1967

Dr. Ross H. Harr
Agricultural Chemists
The Upjohn Company
Kalamazoo, Michigan 49001

Dear Dr. Harr:

We have your letter of February 17, 1967, requesting that tolerance for residues of Botran in or on almond meat be changed from 0.05 part per million to 0.1 part per million.

The proposed tolerance for almond meat in Pesticide Petition No. 7F0558 is being increased from 0.05 ppm to 0.1 ppm as per your request.

Sincerely yours,

James B. Lamb
Petitions Control Branch
Bureau of Science

cc: Pesticides Regulation Division
ARS, USDA (David Bowen)

CC: PCB FSA DTE
JBLamb:mcs 2/27/67 :man 2/24/67
R/D Init: WStokes 2/27/67

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AF 12-868
Blues
7F0558
File: 7F0558

Don't have has
being sent
in the field
- make sure
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PP #770558

2

"popcorn" and "bloss" stages, and at petal fall. Treatments are to be made at the rate of 1.13 lb act/100 gal, equivalent to about 4.5-6.5 lb act/acre. The anticipated built-in pre-harvest interval is 3-4 months.

Nature of the Residue

The metabolism of Botran has previously been discussed (FSA memo, PP #570494, J. Wolff, 6-3-65). Briefly, dissipation of residues on plants is brought about chiefly by volatilization. Metabolites have not been found and on the basis of the available data, the parent compound is the only toxic component of the residue.

Analytical Methods

Residues were determined by the microcoulometric gas chromatographic (MEGC) method. In this method the ground nut meats or hulls are blended with benzene and the residue partitioned between acetonitrile and benzene, and the acetonitrile portion evaporated to dryness. The residue is taken up in benzene and injected into the Dehman instrument.

Control values were 0.01-0.06 ppm for almond meats and 0.01-0.20 ppm for the hulls. The highest values (0.1-0.2 ppm) for the hulls are at least partly attributable to the presence of an interfering substance with a retention time similar to that of Botran. The minimum detectable amount by this method may be as low as 0.01 ppm but based on the blanks or the amount that can reliably be detected, we would estimate the sensitivity to be 0.06 ppm for the meats and 0.2 ppm for the hulls. The relation of these sensitivities to the proposed tolerances is discussed below in the residue section.

Good recoveries (at 0.1-1.0 ppm fortification levels) of 82% or better were obtained except for one atypical value of 68% for meats and one of 70% for hulls at the 0.5 ppm level. The latter can be explained by the high blank associated with this particular study since the recoveries were corrected for the corresponding blanks.

The method is considered to be specific for Botran in the presence of other pesticides with established tolerances on almonds.

The method is considered to be adequate for enforcement purposes, for the above and other reasons given below in the residue section.

No method trial was conducted since the principles involved, including partitioning of the residue into acetonitrile and benzene and the MEGC determinative step, are well established (see SAM, vol. 1).

PP #770558

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A colorimetric method sensitive to 0.1 ppm is available (J. Ag. & Food Chem. 10, 399; 1962) and could probably also be used for determining DDT residues in almonds, (FAH, vol 2). This method has been successfully tried out on lettuce, onion, and peaches in connection with PP #55033A.

Residue Data

Four studies were made in California reflecting the described usage (1-3 applications at the recommended time and rate). The data reflect values in or on the nutmeats, according to Section 126.1(j)(2); and the hulls. For almond meats, there were no values, except one in about 12 treated samples, in excess of the corresponding controls. The exception was a net value of 0.02 ppm which is not significant in relation to its blank of 0.06 ppm. Since residues of DDT do not translocate we would not have expected residues in the nutmeats, and the data support this expectation. In view of the sensitivity of 0.06 ppm which reflects the known range of variability of blanks, we consider the proposed tolerance of 0.1 ppm for almond meats to be adequate.

In the case of almond hulls, residues are in fact present. The apparent values (uncorrected for controls) range up to 0.33 ppm corresponding to net (corrected) values of up to about 0.2 ppm. We therefore conclude that net residues would not exceed 0.2 ppm on the hulls from the described use, and are well within the proposed tolerance. The sensitivity of the method is 0.2 ppm and includes the known range of variability of blanks. Even without a correction for the maximum blank, apparent residues would not exceed an estimated 0.4 ppm, and we consider that the proposed tolerance of 0.5 ppm would be adequate.

Residue in meat or milk

No conventional feeding studies are available.

About 95% of the almond hulls produced in the U.S. (almost all in California) are sent to processors for use in animal feeds, primarily for beef cattle. (Almond Facts, California Almond Growers Exchange, July-Aug. 1957). It is our understanding that the sale of almond hulls by the grower to feed processors is an important economic factor in the profitable growing of almonds. Therefore, it would probably be impractical to propose a feeding restriction for the hulls since it would seem unrealistic to expect that the grower would use a pesticide if he were unable to sell the treated hulls for use in feeds. Also it may be unrealistic to require that the treated hulls which have a definite economic value not be utilized as animal feed.

PP #770558

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We note that there are metabolism studies with the rat (The Upjohn Co. Status Report dated 9-23-63) which indicate that no residues would likely be stored in the tissues (the only detectable residues were found in the GI and urinary tracts and the liver which are involved with the absorption, excretion or metabolism of ingested materials). However, these studies reflected a single high-level dose (8 mg/kg body weight) with analysis of tissues 24 hours later. They are thus not necessarily indicative of the residues to be expected from chronic low-level ingestion of the pesticide by a ruminant such as the cow.

Moreover, the data for almonds indicate that definite detectable residues of Botran would be present in the hulls and since the tolerance of 0.5 ppm is not being proposed to cover a "no-residue" situation, this does not, in our opinion constitute a negligible residue condition.

Therefore, we believe that before a tolerance is established for almond hulls, we are justified in asking for additional information, including low-level feeding studies, to give more positive assurance that residues would not transfer to meat or milk.

We are therefore recommending against the establishment of the proposed tolerances at this time.

D. Duffy

cc
 DTK
 SCI-R
 SCI-OB
 SCI-F
 TSA/OD
 DFC
 TSA/TE (PP #770558)
 TSA/Duffy

Duffy:md
 4-21-67

RD/I--JApart

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F B-75A
PP# 7F0558

Petitions Control Branch and
Division of Toxicological Evaluation

April 21, 1967

Pesticides Branch, Division of Food
Standards and Additives

AF 12-868

PP #7F0558. Botran on almonds. Evaluation of analytical methods and residue data.

The Upjohn Company proposes the following tolerances for residues of the fungicide 2,6-dichloro-4-nitroaniline (trade name Botran):

0.5 ppm on almond husks*

0.1 ppm on almond meats

Tolerances of 20, 15, 10, 5, 1 and 0.25 ppm have previously been established for Botran on a number of fruits and vegetables.

Conclusions

1. An adequate method of analysis is available for enforcement purposes.

2. Residues in almond hulls and meats would not exceed the proposed tolerances with the described usage.

3. Almond hulls are used chiefly in animal feeds and in the absence of a feeding study for Botran, we cannot determine with definite assurance whether or not residues would result in meat or milk if the proposed tolerances were established.

Recommendations

We recommend that the proposed tolerances not be established.

The petitioner should be informed that before a favorable recommendation can be made we will need a feeding study to demonstrate whether or not the ingestion of Botran residues at the proposed tolerance level of 0.5 ppm for almond hulls/would result in residues in meat or milk.

Proposed Usage

Detailed Considerations

Botran (formulated as either the 75% or 50% wettable powder) is to be applied to almonds for the control of brown rot or blossom blight at

*The petitioner refers to the outer coverings as almond "husks" although the term "hulls" is more commonly used. We have used this latter designation in our review.

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File: PP# 7F0558

Petitions Control Branch
Division of Pharmacology and Toxicology

May 13, 1969

Petitions Evaluation Branch
Division of Pesticides

Deletion of Forage Restrictions on Botran Labels.

PRD, USDA (see letter H. G. Alford to J. Alpert, 3/20/69) has asked our opinion on the request of Upjohn Co. that the forage restrictions on the Botran (2,6-dichloro-4-nitroaniline) labeling be deleted. Meat and milk studies were submitted to support their contention that no detectable residues of Botran would result in meat and milk if the restrictions were lifted.

These feeding studies indicate that no detectable residues of Botran per se would result in meat (<0.1 ppm) or milk (<.01 ppm) from the feeding of up to 80 ppm of Botran in the total diet. The method of analysis (MCGC-halogen detector) however, determines the parent compound only. Previous radiotracer studies (PP #7F0558) with the rat using C¹⁴-labeled Botran indicated that Botran is absorbed and metabolized in the animal. Thus three metabolites, namely 3,5-dichloro-4-aminophenol and the glucuronide and sulfate conjugates of this compound, were found in the urine. This raises the possibility at least of the presence of these or other metabolites of Botran in milk or tissues from the consumption of Botran by livestock.

Unless further information is received to resolve this problem, we cannot conclude that the restrictions are unnecessary or what the status of these uses would be under our Regulation 120.6 (statement on need for tolerances in meat, milk, eggs).

D. Duffy

cc:
SC-13 SC-300
SC-12 SC-320
SC-1 CS-40
SC-970

DDuffy:lbc
5/13/69
RD/I - JAlpert:JGCummings

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Petitions Control Branch
Attention: William Stokes

Charles E. Gumlach
Bureau of Veterinary Medicine

Pesticide Petition No. 770558
Botran (2,6-dichloro-4 nitroaniline)

Upjohn Company
Kalamazoo, Michigan
(AF 12-868)

Albert
Beauch
Cunningham
Deffen
File: 770558

Safety to ruminants:

Data not submitted to demonstrate safety to animals consuming tolerance of 0.5 ppm. in or on almond husks or hulls.

It would be necessary to undertake a conventional feeding study using Botran alone and/or Botran treated husks at the normal feeding level. The amount of almond husks produced yearly and the seasonal occurrence would not feed a great number of cattle. Approximately 15,000 tons of husks are produced yearly and is concentrated primarily in two counties of California, such husks are fed in both the green or dry state.

Data shows that Botran is eliminated rather rapidly and therefore a 4-6 week feeding study should be more than ample.

It would be necessary to do such studies on both beef and dairy cattle but since a high percentage would be used in beef cattle, a restriction can be used in dairy cattle. Such restriction may not be necessary since data supports no effects at 10 mg./day/3 months in human males.

Bureau of Veterinary Medicine withholds further comments until a ruminant feeding study can be reviewed.

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to be reviewed

How should question be raised on these points before data goes out?

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JUN 1 1967

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DTE
DAIC
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CEGumlach/cy 5-26-67

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file in PP #7F0558

Petitions Control Branch and
Division of Toxicological Evaluation

May 29, 1967

Pesticides Branch, Division of Food
Standards and Additives

AF 12-868
(The Upjohn Co.)

PP #7F0558. Comment on petitioner's letter of 5-12-67 and need for a low-level feeding study for Botran.

In our evaluation (FSA memo, D.Duffy, 4-21-67) of the data submitted with this petition, we made note of the same metabolism studies with the rat referred to in the petitioner's letter of 5-12-67. We concluded at that time that the results did indicate that no residues would likely be stored in the tissues.

However, these studies reflected only a single high level dose (8 mg/kg body weight) with analysis of tissues 24 hours later and give a poor indication even for a negligible residue condition of the residues in meat or milk to be expected from chronic low-level ingestion of the pesticide by a ruminant such as the cow. Moreover, the data for almonds indicated that definite detectable residues of Botran would be present in the almond hulls from the proposed use and this did not, in our opinion, constitute a negligible residue condition.

We therefore reaffirm our previous conclusion that before the proposed tolerance is established for almond hulls, we would need feeding studies to give more positive assurance that residues do not transfer to meat or milk.

These feeding studies would also be desirable in ascertaining whether or not the feeding restrictions now specified in connection with the uses of Botran on beans, cotton, and Irish potatoes are in fact needed.

D. Duffy

cc:
SCI-R SCI-OD SCI-F DTE
DFC FSA/OD FSA/PB PP #7F0558

DDuffy:md:jrf
5/29/67
RD/I - GJBeusch, JAlpert

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AF 12-868

Pesticide Petition No. 770558

June 2, 1967

Dr. Ross E. Herr
Agricultural Chemicals
The Upjohn Company
Kalamazoo, Michigan 49001

Dear Dr. Herr:

This refers to Pesticide Petition No. 770558 proposing the establishment of tolerances for residues of the fungicide Rotram (2,6-dichloro-4 nitroaniline) at 0.5 part per million on almond hulls and 0.1 ppm on almond meats.

We have reviewed the rat metabolism studies transmitted with your letter of May 12, 1967; however, these studies reflected only a single high level dose (9 mg/kg body weight) with analysis of tissues 24 hours later and give a poor indication even for a negligible residue condition of the residues in meat or milk to be expected from chronic low-level ingestion of the pesticide by a ruminant such as the cow. We affirm that, since treated almond hulls are fed to cattle, feeding studies with cattle are needed for the following reasons:

1. To assure that residues of Rotram do not transfer to meat and milk.
2. To assure safety for cattle consuming Rotram.

Since some time will be needed to complete these studies, this petition should be withdrawn and refiled when the necessary studies are available. Otherwise it may be necessary to establish a tolerance of zero for Rotram on almond hulls and almond meats. Please let us have your reply by June 13.

Sincerely yours,

Drew M. Baker, Jr.
Petitions Control Branch
Bureau of Science

cc: Pesticides Regulation Division,
ARS, USDA

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TSC/Pest. Br.

RD Init: FJMcFarland 6/2/67

cc: PCB **PSA** DTE SCI-R BVM

DMBaker:mak 6/2/67

RD DMB:mcs 6/1/67:ch 6/1/67

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FSA

Alpert
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Cummings
Duffy

File: PP# 770558

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MEMO

TO R. R. Herr

FROM R. L. Johnston
A. W. Neff

DATE June 12, 1967

SUBJECT Botran Protocol for Meat
and Milk Residue and Safety
Studies

E-PP558

RD-126 5-66

The following is the protocol for the Botran meat and milk residue studies that you requested from Dr. Neff and me. Limited safety studies with considerably larger doses and a shorter feeding period will initiate these studies. Milk from these short term studies will be used for the preliminary assay procedures. Chemical, not radioactive, procedures will be utilized.

Based on the residue findings of Botran on Almond hulls and almond meats and on potatoes, the feeding levels selected to be used are given in the table below:

<u>Group</u>	<u>No. of Animals*</u>	<u>Feeding Levels</u>	<u>Duration of Feeding</u>
Control	3	0	30 days
1X	3	0.5 ppm	30 days
2X	3	1.0 ppm	30 days
4X	3	2.0 ppm	30 days
Safety	3	200 mg/kg	5 days

* All milking cows

Milk samples from each cow, except in the safety group, will be taken twice a week for four weeks. Each sample will be a composite of a.m. and p.m. milkings. A total of 96 milk samples will be analyzed for Botran residue.

Meat residue analyses will be done on muscle, liver, fat and kidney taken from cows receiving 2.0 ppm of Botran. Lower level samples will be taken if indicated. A total of 24 meat residue samples will be analyzed.

The animals will be killed while on the treated feed (no withdrawal period).

-2-

The following observations will be made on the animals:

1. Daily clinical observations
2. Food and water consumption
3. Body weight (0, 14, 30 days)
4. Hemograms (0, 30 days)
 - a. Hemoglobin
 - b. hematocrit
 - c. leukocyte
 - d. differentials
5. Clinical chemistry (0, 30 days)
 - a. blood urea nitrogen
 - b. glucose
 - c. Serum transaminases (SGOT, SGPT)
 - d. serum total protein
 - e. Protein-bound iodine
 - f. Alkaline phosphatase
6. Urinalysis (0,30 days)
 - a. Specific gravity
 - b. pH
 - c. Albumin
 - d. glucose
 - e. bile
 - f. acetone
 - g. microscopic
7. Organ weights: liver, kidney, adrenal, thyroid.
8. Histopathology: liver, kidney, adrenal, thyroid, bone marrow and eye. Other tissues will be taken if indicated.

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AGRICULTURAL
CHEMICALS

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

TELEPHONE
Area Code 616
345-3571

June 12, 1967

Mr. Drew M. Baker, Jr.
Petitions Control Branch
Bureau of Science
Department of Health, Education, and Welfare
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Baker:

SUBJECT: Pesticide Petition No. 7F0558

REFERENCE: Your letter of June 2, 1967

In accordance with the instructions in your letter of June 2, 1967, we are withdrawing at this time our petition No. 7F0558 proposing the establishment of tolerances for residues of the fungicide Botran (2,6-dichloro-4-nitroaniline) at 0.5 ppm on almond hulls and 0.1 ppm on almond meats.

I am enclosing five copies of a proposed protocol entitled "Botran Protocol for Meat and Milk Residue and Safety Studies".

We would appreciate it if you will arrange a conference for us with the appropriate persons from the Petitions Control Branch on Friday, June 23, 1967. Attending from Upjohn will be Dr. R. L. Johnston, Dr. A. W. Neff, Dr. A. J. Lemin and myself. Our plane will be arriving in Washington at approximately 10:30 a.m. E.D.T. and departing again at 5:00 p.m. E.D.T., so an early afternoon time would perhaps be most convenient if it can be arranged.

Thank you for your cooperation.

Sincerely yours,

THE UPJOHN COMPANY

Ross R. Herr
Ross R. Herr
Pesticide Regulatory Affairs
Plant Health Products

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FSA/Pest. Br.
JUN 14 1967

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Enclosures

PCB
JUN 13 1967

MEMO

TO R. R. Herr

FROM R. L. Johnston
A. W. Neff

DATE June 12, 1967

SUBJECT Botran Protocol for Meat
and Milk Residue and Safety
Studies

HQ 126 5/66

COPIES TO

The following is the protocol for the Botran meat and milk residue studies that you requested from Dr. Neff and me. Limited safety studies with considerably larger doses and a shorter feeding period will initiate these studies. Milk from these short term studies will be used for the preliminary assay procedures. Chemical, not radioactive, procedures will be utilized.

Based on the residue findings of Botran on Almond hulls and almond meats and on potatoes, the feeding levels selected to be used are given in the table below:

<u>Group</u>	<u>No. of Animals*</u>	<u>Feeding Levels</u>	<u>Duration of Feeding</u>
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The animals will be killed while on the treated feed (no withdrawal period).

-2-

The following observations will be made on the animals:

1. Daily clinical observations
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4. Hemograms (0, 30 days)
 - a. Hemoglobin
 - b. hematocrit
 - c. leukocyte
 - d. differentials
5. Clinical chemistry (0, 30 days)
 - a. blood urea nitrogen
 - b. glucose
 - c. Serum transaminases (SGOT, SGPT)
 - d. serum total protein
 - e. Protein-bound iodine
 - f. Alkaline phosphatase
6. Urinalysis (0,30 days)
 - a. Specific gravity
 - b. pH
 - c. Albumin
 - d. glucose
 - e. bile
 - f. acetone
 - g. microscopic
7. Organ weights: liver, kidney, adrenal, thyroid.
8. Histopathology: liver, kidney, adrenal, thyroid, bone marrow and eye. Other tissues will be taken if indicated.

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MEMO

TO	R. R. Herr	SUBJECT	Botran Protocol for Meat and Milk Residue and Safety Studies
FROM	R. L. Johnston A. W. Neff		
DATE	June 12, 1967		

FD 126 5/66

COPIES TO

The following is the protocol for the Botran meat and milk residue studies that you requested from Dr. Neff and me. Limited safety studies with considerably larger doses and a shorter feeding period will initiate these studies. Milk from these short term studies will be used for the preliminary assay procedures. Chemical, not radioactive, procedures will be utilized.

Based on the residue findings of Botran on Almond hulls and almond meats and on potatoes, the feeding levels selected to be used are given in the table below:

<u>Group</u>	<u>No. of Animals*</u>	<u>Feeding Levels</u>	<u>Duration of Feeding</u>
Control	3	0	30 days
1X	3	0.5 ppm	30 days
2X	3	1.0 ppm	30 days
4X	3	2.0 ppm	30 days
Safety	3	200 mg/kg	5 days

* All milking cows

Milk samples from each cow, except in the safety group, will be taken twice a week for four weeks. Each sample will be a composite of a.m. and p.m. milkings. A total of 96 milk samples will be analyzed for Botran residue.

Meat residue analyses will be done on muscle, liver, fat and kidney taken from cows receiving 2.0 ppm of Botran. Lower level samples will be taken if indicated. A total of 24 meat residue samples will be analyzed.

The animals will be killed while on the treated feed (no withdrawal period).

-2-

The following observations will be made on the animals:

1. Daily clinical observations
2. Food and water consumption
3. Body weight (0, 14, 30 days)
4. Hemograms (0, 30 days)
 - a. Hemoglobin
 - b. hematocrit
 - c. leukocyte
 - d. differentials
5. Clinical chemistry (0, 30 days)
 - a. blood urea nitrogen
 - b. glucose
 - c. Serum transaminases (SGOT, SGPT)
 - d. serum total protein
 - e. Protein-bound iodine
 - f. Alkaline phosphatase
6. Urinalysis (0,30 days)
 - a. Specific gravity
 - b. pH
 - c. Albumin
 - d. glucose
 - e. bile
 - f. acetone
 - g. microscopic
7. Organ weights: liver, kidney, adrenal, thyroid.
8. Histopathology: liver, kidney, adrenal, thyroid, bone marrow and eye. Other tissues will be taken if indicated.

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MEMORANDUM OF CONFERENCE

June 19, 1967

PRESENT: Dr. R. R. Herr) Upjohn Company
 Dr. R. L. Johnston) Kalamazoo,
 Dr. A. J. Lamin) Michigan
 Dr. A. W. Naff) (AF 12-868)

and

Mr. J. Alpert Food Standards and Additives
 Mrs. James B. Lamb Petitions Control Branch

SUBJECT: Meat and Milk Residue Study on Botran

The visitors presented a protocol for a 30-day meat and milk residue study on Botran in milking cows.

The following points were discussed:

1. Whether the proposed feeding levels were high enough to provide data for other crops besides almonds. The visitors agreed to add two additional levels of 5 and 20 ppm to the study.
2. The proposed study did not show how equilibrium in the tissues would be determined, assuming that the compound will store in tissues. The visitors agreed to use as an indicator of equilibrium blood residue levels determined on blood samples taken at the same time as the milk samples, as suggested by Mr. Alpert.
3. Spot check of tissue residues in both high and low feeding level animals will be performed to provide supporting data.
4. Mr. Alpert indicated that the 0.05 ppm sensitivity of the analytical method for meat and milk residues is probably satisfactory for meat but is not satisfactory for milk. A sensitivity of 0.01 - 0.02 ppm is needed for milk. The visitors were told that overdosing would help to support the methodology if the higher levels showed no detectable residues above the sensitivity of the method.

Received
 FSA/Pest. Br.
 JUL 26 1967

James B. Lamb

cc: S-13 S-510 S-990 S-12

JBLamb:mmm 7/24/67; mak 7/19/67

R/D Init:JAlpert 7/20/67

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of
Document

AGRICULTURAL
CHEMICALS

F- PP 558

THE UPJOHN COMPANY

KALAMAZOO, MICHIGAN

TELEPHONE
Area Code 616
345-3571

July 7, 1967

Mr. Drew M. Baker, Jr.
Petitions Control Branch
Bureau of Science
Department of Health, Education, and Welfare
Food and Drug Administration
Washington, D. C. 20204

Dear Mr. Baker:

This is to summarize the results of our meeting of June 23, 1967 concerning a proposed meat and milk study on BOTRAN. Attending were Mr. J. Alpert and Mr. J. B. Lamb of the Petitions Control Branch, and Drs. A. J. Lemin, R. L. Johnston, A. W. Neff, and R. R. Herr of The Upjohn Company. The meeting was held in Mr. Alpert's office.

The protocol for the proposed experiment, which had been submitted with my letter of June 12, 1967, was in general considered satisfactory, subject to the following comments and suggestions:

1. Mr. Alpert questioned whether the proposed feeding levels of 0.5, 1.0, and 2.0 ppm were high enough to provide data for the use of BOTRAN on crops other than almonds, *e.g.* beans, cotton, potatoes. In consideration of this, we are planning to add an additional group of animals and readjust the feeding levels. The new levels will be 0.5, 2.0, 5.0 and 20.0 ppm.
2. Mr. Alpert also pointed out that the experiment as described in the protocol would not show that equilibrium was established in the tissues in the event that tissue residues were found and tolerances were consequently requested. He suggested that the establishment of equilibrium could be demonstrated by determination of blood levels during the feeding study. Such blood levels, therefore, will be determined on blood samples taken at the times that milk samples are collected.
3. It was suggested that animals at the lower feeding levels be checked for tissue residues as well as those at the highest level as stated in the protocol. These animals will be kept on treatment until results at the highest level are known. Some or all of them will then be checked, depending on the high level results.

Received
ESA/Pest. Br.
JUL 13 1967

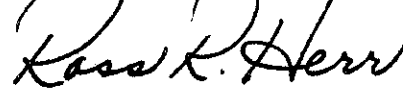
Mr. Drew M. Baker, Jr.
Page 2
July 7, 1967

4. In response to our question of whether an assay sensitivity of 0.05 ppm was sufficient for this study, Mr. Alpert said that this would probably be sufficient for meat residues, but that a sensitivity of 0.01-0.02 ppm was usually desired for milk. If the method is not this sensitive, the feeding level will be considered, *i.e.* higher levels which show no detectable levels will be considered as evidence of negligible residues at proposed tolerance levels.

Thank you for your help in arranging this meeting. If there are any further comments, suggestions or questions, please feel free to contact me at any time.

Sincerely,

THE UPJOHN COMPANY



Ross R. Herr
Pesticide Regulatory Affairs
Plant Health Products

lld

cc: Mr. Jerome Alpert ✓
Mr. James B. Lamb

File: PPT # 7F0558

Petitions Control Branch

July 23, 1969

Petitions Evaluation Branch,
Division of Pesticides

AF 12-868
(Upjohn)

Deletion of Forage Restrictions on Botran labels.

We have again reviewed the data relating to the Upjohn request that the forage restrictions on the Botran labeling be lifted. As indicated previously (our memo of May 13, 1969) the milk-out study shows no residues of Botran per se in meat (<0.1 ppm) and in milk (<0.01 ppm). The ¹⁴C metabolism study with the rat shows the normal type of metabolites in the urine, 3,5-dichloro 4-aminophenol and the glucuronide and sulfate conjugates of this compound. The method of analysis for the meat and milk residue study detects the parent compound only and will not detect these metabolites. We raised the question of the possible presence of these metabolites in milk. The available data do not answer this question.

Upjohn is in effect asking us to make a not unreasonable assumption that these metabolites (which are the normal type of Botran excretory products) are not to be expected in milk. After discussion of the problem with Dr. H. Blumenthal, EPT, we have decided not to make this assumption. Dr. Blumenthal has some concern over the toxicology of this compound and, in view of his concern, we have decided to reiterate the previous adverse conclusion in our memo of May 13, 1969, regarding the Upjohn request.

J. Alpert

cc:
SC-12
SC-970
SC-300
SC-330
Botran subject file
PP #7F0558

JAlpert:jrf
7/23/69



13544

R100025

Chemical:	Dicloran
PC Code:	031301
HED File Code	11500 Petition Files Chemistry
Memo Date:	06/02/2004
File ID:	00000000
Accession Number:	412-05-0036

HED Records Reference Center
10/12/2004