



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 25 1989

007142

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Tox.Chem. 913A
TB Project 9-0664
RD Record 237861

SUBJECT: MANCOZEB --- Dermal Penetration Study, Received Under MRID
No. 409554-01.

EPA ID # 707-78

TO: Susan Lewis/Sidney Jackson, PM 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

FROM: Irving Mauer, Ph.D.
Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

THRU: Judith W. Hauswirth, Ph.D., Chief
Toxicology Branch-I (IRS)
Health Effects Division (H7509C)

Imp. Lauer 4-14-89

*Judith W. Hauswirth
4/24/89*

Registrant: Ronm & Haas, Philadelphia PA

Request: Review and evaluate the following tox. study:

Mancozeb: Dermal Absorption Study in Male Rats,
conducted by H. L. Tomlinson and S. L. Longacre, Toxicology Department,
Ronm & Haas, Spring House, PA, Study No. 88R-218, Final Report dated
November 29, 1988 (EPA MRID # 40955401).

TB Conclusions: The protocol for this study (R & H's 88P-036) was said
to have been "... accepted by the Agency (Conroy, 1988),"* having been
transcribed without change from an assessment by Robert P. Zendzian,
Senior Pharmacologist, TOX. BRANCH.** However, as both the Dynamac re-
viewer and Dr. Zendzian have found, the data submitted are inadequate
(see attached). As a consequence we consider this study UNACCEPTABLE,
because of major deficiencies in both its design and reporting. The
detailed evaluation of this study is also appended to this memo.

* Conroy, A.E. 1988. Letter from A.E. Conroy II/Director, Office of
Compliance Monitoring (EN-342), USEPA/ to J. Gillingier /Product Registra-
tion Manager, Ronm & Haas company, Philadelphia/; Letter received April
21, 1988.

** MEMO: RPT to L. Foster, March 24, 1988.

CONFIDENTIAL BUSINESS
NATIONAL SECURITY INFORMATION (EO 12958)

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- 2 (inc)
EPA No.: 68D80056
DYNAMAC No.: 170-A
TASK No.: 1-70A
April 17, 1989

DATA EVALUATION RECORD

MANCOZEB

Dermal Absorption in Rats

STUDY IDENTIFICATION: Tomlinson, H. L., and Longacre, S. L.
Mancozeb: Dermal absorption study in male rats. (Unpublished
study No. 88R-218 performed and submitted by Rohm and Haas Company,
Spring House, PA; dated November 29, 1988). Accession No. 409554-
01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: *R. J. Weir*

Date: 4/17/89

1. CHEMICAL: Mancozeb.
2. TEST MATERIAL: Commercially-produced Dithane M-45 Fungicide (lot No. 76797) containing 80.6 percent mancozeb as active ingredient.
3. STUDY/ACTION TYPE: Dermal absorption in male rats.
4. STUDY IDENTIFICATION: Tomlinson, H. L., and Lagacre, S. L. Mancozeb: Dermal absorption study in male rats. (Unpublished study No. 88R-218 performed and submitted by Rohm and Haas Company, Spring House, PA; dated November 29, 1988). Accession No. 409554-01.

5. REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Nicolas P. HajjarDate: April 17, 1989

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: William L. McLellanDate: April 17, 19896. APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman PientaDate: April 17, 1989

Irving Mauer, Ph.D.
Insecticide-Rodenticide
Support
Toxicology Branch I (H7509C)

Signature: Judith W. HauswirthDate: 4/24/89

Judith W. Hauswirth, Ph.D.,
Chief
Insecticide-Rodenticide
Support
Toxicology Branch I (H7509C)

Signature: Judith W. HauswirthDate: 4/24/89

7. SUMMARY AND CONCLUSIONS:

The dermal absorption of aqueous suspensions of authentic, commercially produced mancozeb was determined in male rats following application of 100 or 1000 μg active ingredient/rat. The authors believed that it was more appropriate and relevant to study the dermal absorption of an authentic, commercially produced material than a radiolabeled sample since the latter material could not be produced with "the equivalent physical properties" of commercially produced mancozeb. The study was said to have been performed "...In response to a December 4, 1987 decision by the Environmental Protection Agency (EPA) requiring a new dermal penetration study to satisfy regulatory requirements for reregistration. The final protocol (Appendix A) was reviewed and accepted by the Agency (Conroy, 1988)."

Groups of four male rats were treated dermally with 50 μL of an aqueous suspension of mancozeb. The test material was applied on a 2 x 2 cm^2 area of the shaved back and covered with a contoured glass ring equipped with a porous top. The total amount of active ingredient applied was 100 or 1000 μg . At 0, 10, or 24 hours postdosing, animals were anesthetized and the applicator rings, covers and site washings, together with urine and feces were collected. The animals were then killed and the application sites of the rats' skins were removed. All samples, including the carcass, were extracted and analyzed for mancozeb and ethylene thiourea (ETU) by gas chromatography. The low-dose experiment was repeated and the average of the two trials was reported.

The results of these experiments are summarized in Tables 1 and 2 (CBI Tables 1 and 2).

Analysis of mancozeb and ETU in the biological samples could not be adequately performed due to "considerable background interference." The standard method for analyzing Mancozeb was by quantitative conversion to CS_2 and subsequent measurement of the generated CS_2 . This led to high recovery data in the carcass and feces. Less interference was noted in the repeat experiment. Interference was also cited by the authors for the mancozeb found in the application site of the low-dose rats. In animals receiving the high dose, 5 to 6 percent of the applied dose was found at the application site of the skin. It was concluded that this was associated with mancozeb equivalents tightly bound to the outer skin surface and thus not absorbed and metabolized to ETU.

Conroy, A. E. (1988) [Letter: Conroy, Director OCM, USEPA, to J. Ollinger, Product Registration Manager, Rohm and Haas, Philadelphia--received by R&H, April 20, 1988]

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Table 1

Source: CBI Table 1, CBI p. 13.

Page 6 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients.
 - ☐ Identity of product impurities.
 - ☐ Description of the product manufacturing process.
 - ☐ Description of quality control procedures.
 - ☐ Identity of the source of product ingredients.
 - ☐ Sales or other commercial/financial information.
 - ☐ A draft product label.
 - ☐ The product confidential statement of formula.
 - ☐ Information about a pending registration action.
 - ☒ FIFRA registration data.
 - ☐ The document is a duplicate of page(s) _____.
 - ☐ The document is not responsive to the request.
-

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Table 2

Source: CBI Table 2, CBI p. 19.

Page 8 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

- ☐ Identity of product inert ingredients.
 - ☐ Identity of product impurities.
 - ☐ Description of the product manufacturing process.
 - ☐ Description of quality control procedures.
 - ☐ Identity of the source of product ingredients.
 - ☐ Sales or other commercial/financial information.
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 - ☐ The product confidential statement of formula.
 - ☐ Information about a pending registration action.
 - ☒ FIFRA registration data.
 - ☐ The document is a duplicate of page(s) _____.
 - ☐ The document is not responsive to the request.
-

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

The considerable interferences led the authors to determine dermal absorption by subtracting the amount of mancozeb recovered from the application site at 10 and 24 hours from the amount recovered at 0 hours. Results indicated that 2 and 4 percent of the low dose and less than 1 percent of the high dose was dermally absorbed 24 hours postdosing.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES: Several deficiencies were noted in this study, which render it unacceptable. The use of unlabeled test material resulted in interference and major difficulties in extracting and analyzing mancozeb and its metabolites, including ETU, suggesting that the method is not specific. This led to the selective use of some data and not others in the same study. In addition, the use of the application-site recovery data to determine dermal absorption is also unacceptable in view of the fact that excretion/distribution data are inadequate and, thus, do not provide supportive evidence.

Since dermal absorption was expected to be low and the analytical procedures used to analyze the biological samples were inadequate, this study should have been repeated with radiolabeled test material.

The study is unacceptable.

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CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

EPA No.: 68D80056
DYNAMAC No.: 170-A
TASK No.: 1-70A
March 27, 1989

DRAFT

DATA EVALUATION RECORD

MANCOZEB

Dermal Absorption in Rats

STUDY IDENTIFICATION: Tomlinson, H. L., and Longacre, S. L.
Mancozeb: Dermal absorption study in male rats. (Unpublished
study No. 88R-218 performed and submitted by Rohm and Haas Company,
Spring House, PA; dated November 29, 1988). Accession No. 409554-
01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: _____

Date: _____

E. P. A. Comm. 4/14/89
received
4/14/89
ann

1. CHEMICAL: Mancozeb, ~~active ingredient of Dithane M-45 fungicide.~~

2. TEST MATERIAL: Mancozeb was from a commercially-produced (lot No. 76797) with 80.6 percent active ingredient. *Dithane M-45 Fungicide*

Containing Mancozeb as

3. STUDY/ACTION TYPE: Dermal absorption in male rats.

4. STUDY IDENTIFICATION: Tomlinson, H. L., and Longacre, S. L. Mancozeb: Dermal absorption study in male rats. (Unpublished study No. 88R-218 performed and submitted by Rohm and Haas Company, Spring House, PA; dated November 29, 1988). Accession No. 409554-01.

5. REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: _____

Date: _____

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: _____

Date: _____

6. APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: _____

Date: _____

Insecticide-Rodenticide Support

Irving Mauer, Ph.D.
~~Neting Section Head~~
Toxicology Branch ~~(TS-769C)~~

Signature: _____

Date: _____

-I (H 7509C)

~~Mike Ioannou, Ph.D.~~
~~EPA Section Head~~
~~Toxicology Branch (TS-769C)~~

Signature: _____

Date: _____

*Julius W. Hanswirth, Ph.D., Chief
Insecticide-Rodenticide Support
Toxicology Branch - I (H 7509C)*

to a December 4, 1987
decision by the Environmental Protection Agency (EPA) requiring a
new dermal penetration study to satisfy regulatory requirements for
reregistration. The final protocol (Appendix A) was reviewed and
accepted by the Agency (Conroy, 1988). *(*) fact noted below*

7. SUMMARY AND CONCLUSIONS:

The dermal absorption of aqueous suspensions of authentic, commercially produced mancozeb was determined in male rats following application of 100 or 1000 μg active ingredient/rat. The authors believed that it was more appropriate and relevant to study the dermal absorption of an authentic, commercially produced material than a radiolabeled sample since the latter material could not be produced with "the equivalent physical properties" of commercially produced mancozeb. *The study was said to have been performed in response to...*

- application up, covers at site, washes, residue, wash*
- Groups of four male rats were treated dermally with 50 μL of an aqueous suspension of mancozeb. The test material was applied on a 2 x 2 cm^2 area of the shaved back and covered with a contoured glass ring equipped with a porous top. The total amount of active ingredient applied was 100 or 1000 μg . At 0, 10, or 24 hours postdosing, animals were anesthetized and the ~~radioactivity remaining on the application site was recovered.~~ Urine and feces were also collected ~~from~~ the animals were then killed and the application sites of the rats' skins were removed. All samples, including the carcass, were extracted and ~~then~~ analyzed for mancozeb and ethylene thiourea (ETU) by gas chromatography. The low-dose experiment was repeated and the average of the two trials was reported.

The results of these experiments are summarized in Tables 1 and 2 (CBI Tables 1 and 2).

background

Analysis of mancozeb and ETU in the biological samples could not be adequately performed due to considerable interference. ~~Mancozeb is analyzed by quantitative conversion to CS_2 and subsequent measurement of the generated CS_2 .~~ This led to high recovery data in the carcass and feces. Less interference was noted in the repeat experiment. Interference was also cited by the authors for the mancozeb found in the application site of the low-dose rats. In animals receiving the high dose, 5 to 6 percent of the applied dose was found at the application site of the skin. It was concluded that this was associated with mancozeb equivalents tightly bound to the outer skin surface and thus not absorbed and metabolized to ETU.

The considerable interferences led the authors to determine dermal absorption by subtracting the amount of mancozeb recovered from the application site at 10 and 24 hours from the amount recovered at 0 hours. Results indicated that 2 and 4 percent of the low dose and less than 1 percent of the high dose was dermally absorbed 24 hours postdosing.

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12

Conroy, E. E. (1988) - Letter to Bureau, Director, SCM, USEPA, re: Mancozeb Reregistration. Manager, Policy and Admin. Division. Received by R. H. H. April 20, 1988.

007142

Table 1

Source: CBI Table 1, CBI p. 13.

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Table 2

Source: CBI Table 2, CBI p. 19.

8. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES: Several deficiencies were noted in this study, which render it unacceptable. The use of unlabeled test material resulted in interference and major difficulties in extracting and analyzing mancozeb and its metabolites, including ETU, suggesting that the method is not specific. This led to the selective use of some data and not others in the same study. In addition, the use of the application-site recovery data to determine dermal absorption is also unacceptable in view of the fact that excretion/distribution data are inadequate and, thus, do not provide supportive evidence.

Since dermal absorption was expected to be low and the analytical procedures used to analyze the biological samples were inadequate, this study should have been repeated with radiolabeled test material.

The study is unacceptable.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

April 11, 1989

MEMORANDUM

SUBJECT: Mancozeb, Dermal Absorption Study

TO: Irving Mauer, Ph.D.
Geneticist
Toxicology Branch I, HED

FROM: Robert P. Zendzian PhD 4/11/89
Senior Pharmacologist
SAC3, HED (TS-769)

Action Requested

Comment on the acceptability of the following study:

Mancozeb: Absorption Study in Male Rats, H.L. Tomlinson and
S.L. Longacre, Toxicology Department, ROHM & HAAS, Spring
House, PA, Study No. 88R-218, Final Report Nov 29, 1988
MRID 4095540-01

Comments

The study was performed according to a modification of the Agency's Procedure for Dermal Absorption. The registrant asked for the modification, which consisted of a lesser number of exposure durations, because the analysis would be conducted with physical/chemical methods rather than utilizing radiolabel. It was assumed that the registrant would have developed a sufficiently selective and sensitive analytical method. The methodology used relied on quantitative conversion of the sample to CS₂ and measurement of the CS₂ generated. The data generated indicate that the methodology was faulty and that an unquantifiable portion of the recovery was probably due to CS₂ generated from decomposition of protein in the samples. This makes it impossible to quantitate the material absorbed. There is no record in the report of method development which would be expected to detect this problem.

The study is unacceptable. The Agency requires a direct measurement of the quantity of Mancozeb absorbed as ETU.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

007142

MAR 8 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Mancozeb, Registrant's Comments re Need for Dermal Absorption Studies

TO: Lois Rossi PM-21
Registration Division (TS-767)

FROM: Robert P. Zendzian PhD
Senior Pharmacologist
Toxicology Branch
HED (TS-769)

THROUGH: William Burnam
Deputy Chief
Toxicology Branch

W. Burnam
3/1/88

gms
3/4/88

Compound; Mancozeb

Tox Chem #913A

Registration #707-78

Registrant; Rohm and Haas

Accession #N/A

Tox Project #8-0409

Action Requested

The Registrant requests clarification of the status of a previously submitted dermal absorption study (Haines 1980) and the Agency's requirement for a new dermal absorption study.

The registrant requests evaluation of the following protocol for a dermal absorption study of mancozeb;

Mancozeb: Dermal absorption of mancozeb in male rats. P.K. Chan, and P.R. Goldman, Rohm and Haas, Toxicology Department and Residue Metabolism Environmental Fate Department. Protocol No. 37P-pkc, undated.

The Registrant requests a nine-month extension of the Due-date for submitting the dermal absorption study.

Conclusions

1. The Haines study is acceptable according to our understanding of dermal absorption studies in 1984. However, the dose used is not appropriate for field exposure and a new study using appropriate doses is required. The new study will be performed according to our present knowledge of how to do dermal absorption studies.

2. The protocol (No. 87-pkc) as submitted is acceptable. However, the Registrant is advised that in removing residual compound at the end of the exposure period, it is necessary to wash the skin before sacrificing the rat.

3. Considering the number and complexities of the assays required for this study and the necessity of obtaining Agency approval of the protocol, the request for a nine-month extension of time for submitting the dermal absorption study is justified.

Background

In response to an Agency Data Call-In Notice (DCI) of Jan 17, 1983 the Registrant submitted the following dermal absorption study:

Dithane M-45 (Mancozeb) Percutaneous absorption in rats, L.D. Haines, Rhom and Hass Co Technical Report No. 34F-80-9, 5/78/80.

The study was reviewed by Zendzian (1984) who considered the study "Acceptable" and commented as follows;

"I have reviewed the study and a DER is attached. The data generated in this study allow the estimation of dermal absorption of EBDC in two ways, by determining the amount that disappears from the site of application and by determining the amount that is excreted. The values from disappearance data are 0.83% for 6 hours and 0.89% for 24 hours. The value from 24 hour excretion data is 1.01%. The values calculated by these two methods are in reasonable agreement and a general value of 1.0% dermal absorption can be utilized. Since only one dose was used it is impossible to determine if a maximum absorption rate was reached."

In the mancozeb Registration Standard issued April 1987, the Agency required a new dermal absorption study. This requirement was based on a rereview of the 1980 dermal absorption study by Mauer (1986). In the Toxicology Chapter of the Standard Mauer stated;

"85-3: Dermal (Percutaneous) Absorption/Penetration

Also in response to the Data Call-In Notice of January 17, 1983, the registrant submitted a dermal penetration study

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

in which 10 mg of commercial Dithane M-45 (8.3% ai, containing [REDACTED] ETU) was applied to a 20-cm² shaved area of the dorsum of adult female Sprague-Dawley rats, and secured in place under an elastic bandage for 6 hours (MRID 127950) Calculation of residues in the urine and feces collected over the 6-hour exposure time and 18 hours later (following termination of treatment), permit a general value of 1% absorption to be utilized. Since only one dose was employed, however, the maximum absorption rate cannot be determined.

A study using technical mancozeb must be submitted to satisfy regulatory requirements."

The Registrant replied on July 11, 1987 that there was an error in the Zendzian review, the DITHANE M-45 was 83 % A.I., and requested reevaluation of the Agency's requirement for a dermal absorption study.

The Agency responded (Mauer Dec 4, 1987) acknowledging the error in mancozeb concentration but retaining the requirement for a new dermal absorption study.

The Registrant has now restated the progression of events and requested an Agency evaluation of the situation.

Discussion

This situation has developed as a complicated interaction of our changing understanding as to what is necessary for a good dermal absorption study, a determination of the proper doses necessary for a dermal absorption study of mancozeb and the handling of this case by more than one individual.

1. The 1980 dermal absorption study and its evaluation by the Agency.

The dermal absorption study submitted by the Registrant in 1983 was evaluated on the basis of our understanding of dermal absorption studies at that time and was considered "Acceptable". It was also considered of limited value since only one dose was tested and dermal absorption rates, defined as percent of dose absorbed per unit time, vary significantly and in a nonlinear manner with the dose per unit area. Since then we have received some 25 studies on the dermal absorption of various pesticides and have used the information developed therein to improve and refine our Procedure for Studying Dermal Absorption which is now in its fourth edition. If submitted today the 1980 study would be considered "Unacceptable" based primarily on the method of application. "A 10mg dose of Dithane M-45 was spread evenly on the nonadhesive side of an elastic bandage and the bandage wrapped around the rat so that the compound contacted the shaven area." (Zendzian 1984). We have found that some compounds bind strongly to cloth so as to limit their availability for absorption. One compound

-4-

could not be liquid extracted from a gauze bandage and required alkaline digestion for recovery. The "Procedure" now specifies that the treated area be covered with a protective cover that does not contact the test material. However, even if the 1980 study had been acceptable in light of our present knowledge, the data from the single dose used would not be usable in estimating absorption from the actual exposure.

2. Usefulness of the data from the 1980 study and selection of a proper dose.

The dermal absorption protocol submitted by the Registrant (Protocol No. 87-pkc) contains a justification of the doses to be used in the new study. Working from the EPA exposure estimate the calculations of dose/unit area show that the 1980 study used a dose that was several times higher than could be expected in field use. The justification concludes; "Therefore, 25 ug/cm² is chosen as the low dose and 250 ug/cm² is chosen as the 10-fold higher dose. These doses should cover the range of most estimated worker exposures. In a previous dermal absorption study (Haines, L.D. 1980), a high dose of approximately 500 ug/cm² was tested and a dermal absorption rate of 1% has been determined (EPA, 1984)."

Experience has shown that although the quantity of compound absorbed per unit time decreases with decreasing dose the percent of dose absorbed per unit time increases. This inverse relationship is not immediately apparent but can be explained generally as follows. No matter how rapidly a substance is absorbed through the skin, one can pile on sufficient material to reach and exceed the maximum amount that can be absorbed in a limited time. As one increases the dose to approach, reach and exceed that maximum amount absorbable the percent of the applied dose that is absorbed decreases. On the other extreme, no matter how little a particular compound penetrates the skin, one may apply a sufficiently small dose so that it will be completely absorbed in a limited time (100% absorption rate).

This inverse relationship has been shown experimentally. It is not linear and the change in absorption (absolute and percent) per change in dose varies with the compound and the dose applied. Because of this relationship the EPA "Procedure" states "The doses should span the range of dose per unit area of skin which can be expected to occur in human exposure." The doses proposed in the protocol submitted by the Registrant will satisfy this requirement.

3. Evaluation of the dermal absorption protocol submitted by the Registrant (Protocol No. 87-pkc).

The protocol has been evaluated and discussed with Dr. P. Chan of Rohm and Hass. The protocol as submitted can be expected to supply the dermal absorption data necessary to

estimate dermal absorption of mancozeb and any ETU present in the mancozeb under field conditions.

- Because of the necessity of determining mancozeb and ETU separately, radiolabeling could not be used in this study. Complex and time consuming analytical determinations will be made on each of numerous samples. Therefore, the number of doses and exposure times tested have been limited to an absolute minimum, two doses, 25 and 250 ug/cm², and three exposure durations, 0, 10 and 24 hours, for each dose.

Dr. Chan was advised of problems that had been identified with washing residual test material from the skin at the end of the exposure period. Experience has shown that it is necessary to wash the skin before sacrificing the rat.

References

Haines, L.D., Dithane M-45 (Mancozeb) Percutaneous absorption in rats, Rhom and Hass Co Technical Report No. 34F-80-9, 5/78/80.

Memo, Zendzian to Sandusky, re EBDC, Dithane M-45, Review of dermal absorption study. (1984)

Mauer (1986) MANCOZEB - Toxicology Chapter of the Registration Standard

Memo, Mauer to Rossi, Mancozeb - Company Response to TB Assessment of Certain Studies in the Toxicology Chapter of the Mancozeb Registration Standard, Dec 4, 1987

Zendzian Procedure for Studying Dermal Absorption, 4th Edition, Sept 18, 1987.