11-20-97

DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-1; Acute Oral Toxicity - Rats

Work Assignment No. 3-01A (MRID 44170139)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Tech
Acutes

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
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Date: 11/20/97

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Mary Menetrez, Ph.D.

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Quality Assurance:
Reto Engler, Ph.D.

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Disclaimer

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EPA Reviewer: P. V. Shah, Ph.D. P.V. Shah 5/12/98
Registration Action Branch 1 (7509C)

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T. M Copley 5/18/98
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat
OPPTS Number: 870.1100 OPP Guideline Number: §81-1

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.).

SYNONYMS: None

CITATION: McRae, L. (1995) SAN 835 H Technical acute oral toxicity to the rat. Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 188a. November 3, 1995. MRID 44170139. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 44170139), five Hsd/Ola:SD(CD) rats/sex were given a single oral dose of SAN 835 H Technical (96.4% a.i.) at a 50% (w:v) concentration in 1% (w:v) aqueous methylcellulose at 5,000 mg/kg (limit dose). Animals were observed for clinical signs of toxicity and mortality for up to 14 days postdosing.

Oral LD_{50} Males = >5,000 mg/kg (observed)
Females = >5,000 mg/kg (observed)

All animals survived during the 14-day observation period. Clinical effects included piloerection, pallor of the extremities, hunched posture, soft to liquid feces, and abnormal gait (males only). Effects subsided from all animals by day 2. Slightly low body weight gains were noted for 4/5 males between 7 and 14 days and for 3/5 females between 0 and 7 days. Otherwise, no treatment-related effect on body weight was observed. Necropsy after 14 days revealed no gross abnormalities.

SAN 835 H Technical is classified as **TOXICITY CATEGORY IV** based on the observed LD_{50} values in both sexes.

This study is classified **acceptable (§81-1)**, and satisfies the guideline requirement for an acute oral study in the rat.

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COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   CAS #: Not provided

2. Vehicle: 1% w/v Aqueous methylcellulose

3. Test animals: Species: Rat
   Strain: Hsd/Ola:SD(CD)
   Age: Young adult (7-10 weeks)
   Weight: 247-260 g males; 220-253 g females
   Source: Harlan Olac Ltd., Bicester, Oxon, England
   Acclimation period: 13 Days
   Diet: SDS LAD 1, ad libitum, except overnight prior to and approximately 4 hours after dosing
   Water: Tap water, ad libitum
   Housing: ≤5/cage, separated by sex

B. STUDY DESIGN and METHODS:

1. In-life dates: May 10-31, 1995

2. Animal assignment and treatment: The initial dose level of 5,000 mg/kg (limit dose) was based on data obtained from a preliminary experiment using two animals/sex and a dose level of 3,200 mg/kg. Following an overnight fasting period, rats were given a single oral dose of SAN 835 H Technical by gavage. The test material was prepared at a 50% (w:v) concentration in 1% (w:v) aqueous methylcellulose and administered at a constant dosing volume of 10 mL/kg. The rats were observed for signs of toxicity and/or mortality frequently on the day of dosing, and twice daily thereafter for the remainder of the 14-day study; body weights were recorded at 0 (prior to dosing), 7, and 14 days. At 14 days, the surviving animals were sacrificed, and all animals were necropsied and examined for gross pathological changes.

3. Statistics: Not applicable to this study.

II. **RESULTS AND DISCUSSION:**

A. Mortality: All animals survived the 14-day observation period.

Oral LD_{50} Males = >5,000 mg/kg (observed)
Females = >5,000 mg/kg (observed)

B. Clinical observations: Piloerection and pallor of the extremities were observed in 10/10 rats within 5 minutes of dosing and persisted, accompanied by hunched posture and soft to liquid feces. All males exhibited abnormal gait. Effects subsided from all animals by day 2. Individual clinical observations were not provided.

C. Body Weight: Slightly low body weight gains were noted for 4/5 males between 7 and 14 days and for 3/5 females between 0 and 7 days. Otherwise, no treatment-related effect on body weight was observed, with overall average increases of 40% for males and 28% for females.

D. Necropsy: Necropsy after 14 days revealed no gross abnormalities. Data were not provided.

E. Deficiencies: Individual clinical and macroscopic data should have been provided. However, this deficiency does not alter the acute oral LD_{50} values or subsequent Toxicity Category for SAN 835 H Technical and is therefore considered minor.

DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-2; Acute Dermal Toxicity - Rabbits

Work Assignment No. 3-01B (MRID 44170140)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
2275 Research Boulevard
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Date: 11/20/97

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Signature: Mary Menetrez
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Quality Assurance:
Reto Engler, Ph.D.

Signature:
Date:

Disclaimer

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EPA Reviewer: P. V. Shah, Ph.D. P.V.Shah 5/12/98
Registration Action Branch 1 (7509C)

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T. M Copley 5/13/98
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit
OPPTS Number: 870.1200 OPP Guideline Number: §81-2

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: McRae, L. (1995) SAN 835 H Technical acute dermal toxicity to the rabbit. Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 189a. November 3, 1995. MRID 44170140. Unpublished.

Graben, M. (1997) Diflufenzopyr: 7969-EUP-37:Response to three questions on acute toxicology studies. BASF Corporation, Research Triangle Park, NC. August 19, 1997. MRID 44374701. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 44170140 and 44374701), five young adult New Zealand White rabbits/sex were dermally exposed to SAN 835 H Technical (96.4% a.i.) at 5,000 mg/kg (>2X limit dose) in 1% w/v aqueous methylcellulose for 24 hours; the test substance was applied to approximately 10% of the total body surface area. Animals were observed for clinical signs of toxicity and mortality for up to 14 days postdosing.

Dermal LD_{50} Males = >5,000 mg/kg (observed)
Females = >5,000 mg/kg (observed)

SAN 835 H Technical is classified as **TOXICITY CATEGORY IV** based on the observed LD_{50} values in both sexes.

All animals survived and appeared normal during the 14-day study. Well-defined erythema and slight edema were observed at 10/10 application sites on day 1. Erythema subsided from all sites by day 8, and edema subsided from all sites by day 2. Two males

lost weight and two additional males had low body weight gains between 0 and 7 days. Otherwise, no treatment-related effect on body weight was observed. Gross necropsy of animals sacrificed after 14 days revealed no internal abnormalities, except for kidney congestion in one female.

This study is classified **acceptable (§81-2)**, and satisfies the guideline requirement for an acute dermal study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   CAS #: Not provided

2. Vehicle: 1% w/v Aqueous methylcellulose

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (approximately 10-13 weeks)
   Weight: 2.3-2.8 kg (combined sexes)
   Source: Froxfield Ltd., Petersfield, Hampshire, England
   Acclimation period: 7 Days
   Diet: SDS Rabbit Diet SQC, ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: May 18-June 1, 1995

2. Animal assignment and treatment: Fur from the dorso-lumbar regions of five animals/sex was clipped 1 day prior to dermal administration of SAN 835 Technical at 5,000 mg/kg (>2X limit dose). The test substance was applied at a concentration of 66.67% w/v in 1% w/v aqueous methylcellulose to a 100- x 100-mm area per animal (equivalent to approximately 10% of the total body surface area, as amended MRID 44374701). Each site was immediately covered with two layers of gauze secured with elastic adhesive bandage and waterproof strapping BP tape. Twenty-four hours following application, the coverings were removed and the test site was gently washed with warm water and blotted dry. Each animal was fitted with an Elizabethan collar for the remainder of the day. The rabbits were observed for signs of toxicity and/or mortality soon after dosing and at frequent intervals for up to 5 hours following dosing, and for signs of toxicity, mortality, and/or dermal irritation twice daily thereafter for the

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remainder of the 14-day study; body weights were recorded at 0 (prior to dosing), 7, and 14 days. At 14 days, surviving animals were sacrificed, necropsied, and examined for gross pathological changes.

3. Statistics: Not applicable to this study.

II. **RESULTS AND DISCUSSION:**

A. Mortality: All animals survived the 14-day observation period.

Dermal LD_{50} Males = >5,000 mg/kg (observed)
Females = >5,000 mg/kg (observed)

B. Clinical observations: An occasional animal had a loss of appetite (characterized by low food consumption and little or no feces) from days 2 to 6.

Well-defined erythema (score of 2) and slight edema (score of 1) were observed at 10/10 application sites on day 1. Erythema subsided from 9/10 application sites by day 6 and from all sites by day 8. Edema subsided from all sites by day 2.

C. Body Weight: Two males lost weight and two additional males had low body weight gains between 0 and 7 days. Otherwise, no treatment-related effect on body weight was observed, with overall average increases of 14% for males and 20% for females.

D. Necropsy: Kidney congestion was observed in one female. Otherwise, gross necropsy of animals sacrificed after 14 days revealed no internal abnormalities.

E. Deficiencies: No scientific deficiencies were noted in this study.

DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-3; Acute Inhalation Toxicity - Rats

Work Assignment No. 3-01C (MRID 44170141)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
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Date: 11/20/97

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Mary Menetrez, Ph.D.

Signature: Mary Menetrez
Date:

Quality Assurance:
Reto Engler, Ph.D.

Signature:
Date:

Disclaimer

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EPA Reviewer: P. V. Shah, Ph.D.
Registration Action Branch 1 (7509C)

P.V. Shah. 5/12/98

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T.
Registration Action Branch 1 (7509C)

6/18/98

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat
OPPTS Number: 870.1300 OPP Guideline Number: §81-3

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Jackson, G. (1996) SAN 835 H Technical acute inhalation toxicity in rats 4-hour exposure. Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 183. June 13, 1996. MRID 44170141. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44170141), five young adult Sprague-Dawley albino rats/sex were exposed by nose-only inhalation to SAN 835 H Technical (96.4% a.i.) at 2.93 mg/L (>limit dose) for 4 hours. Animals were observed for clinical signs of toxicity and mortality for up to 14 days following exposure.

Inhalation LC_{50} Males = >2.93 mg/L (observed)
Females = >2.93 mg/L (observed)

SAN 835 H Technical is classified as **TOXICITY CATEGORY IV** based on the observed LC_{50} values in both sexes.

All animals survived the 4-hour exposure and 14-day observation periods. No exposure-related effects were observed during the study. No significant treatment-related effect on body weight was observed, and necropsy of test and control animals revealed no treatment-related gross pathological changes.

This study is classified **acceptable (§81-3)**, and satisfies the guideline requirement for an acute inhalation study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

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EPA Reviewer: P. V. Shah, Ph.D. P.V.Shah. 5/12/98
Registration Action Branch 1 (7509C)

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T. Marion Copley 6/8/98
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat
OPPTS Number: 870.1300 OPP Guideline Number: §81-3

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Jackson, G. (1996) SAN 835 H Technical acute inhalation toxicity in rats 4-hour exposure. Huntingdon Life Sciences Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 183. June 13, 1996. MRID 44170141. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 44170141), five young adult Sprague-Dawley albino rats/sex were exposed by nose-only inhalation to SAN 835 H Technical (96.4% a.i.) at 2.93 mg/L (>limit dose) for 4 hours. Animals were observed for clinical signs of toxicity and mortality for up to 14 days following exposure.

Inhalation LC_{50} Males = >2.93 mg/L (observed)
Females = >2.93 mg/L (observed)

SAN 835 H Technical is classified as **TOXICITY CATEGORY IV** based on the observed LC_{50} values in both sexes.

All animals survived the 4-hour exposure and 14-day observation periods. No exposure-related effects were observed during the study. No significant treatment-related effect on body weight was observed, and necropsy of test and control animals revealed no treatment-related gross pathological changes.

This study is classified **acceptable (§81-3)**, and satisfies the guideline requirement for an acute inhalation study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: Not stated in the report. However, 96.4% a.i. reported purity of lot 6500-19 used in other studies.
   CAS #: Not provided

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rat
   Strain: Sprague-Dawley, albino
   Age: Young adult (8 weeks)
   Weight: 294-351 g males; 217-239 g females
   Source: Charles River UK Ltd., Margate, Kent, England
   Acclimation period: ≥5 Days
   Diet: SDS RM1, ad libitum, except during exposure
   Water: Tap water, ad libitum, except during exposure
   Housing: Five/cage, separated by sex

B. STUDY DESIGN and METHODS:

1. In-life dates: June 21-July 12, 1995

2. Exposure conditions: A cylindrical 5-L nose-only exposure chamber was used. The chamber was equipped with radial ports for attachment of individual tapered polycarbonate animal restraining tubes during exposure, and was enclosed within a fume cupboard exhausting to atmosphere through an absolute filter.

   Test atmosphere (dust) was generated via a Wright dust generator by suspending material scraped from the surface of a compressed powder in a stream of dry compressed air. The test atmosphere was passed through an elutriation column to reduce, by sedimentation, the amount of non-respirable particulate in the test atmosphere. The resultant aerosol entered the top of the chamber and exited through a port at the base of the cylindrical section below the level of the rats. The mean chamber airflow averaged 15 L/min (equivalent to 180

turnovers/hour). The time required for 90% equilibration was 1 minute, and the restraining tubes were affixed to the chamber prior to the equilibration period.

The nominal test atmosphere concentration was determined at the end of the exposure period by dividing the total amount of test material delivered to the chamber by the total air volume that passed through the chamber during the exposure time. The actual test atmosphere concentration was determined analytically five times during the exposure period; samples were collected from an unspecified sampling site at a rate of 4 L/min and drawn through Whatman glass fiber filters. The filters were extracted by sonicating for 10 minutes with methanol, and aliquots of the extracts were analyzed for SAN 835 H Technical using HPLC. The nominal and average analytical test concentrations were 17.5 and 2.93 mg/L, respectively.

Particle size was determined twice during the exposure period using a Marple cascade impactor. Samples were collected from an unspecified sampling site at a rate of 2 L/min approximately 1.5 and 3.5 hours into exposure. The sections of the impactor were disassembled, extracted, and analyzed as previously described. The calculated average mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were 3.5 and 2.2 μm.

During exposure, the mean temperature was 21 °C, and the mean relative humidity was 25-30%; although not monitored, the turnover rate (180 per hour) ensured an oxygen level of ≥19%.

3. Animal assignment and treatment: Five young adult albino rats/sex were exposed via nose-only inhalation to SAN 835 H Technical at 2.93 mg/L (>limit concentration) for 4 hours. To serve as controls, an additional five animals/sex were exposed (in chamber) to clean dry air only. The animals were observed for signs of toxicity and/or mortality continuously during the exposure and at least twice daily throughout the 14-day observation period. Clinical signs were recorded at the end of the equilibration period, at 0.25, 0.5, and 1.0 hours and hourly during the exposure, and at least once daily thereafter during the 14-day observation

period. Body weights were recorded daily. After 14 days, the surviving animals were sacrificed, necropsied, and examined for gross pathological changes. In addition, the lung weight was recorded, and sections of the lungs, liver, and kidneys were prepared and subject to microscopic examination.

4. Statistics: Not applicable to this study.

II. RESULTS AND DISCUSSION:

A. Mortality: All animals survived the 4-hour exposure and 14-day observation periods.

Inhalation LC_{50} Males = >2.93 mg/L (observed)
Females = >2.93 mg/L (observed)

B. Clinical observations: No exposure-related effects were observed during the study. Fur soiled with excreta was observed in all animals from the test and control groups 1 to 4 hours during exposure and immediately following exposure, and was attributed to the method of restraint.

C. Body Weight: No significant treatment-related effect on body weight was observed upon comparison of the 0-, 7-, and 14-day data for test and control animals, with overall (0-14 days) average increases of 20-22% for males and 8-13% for females.

D. Necropsy: Necropsy of test and control animals revealed no treatment-related gross pathological changes and similar lung to body weight ratios for test and control animals.

E. Deficiencies: The site used for sampling of atmosphere for test concentration and particle sizing was not specified. Since the figure supplied for the exposure system did not illustrate a unique sampling port, it is assumed that a vacant animal port was used, and this deficiency is considered minor.

The aerodynamic particle size should have been determined hourly during the exposure. This deficiency is considered minor since the size was determined twice during exposure, and since the calculated MMAD values were within the ideal range (1-4 μm), this deficiency is considered minor.

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DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-4; Primary Eye Irritation - Rabbits

Work Assignment No. 3-01D (MRID 44170142)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Pesticide Health Effects Group
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Date: 11/20/97

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Quality Assurance:
Reto Engler, Ph.D.

Signature:
Date:

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: P. V. Shah, Ph.D.
Registration Action Branch 1 (7509C)

M Copley For P. V. Shah 5/12/98

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T.
Registration Action Branch 1 (7509C)

M Copley 6/18/98

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit
OPPTS Number: 870.2400 OPP Guideline Number: §81-4

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Parcell, B. (1995) SAN 835 H Technical eye irritation to the rabbit. Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Laboratory Study Number SNC 191a. September 25, 1995. MRID 44170142. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 44170142), 30 mg of SAN 835 H Technical (96.4% a.i.) was instilled into the conjunctival sac of one eye of seven young adult male New Zealand White rabbits. The treated eye of one female animal was rinsed with distilled water 30 seconds after instillation for approximately 30 seconds. The treated eyes of the remaining animals were not rinsed. The animals were observed for up to 7 days following treatment, and eye irritation was scored using a modified Draize scheme.

One hour following instillation, dulling of the normal corneal lustre was observed in 2/6 treated unwashed eyes, slight conjunctival redness was observed in 6/6 eyes, very slight conjunctival chemosis was observed in 5/6 eyes, and slight to moderate conjunctival discharge was observed in 6/6 eyes. No iridial changes were observed during the study. At 24 hours, slight conjunctival redness was observed in 3/6 eyes. Irritation subsided from all treated unwashed eyes by 2 days.

In this study, **SAN 835 H Technical is a slight ocular irritant,** and is classified as **TOXICITY CATEGORY III** based on the minimal irritation which subsided from 4/6 treated eyes by 2 days.

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This study is classified **Unacceptable (§81-4)**, and **does not** satisfy the guideline requirement for a primary eye irritation study in the rabbit. However, this study is **upgradable** if the registrant provide satisfactory justification for using 0.03 g of the test article rather than 0.1 g.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

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I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   CAS #: Not provided

2. Vehicle and/or positive control: None employed

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (11-17 weeks)
   Weight: 2.5-3.8 kg (combined sexes)
   Source: Froxfield Ltd., Petersfield, Hampshire, England
   Acclimation period: Not specified
   Diet: SDS Stanrab (P) Rabbit Diet, ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: May 30-June 19, 1995

2. Animal assignment and treatment: A 30-mg sample of SAN 835 H Technical was instilled into the conjunctival sac of one eye of seven young adult rabbits. The upper and lower lids were held together for approximately 1 second before releasing to prevent loss of the material. The treated eye of one animal was rinsed with distilled water 30 seconds after instillation for approximately 30 seconds. The treated eyes of the remaining animals were not rinsed, and the contralateral eye of each animal served as an untreated control. The animals were observed for ocular irritation and signs of general toxicity at 1 hour and 1, 2, 3, 4, and 7 days following instillation. Eye irritation was scored by a modified Draize scheme[1].

II. RESULTS AND DISCUSSION:

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[1]The area of corneal opacity was not scored but not graded.

A. Clinical observations: One hour following instillation, dulling of the normal corneal lustre was observed in 2/6 treated unwashed eyes, slight conjunctival redness (score of 1) was observed in 6/6 eyes, very slight conjunctival chemosis (score of 1) was observed in 5/6 eyes, and slight to moderate conjunctival discharge (scores of 1-2) was observed in 6/6 eyes. No iridial changes were observed during the study. At 24 hours, slight conjunctival redness was observed in 3/6 eyes. Irritation subsided from all treated unwashed eyes by 2 days. Based on the results of this study, SAN 835 H Technical is a slight ocular irritant.

One hour following instillation, moderate conjunctival redness (score of 2), very slight conjunctival chemosis (score of 1), and slight conjunctival discharge (score of 1) were observed in the single treated washed eye. All effects subsided by 1 day.

No other signs of toxicity or ill health were observed during the study.

B. Deficiencies: Justification for using 0.03 g of test article instead of 0.1 g or 0.1 ml(liquid) required by the guideline was not given in the report. Therefore, this study is classified **supplementary/upgradable (§81-4)**, and **does not** satisfies the guideline requirement for a primary eye irritation study in the rabbit. However, this study is upgradable if the registrant provide the justification for using 0.03 g of the test article. There were no other deficiencies that affected the validity of the study results.

DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-5; Primary Dermal Irritation - Rabbits

Work Assignment No. 3-01E (MRID 44170143)

Prepared for

Health Effects Division
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Date: 11/20/97

Program Manager:
Mary Menetrez, Ph.D.

Signature: Mary Menetrez
Date:

Quality Assurance:
Reto Engler, Ph.D.

Signature:
Date:

Disclaimer

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52-21

EPA Reviewer: P. V. Shah, Ph.D. P.V.Shah 5/12/98
Registration Action Branch I (7509C)

Work Assignment Manager: Marion Copley, D.V.M., D.A.B.T. Mcopley 6/18/98
Registration Action Branch 1 (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS Number: 870.2500 OPP Guideline Number: §81-5

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Parcell, B. (1995) SAN 835 H Technical skin irritation to the rabbit. Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 190a. September 25, 1995. MRID 44170143. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 44170143), six young adult male New Zealand White rabbits were dermally exposed to 0.5 g of SAN 835 H Technical (96.4% a.i.) moistened with 0.5 mL of distilled water for 4 hours. The test substance was applied as received to a single intact 6.25-cm^2 site/animal. Animals were observed for dermal irritation for up to 72 hours following application, and erythema and edema were scored separately using the Draize scale.

No dermal irritation was observed at any of the test sites following patch removal.

In this study, **SAN 835 H Technical is not a dermal irritant**, and is classified as **Toxicity Category IV** for primary dermal irritation.

This study is classified **acceptable (§81-5)**, and satisfies the guideline requirement for a primary dermal irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   CAS #: Not provided

2. Vehicle: 0.5 mL of distilled water

3. Test animals: Species: Rabbit
   Strain: New Zealand White
   Age: Young adult (9-11 weeks)
   Weight: 2.2-2.5 kg (all male)
   Source: Froxfield Ltd., Petersfield, Hampshire, England
   Acclimation period: Not specified
   Diet: SDS Stanrab (P) Rabbit Diet, ad libitum
   Water: Tap water, ad libitum

B. STUDY DESIGN and METHODS:

1. In-life dates: May 23-26, 1995

2. Animal assignment and treatment: Fur from the dorso-lumbar regions (approximately 100 x 100 mm) of six young adult male animals was clipped 24 hours prior to dermal administration of 0.5 g of SAN 835 H The test material was moistened with 0.5 mL of distilled water, and applied to a single intact site/animal using a 6.25-cm^2 gauze pad secured with Elastoplast adhesive tape. The coverings were removed 4 hours following application, the treated site was gently washed with warm water, and the treated area was blotted dry with absorbent paper. The rabbits were observed for dermal irritation 60 minutes following patch removal, and at 24, 48, and 72 hours following exposure. Erythema and edema were scored separately using the Draize scale. In addition, the animals were observed daily for signs of general toxicity.

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II. **RESULTS AND DISCUSSION:**

A. Clinical observations: No dermal irritation was observed at any of the test sites following patch removal. Based on the results of this study, SAN 835 H Technical is not a dermal irritant.

No signs of toxicity or ill health were observed during the study.

B. Deficiencies: There were no deficiencies that affected the validity of the study results.

DATA EVALUATION RECORD

SAN 835H TECHNICAL

Study Type: 81-6; Dermal Sensitization - Guinea pigs

Work Assignment No. 3-01F (MRID 44170144)

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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pig.
OPPTS Number: 870.2600 OPP Guideline Number: §81-6

DP BARCODE: D232811 SUBMISSION CODE: S516012
P.C. CODE: 057701 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Allan, S. (1995) SAN 835 H Technical skin sensitization to guinea pig. Huntingdon Research Centre Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Project Number SNC 192a. September 20, 1995. MRID 44170144. Unpublished.

Graben, M. (1997) Diflufenzopyr: 7969-EUP-37:Response to three questions on acute toxicology studies. BASF Corporation, Research Triangle Park, NC. August 19, 1997. MRID 44374701. Unpublished.

SPONSOR: Sandoz Agro, Inc., 1300 East Touhy Avenue, Des Plaines, IL

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 44170144 and 44374701) conducted with SAN 835 H Technical (96.4% a.i.), 20 male guinea pigs were tested using methods based on those derived by Buehler. Positive control data were provided from a study conducted in the same manner using hexyl cinnamic aldehyde and ten animals.

No dermal irritation was observed 24, 48, or 72 hours following a single challenge application to either previously-induced or control animals. Acceptable positive control data were provided to validate the test methodology. Based on the results of this study, **SAN 835 H Technical is not a dermal sensitizer**.

This study is classified as **Unacceptable (§81-6)**, and **does not** satisfy the guideline requirement for a dermal sensitization study in the guinea pig. However, this study is **upgradable** if the registrant provide satisfactory justification for using 50% dilution of the test article instead of using slightly irritating concentration or the neat material.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   CAS #: Not provided

2. Vehicle and positive control: Alembicol D was used as a test substance vehicle for both phases of the definitive study.

   Positive control data from a study conducted by the same laboratory (Study Number SNC 206) were provided using hexyl cinnamic aldehyde (HCA; purity not specified). The positive control material was used as received for both phases of the study.

3. Test animals: Species: Guinea pig
   Strain: Dunkin/Hartley
   Age: Young adult (6-7 weeks)
   Weight: 277-374 g males (definitive study)
   Source: D. Hall, Newchurch, Staffordshire, England
   Acclimation period: 8 Days
   Diet: Vitamin C-enriched guinea pig diet FD2, ad libitum; hay provided weekly
   Water: Tap water, ad libitum
   Housing: Five/cage

B. STUDY DESIGN and METHODS:

1. In-life dates: May 24-July 8, 1995 (definitive study). The positive control study was conducted between June 2 and July 8, 1995 (MRID 44374701).

2. Animal assignment and treatment: The study was conducted using methods based on those derived by Buehler [Buehler, E., Arch. Dermatol. 91:171-177 (1965)]. Based on the results of preliminary testing using four male animals and 0.5 Ml of SAN 835 H Technical at 20 (w:v), 30, 40 or 50% dilutions in Alembicol D, the test substance was administered at 50% (w:v) in Alembicol D for both phases of the definitive study.

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For the induction phase, fur from the left shoulder region of 20 young adult male animals was clipped just prior to dermal administration of 0.5 Ml of 50% (w:v) SAN 835 H Technical in Alembicol D. The test substance was applied using a 3-ply, 2- x 2-cm surgical gauze patch. Single untreated patches were also affixed to ten male control animals. Each patch was covered with Blenderm plastic adhesive tape and the torso of each animal was wrapped with Elastoplast adhesive bandage secured with Sleek tape. Following a 6-hour exposure period, the coverings were removed. Removal of the test substance from the skin was not described. The test substance was applied to the same site three times per week over a 3-week period, for a total of nine applications. The treated and control animals were observed for dermal irritation approximately 24 hours after each induction application.

Two weeks following the final induction treatment, previously-untreated 5- x 5-cm areas of fur from the right flanks of each animal were clipped just prior to a single challenge treatment with 0.5 Ml of 50% (w:v) SAN 835 H Technical in Alembicol D to both test and control animals. Application was made in the same manner described for the induction phase. One animal died prior to the challenge application. The guinea pigs were observed for dermal irritation 24 and 48 hours following each induction treatment, and 24, 48, and 72 hours following the challenge exposure. Erythema and edema were scored separately using the Draize scale. In addition, the animals were observed daily for signs of general toxicity.

Body weights of each animal were recorded at the start (day 0) and termination (day 36) of the study.

The study author reported that the positive control study was conducted in the same manner as the definitive experiment; however, aside from using 20 animals (10 test/10 control), details concerning the methodology were not provided.

II. **RESULTS AND DISCUSSION:**

A. Induction reactions and duration: No dermal irritation was observed at test or control sites during the induction phase.

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B. Challenge reactions and duration: No dermal irritation was observed 24, 48, or 72 hours following a single challenge application to either previously-induced or control animals. Based on the results of this study, SAN 835 H Technical is not a dermal sensitizer.

No signs of toxicity or ill health were observed during the study, and no treatment-related effects on body weight were observed between animals from the treated and control groups, with average increases of 80-81%.

C. Positive control: The study author reported that generally well-defined irritation (not further defined) was observed at an unspecified number of test sites during the induction phase; no dermal effects were observed at the control sites. Individual data were not provided.

Twenty-four hours following a single challenge treatment to previously-induced animals, slight to well-defined erythema (scores of 1-2) and slight edema (score of 1) were observed at 8/10 and 6/10 sites, respectively. Forty-eight hours or 72 hours following the challenge treatment, slight to well-defined erythema was observed at 7/10 sites, and slight edema was observed at 5/10 and 4/10 sites, respectively. In addition, thickening, dryness, and sloughing of the epidermis were observed at a single site at 48 and 72 hours.

In comparison, 24 hours following a single challenge treatment to control animals, slight erythema (score of 1) and slight edema (score of 1) were observed at 3/9 and 2/9 sites, respectively. Forty-eight or 72 hours following a single challenge treatment to control animals, slight erythema (score of 1) were observed at 4/9 and 2/9 sites, respectively. A localized dermal reaction was observed at individual sites at 24, 48, and 72 hours. Based on these results, 6/10 test sites were considered to have a positive score, and these data confirm the adequacy of the test species and method employed.

D. Comment: Since no dermal irritation was observed during the induction phase using a 50% dilution of SAN 835H Technical, a slightly irritating concentration or the maximum concentration (of 100%) was not tested. As a result, additional testing on the dermal sensitizing potential of SAN 835H may be required.

E. Deficiencies: Fur from the test sites should have been clipped at least 24 hours prior to test substance application. In this study, it was implied that the sites were clipped just prior to application. Presuming that this procedure was consistent for both definitive and positive control studies, this deficiency should have no significant effects on the results of this study and is considered minor.