Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/19/93
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (7509C) MPCopley 10/19/93

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Oral—Rat** (81-1)
PC NO.	118202
TOX. CHEM NO.	None
MRID NO.	426485-14
TEST MATERIAL	DE-473
SYNONYMS	Hexaflumuron Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-
STUDY NUMBER	DR-0210-2650-004A
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Acute Oral Toxicity in Fischer 344 Rats
AUTHORs	P.F. Cosse, K.V. Sames and N.M. Berdasco
REPORT ISSUED	January 21, 1993

CONCLUSIONS:

DE-473 was administered once orally to 5 male and 5 female Fischer 344 rats per group at 5000 mg/kg and observed for 14 days.

LD_{50}: >5000 mg/kg

Clinical signs observed at 5000 mg/kg included urine and fecal perineal soiling

Tox. Category: IV

Classification: Acceptable

This study satisfies the guideline requirements (81-1) for Acute Oral Toxicity for DE-473, and is acceptable for regulatory purposes.

1

MATERIALS

1. **Test Compound**: DE-473 (Hexaflumuron)
   Description: crystalline solid. Batch No. Sample Ref:TSN100051; Purity: 99.5%; Stability: Not specified.

2. **Test Animal**: Species: Rat, Strain: Fischer 344
   Age: approx. 9 wks. Weight: Male—200-205 gm, Female—106-133 gm.
   Source: Charles River Breeding Labs., Kingston, NY.

3. **Environment**: Rats were housed 2 - 3 to a cage (type not specified). Temperature: not specified; described as adequate; Humidity: not specified; described as adequate; Photoperiod: not specified Food: Purina Rodent Laboratory Chow (#5002) *ad libitum*; Water: tap *ad libitum.*

METHODS

Animals were fasted overnight prior to dosing. Groups of five male and five female rats received a single doses of 5000 mg/kg of DE-473 as a 50% suspension in METHOCEL orally by gavage.

Observations for toxicity and mortality were made frequently on the day of dosing, and at least once daily during working days for two weeks. Each surviving animal was weighed on day of treatment, and on days 2, 8, and 15. Terminal body weights were taken on all animals that died during the study. Necropsy was performed on all animals.

Animals were euthenatized on day 14 after treatment. Gross necropsy was performed on all animals that died during the study, and those sacrificed on day 14.

The quality assurance statement was signed by T.S. Gushow on Jan. 23, 1993.

RESULTS AND DISCUSSION

Mortality No male or female deaths were observed during the course of the study. The LD50 is therefore >5000 mg/kg.

Clinical Signs Treatment-related signs of toxicity consisted of perineal fecal soiling in four of five males, and perineal urine staining in one of five males and one of five females. No other signs were observed.

Body Weight Body weight gain was stead over the 2 week period: 21% in males and 25% in females. There was no indication that body weight or body weight gain was adversely affected by treatment.

Gross Lesions No gross lesions were observed.

Based on these results, it is concluded that the acute LD_{50} is greater than 5000 mg/kg for males and females.

There were no major deficiencies in this study.

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/19/93
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (7509C) Marion Copley 10/19/93

DATA EVALUATION REPORT

STUDY TYPE:	**Acute Dermal Toxicity—Rabbit** (81-2)
PC NO.	118202
TOX. CHEM NO.	None
MRID NO.	426485-15
TEST MATERIAL	DE-473
SYNONYMS	Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-Hexaflumuron
STUDY NUMBER	DR-0210-2650-004D
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Acute Dermal Toxicity Study in New Zealand White Rabbits
AUTHORs	P.F. Cosse, K.V. Sames and T.K. Jeffries
REPORT ISSUED	January 21, 1993

CONCLUSIONS:

DE-473 was administered once dermally to 5 male and 5 female New Zealand White rabbits per group at 2000 mg/kg and observed for 14 days.

LD_{50}: >2000 mg/kg

At 2000 mg/kg scaling and erythema were observed; no clinical signs were observed.

Tox. Category: III
Classification: Acceptable.

This study satisfies the guideline requirements (81-2) for Acute Dermal Toxicity on the DE-473 formulation, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** DE-473
   Description: crystalline. Batch No. TSN1000051. Purity: 99.5%
   Stability: Not specified.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: not specified; Weight: 2.1 to 2.6 kg. Source: Hazleton Research Products, Inc., Kalamazoo, Michigan.

3. **Environment:** Animals were housed individually in fully accredited facilities. Temperature, Humidity and Photoperiod: unspecified. Food: Purina Laboratory Rodent Chow (#5322); Water: tap *ad libitum.*

METHODS

Trunks of each animal was shaved the day prior to exposure. Groups of five male and five female rabbits received a dose of 2000 mg/kg of test substance, diluted in deionized water. The applied material was held in contact with the skin with a piece of gauze backed with plastic and secured with hypoallergenic tape. All items were removed 24 hr later, and the area was cleansed. Animals were fitted with a collar to prevent ingestion of possible residue. Collars were removed at the discretion of study personnel.

Observations for toxicity and mortality were made frequently on the day of treatment, and at least once daily on work days for the next two weeks. Body weights were taken on the day of treatment, and on days 2, 8, and 15 post treatment.

Animals were subjected to gross pathological examination after sacrifice (Carbon dioxide anesthetic followed by euthanasia) on day 14 post treatment.

The quality assurance statement was signed by T.S. Gushow on Jan. 21, 1993.

RESULTS AND DISCUSSION

No deaths occurred at the limit dose of 2000 mg/kg during this study, therefore the LD_{50} was determined to be >2000 mg/kg. Local toxicity consisted of scaling in one male and erythema in one female. The severity and deration of these effects were not reported. There was a 4% loss in male mean body weight between days one and two of treatment; the body weight gain over the 14 day treatment period was 6.1% in males and 8.4% in females. No gross lesions were noted.

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/19/93
Section IV, Tox Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T. Marion Copley 10/19/93
Section IV, Tox Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE:	**Inhalation -- Rat** (81-3)
TOX. CHEM. NO.:	None
PC NUMBER:	118202
MRID NO.:	426485-16
TEST MATERIAL:	**DE-473**
SYNONYMS:	Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-Hexaflumuron
STUDY NUMBER	DR-0210-2650-005
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Acute Aerosol Inhalation Study with Fischer 344 Rats
AUTHORs	F.S. Ciesziak
REPORT ISSUED	December 4, 1992

CONCLUSIONS

DE-473 was administered for 4 hr once by inhalation to five male and five female Fischer 344 rats per group at a dose of 7.0 mg/l and observed for 14 days.

LC_{50}	>7.0 mg/l
Toxicity Category:	IV
Classification:	Acceptable.

This study satisfies the guideline requirements for an inhalation study in the rat (81-3) for DE-173, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** DE-473; Description: white crystalline powder; Batch No. TSN1000 ; Purity: 99.5%; Stability: Not specified.
51

2. **Test Animals:** Species & Strain: Rat, Fischer 344; Age when tested: approx. 8 weeks; Weight when tested: Males—185-197 gm, Females—102-109 gm; Source: Charles River Breeding Labs., Kingston, NY.

3. **Environment:** Animals were housed two per cage in stainless steel wire cages. Temperature: not specified. Relative Humidity: not specified. Photoperiod: 12 hour light-dark cycle. Food: Purina Rodent Laboratory Chow #5002, available *ad libitum* except during exposure. Water: Municipal, available *ad libitum* except during exposure.

METHODS

Aerosol Generation

The aerosol dust was successfully generated by a Jet Mill. Test substance concentrations and particle size distribution were measured near the rats' breathing zone.

Exposure and Observations

Groups of five male and five female rats were exposed (nose only) in a single 4-hour exposure to an analytical concentration of 7.0 mg/l test material. Animals were observed for signs of toxicity or mortality frequently on the day of exposure, and at least once/day thereafter for 14 more days. Individual body weights were recorded just prior to exposure, and on days 1, 2, 4, 8, 11, and 15 of the study. On day 15 all surviving animals were anesthetized with methoxyflurane and euthanized. A complete gross necropsy was performed on each rat sacrificed at that time, and also on those that died during the course of the study.

RESULTS

Clinical Signs and Mortality

All animals survived the four hour exposure period and the 14 day post-exposure observation period. No clinical signs were observed.

Body Weight Gain

Mean body weights were 2 to 4% less on day 2 compared with pre-exposure in male and female rats. All animals recovered without difficulty.

Gross Pathology

No gross lesions or other effects were observed.

Particle Size

The mass median aerodynamic diameter (MMAD) for the aerosol was 3.3 μm, with a geometric standard deviation of 2.7. Approximately 12% of the total mass was less than 1 micron in size, and 79% of the total mass was less than 6 microns in size. Due to the nature of the test compound, it was not possible to reduce the MMAD.

DISCUSSION

DE-473 was not acutely toxic to male and female rats by the inhalation route at the concentration tested, which was above the 5 mg/l limit dose level. The LC_{50} is determined to be >7 mg/l for males and females, with a Toxicity Category of IV.

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/19/93
Section IV, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (H7509C) Marion Copley 10/19/93

DATA EVALUATION REPORT

STUDY TYPE:	**Primary Ocular Irritation—Rabbit** (81-4)
PC NO.	118202
TOX. CHEM NO.	None
MRID NO.	426485-17
TEST MATERIAL	DE-473
SYNONYMS	Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-Hexaflumuron
STUDY NUMBER	DR-0210-2650-004C
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Primary Eye Irritation Study in New Zealand White Rabbits
AUTHORs	P.F. Cosse, K.V. Sames and T.K. Jeffries
REPORT ISSUED	January 21, 1993

CONCLUSION:

DE-473 was introduced into the conjunctival sac of the right eye of six male New Zealand White rabbits at 0.1 gm of pulverized test material/animal. The left eye served as control in each animal. Animals were observed for 72 hours.

Minimal Eye Irritation, resolved by 24 hours

Tox. Category: IV

Classification: Acceptable

This study satisfies the guideline requirements (81-4) for Primary Ocular Irritation on DE-473, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** DE-473
   Description: crystalline. Batch No. TSN1000 51. Purity: 99.5%
   Stability: Not specified.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: not specified; Weight: 2.1 to 2.4 kg. Sex: male and female (ratio unspecified)
   Source: Hazleton Research Products, Inc., Kalamazoo, Michigan.

3. **Environment:** Animals were housed individually in fully accredited facilities. Temperature, Humidity and Photoperiod: unspecified. Food: Purina Laboratory Rodent Chow (#5322); Water: tap *ad libitum.*

METHODS

One-tenth of a gm of test substance was placed into the conjunctival sac of the right eye of each of six adult rabbits. The eye lids were held together for about one second. The left eye was not treated, and served as a control.

Rabbits were observed for signs of toxicity to the cornea, iris and conjunctivae according to the Draize method. Lacrimation was also assessed. Observations were made 1 hr, 24 hr, 48 hr, and 72 hr post dosing, as long as irritation persisted.

The quality assurance statement was signed by T.S. Gushow on Jan. 21, 1993.

RESULTS AND DISCUSSION

The cornea and iris were not adversely affected in any of the animals. As seen in Table 1, ocular irritation was observed in four of the six animals, namely, slight redness and chemosis. All signs of ocular irritation were resolved by 24 hours post treatment. The test was terminated 72 hours post treatment.

Non-ocular lesions or other signs of toxicity were not observed. The test substance is considered a minimal eye irritant with a Toxicity Category of IV.

SUMMARY OF RESULTS

TIME (hour, day)	1 hr	24 hr	48 hr	72 hr	7 days	14 days
IRRITATION SCORE	0.67	0.0	0.0	0.0	N/A	N/A

HEXAFLUMURON

Page_____ is not included in this copy.

Pages 11 through 14 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.

X 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.

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/19/93
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (7509C) Marion Copley 10/19/93

DATA EVALUATION REPORT

STUDY TYPE:	**Dermal Irritation—Rabbit** (81-5)
PC NO.	118202
TOX. CHEM NO.	None
MRID NO.	426485-18
TEST MATERIAL	DE-473
SYNONYMS	Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-Hexaflumuron
STUDY NUMBER	DR-0210-2650-004B
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Primary Dermal Irritation Study in New Zealand White Rabbits
AUTHORs	P.F. Cosse, R.J. McGuirk, and N.M. Berdasco
REPORT ISSUED	January 21, 1993

CONCLUSION:

DE-473 was administered for 4 hr once dermally to shaved backs of four male and two female New Zealand White rabbits at 500 mg/animal, and observed for 7 days.

PIS: 0.04 (slightly-irritating)

Tox. Category: IV

Core Classification: Acceptable

This study satisfies the guideline requirements (81-5) for Primary Dermal Irritation on DE-473, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** DE-473
   Description: crystalline. Batch No. TSN1000'51. Purity: 99.5%
   Stability: Not specified.

2. **Test Animal:** Species: Rabbit, Strain: New Zealand White; Age: not specified; Weight: 2.0 to 2.2 kg. Source: Hazleton Research Products, Inc., Kalamazoo, Michigan.

3. **Environment:** Animals were housed individually in fully accredited facilities. Temperature, Humidity and Photoperiod: unspecified. Food: Purina Laboratory Rodent Chow (#5322); Water: tap *ad libitum.*

METHODS

The backs (10 cm^2) of four male and two female rabbits were shaved the day prior to treatment. 500 mg of the test substance was applied and secure with gauze and hypoallergenic tape; it was removed approximately 4 hr after treatment. The treated area was cleaned with moistened disposable towels.

Animals were observed for signs of erythema and edema formation 1 hr, 24 hr, 48 hr, 72 hr and 7 days post dosing; findings were recorded in harmony with the Draize method.

The quality assurance statement was signed by T.S. Gushow on Jan. 21, 1993.

RESULTS AND DISCUSSION

Erythema (grade 1) with desquamation was observed in one animal 72 hr following exposure. All signs of irritation were resolved within 7 days. A Primary Irritation Index of 0.04 was calculated. No lesions or other toxic signs were observed. DE-473 can be classified in Toxicity Category IV for dermal irritation.

Reviewed by: Myron S. Ottley, Ph.D. MSOttley 10/9/93
Section IV, Tox. Branch I (7509C)
Secondary Reviewer: Marion P. Copley, D.V.M., D.A.B.T.
Section IV, Tox Branch I (7509C) Marion Copley 10/9/93

DATA EVALUATION REPORT

STUDY TYPE:	**Dermal Sensitization—Guinea Pig** (81-6)
PC NO.	118202
TOX. CHEM NO.	None
MRID NO.	426485-19
TEST MATERIAL	DE-473
SYNONYMS	Benzamide: N-(((3,5-dichloro-4(1,1,2,2-tetrafluoroethoxy)phenyl)amino)carbonyl)-2,6-difluoro-Hexaflumuron
STUDY NUMBER	DR-0210-2650-004E
SPONSOR	DowElanco
TESTING FACILITY	Dow Chemical Co., Midland, Michigan 48674
TITLE OF REPORT	DE-473: Dermal Sensitization Potential in the Hartley Albino Guinea Pig
AUTHORs	P.F. Cosse, R.J. McGuirk and N.M. Berdasco
REPORT ISSUED	January 21, 1993

CONCLUSION:

DE-473 was administered to shaved backs of 10 male Hartley albino guinea pigs at 0.4 ml of 50% (w/v) suspension per animal, following the induction/sensitization protocol. One week prior to the topical induction, intradermal induction was performed with three 0.4 ml injections/animal.

Not a Sensitizer

Core Classification: Acceptable

This study satisfies the guideline requirements (81-6) for Dermal Sensitization on DE-473, and is acceptable for regulatory purposes.

MATERIALS

1. **Test Compound:** DE-473
   Description: white crystalline powder. Sample Ref. No. TSN1000 51
   Purity: 99.5%
   Stability: Not specified.

2. **Test Animal:** Species: Guinea Pig (male), Strain: Hartley albino; Age: not specified; Weight: 318 - 360 g; Source: Charles River Breeding Labs., Kingston, NY

3. **Environment:** Animals were housed 5/cage in cages of unspecified design. Temperature: not specified; Humidity: not specified; Photoperiod: not specified; Food: Purina Guinea Pig Chow (#5026) *ad libitum*; Water: municipal *ad libitum.*

METHODS

Using a modified Buehler method, a 0.4 ml volume of a 50% solution of test substance in dipropylene glycol monomethyl ether (DPGME) was applied for 6 hours to the left side of guinea pigs under a gauze patch which was secured with non-irritating tape. A second group of 10 animals was treated similarly with a 10% solution of DER 331 epoxy resin in DPGME as a positive control. The concentration of DER 331 was reduced to 7.5% due to erythema observed at the application site of one animal after the second induction application.

Animals in the test groups received three topical induction applications (6-hr duration) once/week for three consecutive weeks. followed by a topical challenge application (6 hr duration) approximately two weeks follow the last treatment. Animals in the DE-473 and DER 331 (reduced to 5% due to erythema) non-induced control groups received only a single 24-hr application. The left side was used as the dose site for all three induction applications, and the right side was used for the challenge dose site.

Dermal irritation scores were determined approximately 24 and 48 hr after unwrapping for each induction a challenge treatment. After the challenge dose, the dose site and naive area were depilated (with Nair Lotion hair Remover) for scoring irritation.

Body weights were recorded for all animals on days 7 and 31.

The quality assurance statement was signed by T.S. Gushow on January 21, 1993.

RESULTS AND DISCUSSION

Challenge application with the positive control caused slight to moderate (scores of 1 or 2) erythema in four of 10 animals tested, 24 and/or 48 hours after challenge. Challenge application with DE-473 caused slight (score of 1) erythema in one of 10 animals tested 48 hours after challenge.

There was no mortality. Mean body weight gain for DE-473 test animals was 161 g, and 162 g for DER 331 test animals. No naive controls were used to allow comparison of body weight gain data.

It is concluded that DE-473 is not a dermal sensitizer in the guinea pig.