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

APR - 9 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: V-53482 WP Herbicide (Flumioxazin). Application for a temporary tolerance for use in soybeans.
PC-Code 129034
Submission No. S446973
MRID Nos. 42884002
Case No. 285019
Action No. 240 G Pet-Temp Toler
DP Barcode No. D194595
ID No. 3G04250

From: Alberto Protzel, Ph.D. 4/8/96
Review Section III
Toxicology Branch II
Health Effects Division (7509C)

To: Ms. Joanne Miller/ Mr. D. Kenny
Product Manager, Team 23.
Registration Division (7505C)

Thru: James N. Rowe, Ph.D., Head 4/8/95
Review Section III
Toxicology Branch II
Health Effects Division (7509C)

and

Stephanie Irene, Ph.D., Acting Chief J.N. Rowe for 4/9/96
Toxicology Branch II
Health Effects Division (7509C)

ACTION:

Valent U.S.A. Corporation (Walnut Creek, CA) has applied for a temporary tolerance for use of V-53482 WP Herbicide (Flumioxazin) in soybeans. Tolerances are proposed for flumioxazin in or on the following agricultural food or feed commodities:

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Food or Feed Commodity	Proposed tolerance:
Soybean seed	0.01 ppm
Soybean forage	0.01 ppm

TB-II has been asked to review the toxicology database on the chemical and to determine if the data are acceptable to support the request for the temporary tolerance.

CONCLUSIONS:

1. Temporary Tolerance:

The available toxicity data base of flumioxazin and its formulation have been examined. Although an appreciable number of the studies have been classified as CORE Supplementary, the information appears to be sufficient to determine if the data support the request for a temporary tolerance.

In a combined chronic/carcinogenicity study in rats, the technical material has been found (at the time of the 1-year interim report) to have a systemic LOEL of 20.8 (♂)-25.3 (♀) mg/kg/day (based on anemia in rats of both sexes), with a systemic NOEL of 2.1 (♂)-2.5 (♀) mg/kg/day. In addition, the technical induces reproductive effects (LOEL/NOEL: 15.1/7.6 mg/kg/day) and developmental effects orally (LOEL/NOEL: 10/3 mg/kg/day) and dermally (LOEL/NOEL: 100/30 mg/kg/day) in rats at doses below the maternally toxic level.

Based on the examination of the toxicity database, TB-II does not have any objections to an approval of the request for temporary tolerances provided that:

- o The residue chemistry data are acceptable to Chemistry Branch (I/II) and if granting these temporary tolerances will not result in dietary exposures [as determined by the Dietary Risk Evaluation System (DRES Section) in the Science Analysis Branch] exceeding 100% of the Interim RfD (0.021 mg/kg/day).

- o No significant exposure results to males or females (e.g. applicators) which might impair their reproductive capabilities or endanger a pregnant female (developmental effects).

- o Adequate protection (dust/mist filtering respirator) is provided to individuals receiving significant inhalation exposure to dusts/mists in the course of the study.

While dietary exposure concerns appear to be addressed by the Applicant, DRES is requested to comment on the adequacy of the dietary exposure levels resulting from the proposed tolerances. OREB is requested to comment on the adequacy of the occupational exposure protocol to prevent significant dermal or inhalation exposure to the workers involved in the study. The dermal developmental NOEL of 30 mg/kg/day should be used.

2. Review of an Acute Inhalation Study:

The study V-53482 50 WDG: Acute Inhalation Toxicity in Rats, 4-Hour Exposure

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[Huntingdon Research Centre Ltd. Laboratory Project Identification VLT 15/920416. July 6, 1993. MRID 42884002] has been reviewed. This acute inhalation study is classified as acceptable and satisfies the guideline requirement for an acute inhalation study (81-3) in the rat for V-53482 50 WDG. The formulation V-53482 50 WDG is given an Acute Toxicity Category of III.

The formulation V-53482 50 WDG has been found to produce lesions in the ventral cartilage of the larynx at doses of 0.173 and 0.969 mg/L in a 4-hour inhalation experiment. Thus, although V-53482 50 WDG is in Inhalation Toxicity Category III, it is recommended that the use of a dust/mist filtering respirator be required under use conditions that may result in inhalation of aerosols/dusts of V-53482 50 WDG.

DETAILED CONSIDERATIONS:

I. Background.

Valent U.S.A. Corporation (Walnut Creek, CA) has applied for a temporary tolerance for the use of V-53482 WP Herbicide in soybeans. V-53482 WP Herbicide, a pesticide that uses the new chemical flumioxazin as its active ingredient. Flumioxazin (Technical) has also been called S-53482 or V-53482.

Flumioxazin is formulated as a wettable powder (V-53482 WP Herbicide) or as water dispersible granules (V-53482 WDG Herbicide); when the granules are pulverized both formulations are identical. The V-53482 WP Herbicide is furnished in polyvinyl alcohol (PVA) water-soluble packets; the bag constitutes about 2% w/w of the package. For use, the entire packet and its contents dissolve and disperse in water.

It is noted that although the study will be conducted using the wettable powder in the PVA bags (V-53482 WP Herbicide) the reported acute studies with the formulation were conducted with the dispersible granules (V-53482 50 WDG). It does not appear at present that the toxicity categories will be significantly different for the two formulations.

Examination of the draft protocol submitted by the Applicant indicates that the EUP program is scheduled for a two-year duration. Valent U.S.A. is requesting EPA approval for the use of 198.1 lbs. active ingredient used over 2070 acres.

II. Examination of the toxicology data base for flumioxazin.

The toxicology database of flumioxazin and its formulation V-53482 WDG Herbicide is summarized in Tables 1 and 2. The data base appears adequate for evaluating a temporary Tolerance in soybeans.

III. Issues.

A. Carcinogenicity:

No treatment-related increases in tumor incidence were seen in rats administered flumioxazin technical in the diet (0, 50, 500, or 1000 ppm for 53 weeks; (Combined chronic/carcinogenicity study, Interim Report, MRID

4426849-37). Final determination of the carcinogenicity of flumioxazin awaits submission and review of the Final Reports for rats and mice.

B. Reference Dose (RfD):

This chemical has not been evaluated by the HED RFD/Peer Review Committee. Examination of Table 2 indicates that for the purposes of this tolerance petition an Interim RfD can be calculated using data from the 1-year interim report for the combined chronic/carcinogenicity study in rats (MRID 426849-37). The technical material was found (at the time of the 1-year interim report) to have a systemic LOEL of 20.8 (♂)-25.3 (♀) mg/kg/day (based on anemia in rats of both sexes), and a systemic NOEL of 2.1 (♂)-2.5 (♀) mg/kg/day. Use of the NOEL of 2.1 mg/kg/day and an uncertainty factor of 100, results in an Interim RfD of 0.021 mg/kg/day.

It is recommended that the Interim RfD of 0.021 mg/kg/day be used for DRES analysis for the purposes of this temporary tolerance petition.

Final determination of the RfD of flumioxazin awaits evaluation of the data by the HED RfD/Peer Review Committee.

C. Pending Regulatory Actions:

Evaluation by the HED RfD and Carcinogenicity Peer Review Committees awaits submission and review of the completed data base for the chemical.

IV. Review of an acute inhalation study in rats:

A 4-hour inhalation toxicity study (VLT 11/9142 EPA MRID No. 426849-16) of V-53482 50 WDG was initially conducted in rats at a concentration of 0.19 mg V-53482 50 WDG/L. This study was classified as supplementary pending additional work at higher concentrations (to obtain an LC_{50}) or presentation of satisfactory evidence that the concentration used in this study is the maximum attainable concentration with the test material.

Additional data have now been presented by the Registrant [G.C. Jackson, C.J. Hardy, R.L. Gregson and C. Gopinath (1993). V-53482 50 WDG: Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Laboratory Project Identification VLT 15/920416. July 6, 1993. MRID 42884002]. The results of the review of the data are summarized below:

Groups of young adult Sprague-Dawley rats (5/sex/dose) were exposed by the inhalation route to V-53482 50 WDG (51% a.i. formulation of flumioxazin) in distilled water for 4 hours (whole body) at concentrations of 0.037, 0.051, 0.173, or 0.969 mg/L. Additionally, the rats were exposed to a blank V-53482 50 WDG formulation (i.e. no a.i.) for 4 hours (whole body) at a concentration of 1.35 mg/L. Animals then were observed for 14 days.

The LC_{50} for both sexes was greater than 0.969 mg/L (No mortality, the highest dose was a Maximum Attainable Concentration). V-53482 50 WDG is TOXICITY CATEGORY III based on a 4hr-LC_{50} greater than 0.969 mg/L for both sexes. The following signs were observed at the high dose (0.969 mg/L) in all rats, and both

sexes, starting at the following times and continuing through the end of exposure: eyes partially closed and fluid discharge from mouth (equilibration period), wet around the eyes and exaggerated respiratory movements (0.25 hours), and pilo-erection (2.0 hours). Exaggerated respiratory movements were still observed at the high dose through day 3 of the observation period. No clinical signs were observed at 0.037 and 0.051 mg/L during or after exposure. Microscopic examination of the larynx at the end of the 14-day observation period revealed dose-related increases in mineralization, partial resorption, and focal necrosis of the ventral cartilage of the larynx at 0.173 and 0.969 mg/L. Similar effects on the larynx were found with the blank formulation (i.e. containing all ingredients except the a.i.). No effects on the larynx were found with the water aerosol (control) or the two lower doses 0.037 and 0.051 mg/L. The concentration of 0.969 mg/L was found to be a maximum attainable concentration.

Although based on lethality V-53482\50 WDG is placed in Category III or greater for acute inhalation, it is recommended that a respiratory protection device be required as follows. Based on the potential for lesions of the larynx upon inhalation of V-53482 50 WDG, it is recommended that the use of a dust/mist filtering respirator be required under use conditions that may result in inhalation of aerosols/dusts of V-53482 50 WDG.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (81-3) in the rat for V-53482 50 WDG.

IV. Conclusions.

1. Temporary Tolerances:

Based on the examination of the toxicity database, TB-II does not have any objections to an approval of the request for temporary tolerances provided that:

- o The residue chemistry data are acceptable to Chemistry Branch (I/II) and if granting these temporary tolerances will not result in dietary exposures [as determined by the Dietary Risk Evaluation System (DRES Section) in the Science Analysis Branch] exceeding 100% of the Interim RfD (0.021 mg/kg/day).
- o No significant exposure results to males or females (e.g. applicators) which might impair their reproductive capabilities or endanger a pregnant female (developmental effects).
- o Adequate protection (dust/mist filtering respirator) is provided to individuals receiving significant inhalation exposure to dusts/mists in the course of the study.

While dietary exposure concerns appear to be addressed by the Applicant, DRES (SAB) is requested to comment on the adequacy of the dietary exposure levels resulting from the proposed tolerances. OREB is requested to comment on the adequacy of the occupational exposure protocol to prevent significant dermal or inhalation exposure to the workers involved in the study.

2. Review of an Acute Inhalation Study:

The study V-53482 50 WDG: Acute Inhalation Toxicity in Rats, 4-Hour Exposure [Huntingdon Research Centre Ltd. Laboratory Project Identification VLT 15/920416. July 6, 1993. MRID 42884002] has been reviewed. This acute inhalation study is classified as acceptable and satisfies the guideline requirement for an acute inhalation study (81-3) in the rat for V-53482 50 WDG. The formulation V-53482 50 WDG is given an Acute Toxicity Category of III.

The formulation V-53482 50 WDG has been found to produce lesions in the ventral cartilage of the larynx at doses of 0.173 and 0.969 mg/L in a 4-hour inhalation experiment. Thus, although V-53482 50 WDG is in Inhalation Toxicity Category III, it is recommended that the use of a dust/mist filtering respirator be required under use conditions that may result in inhalation of aerosols/dusts of V-53482 50 WDG.

cc John Tice (HED/OREB)
cc Beth Doyle (HED/SAB/DRES)

Table 1. Results of acute toxicity testing with S-53482 Technical and V-53482 50 WDG.

Guideline #	Test Type	Species	MRID	LD_{50} (mg/kg)	LC_{50} (4h) mg/l	Remarks	Toxicity Category	CORE Classification
				S-53482 Technical				
81-1	Acute Oral	Rat	426849-11	>5000 (M&F)	-	No deaths or abnormal clinical signs.	IV	Minimum
81-2	Acute Dermal	Rat	426849-13	>2000 (M&F)	-	No deaths or abnormal clinical signs.	IV	Minimum
81-3	Acute Inhalation	Rat	426849-15	_	Not Defined	MMAD: 4.5-5.3 & 5.99-6.18 μm	-	Supplementary
81-4	Eye Irritation	Rabbit	426849-17	-	-	Irritation clearing within 7 d. or less.	III	Minimum
81-5	Skin Irritation	Rabbit	426849-17	-	-	No irrit. or edema; scores = 0	IV	Minimum
81-6	Dermal Sensitization	Guinea pig	426849-21	-	-	Not a sensitizer by this test.	-	Minimum
				V-53482 50 WDG				
81-1	Acute Oral	Rat	426849-12	>5000 (M&F)	-	No deaths; piloerection on 1st. day only.	IV	Minimum
81-2	Acute Dermal	Rat	426849-14	>2000 (M&F)	-	No deaths or abnormal clinical signs.	IV	Minimum
81-3	Acute Inhalation	Rat	428840-02	-	>0.969 mg/l	Mineralization, partial resorption and focal necrosis of the ventral cartilage of the larynx	III	Minimum[1]
81-4	Eye Irritation	Rabbit	426849-18	-	-	Irritation clearing within 7 d. or less.	III	Minimum
81-5	Skin Irritation	Rabbit	426849-19	-	-	Mild or slight irritation at 72 hours.	IV	Minimum
81-6	Dermal Sensitization	Guinea Pig	426849-20	-	-	Not a sensitizer by this test.	-	Minimum

Table 2. Results of testing (other than acute toxicity) with S-53482 Technical and V-53482 50 WDG.

Guideline #	Test type	Species	MRID	Systemic (M/F) or Maternal[a]		Develop. or Reproduct.		Remarks	CORE Classification
				LOEL	NOEL	LOEL	NOEL		
				mg/kg/day	mg/kg/day	mg/kg/day	mg/kg/day		
82-1	90-D feeding	Rat	426849-22	65.0/22.4	19.3/2.2	-	-	Anemia & extramed. hematopoiesis	Minimum
"	"	Rat	426849-23	69.7/71.5[b]	20.7/21.7[b]	-	-	Anemia & extramed. hematopoiesis	Supplementary
"	"	Dog	426849-24	100/100	10/10	-	-	Dose-dep. incr. in AP and Chol.	Supplementary
83-3	Develop. (Oral)	Rat	426849-25	Not Detnd.	$\geq$ 30	10	3	Fetal cardiovasc. abnormalities[c]	Supplementary
"	Develop. (Dermal)	Rat	426849-26	Not Detnd.	$\geq$ 300	100	30	Fetal cardiovasc. abnormalities[c]	Supplementary
"	Develop. (Oral)	Rabbit	426849-28	3000	1000	Not Detnd.	$\geq$ 3000	No fetal effects	Guideline
"	Special Study	Rat	426849-31	-	-	-	-	Dermal absorp. in preg. rat = 5.8%	Acceptable
								of dose at 100 mg/kg at 48 hrs.	
"	Special Study	Rat	426849-32	-	-	-	-	Similar blood levels with dermal at	Acceptable
								200 mg/kg and oral at 1 mg/kg.	
83-4	2-Gen. Reproduct.	Rat	426849-45	22.7[b]	15.1[b]	15.1[b]	7.6[b]	Liveborn pups ↓; pup b. wt. ↓	Guideline
83-5	C. Chron./Carcino.	Rat	426849-37	20.8/25.3	2.1/2.5	-	-	Interim Rpt: Anemia: ♂: 20.8 & ♀: 25.3 mg/kg	Supplementary
84-2	Mutagenicity	Bacter	426849-38	-	-	-	-	Sal./mammalian microso. plate inc.: equivoc.	Acceptable
"	"	Hamst.	426849-39	-	-	-	-	In vitro chromos. aberr.: pos. (+S9); neg. (-S9)	Acceptable
"	"	Rat	426649-40	-	-	-	-	In vivo chromos. aberr.: negative	Acceptable
"	"	Rat	426649-41	-	-	-	-	UDS rat hepatocytes: negative	Acceptable
"	"	Rat	426649-42	-	-	-	-	Micronucleus test; no conclusion could be drawn	Unacceptable
85-1	Metabolism	Rat	426649-43	-	-	-	-	Oral absorption $\geq$ 90.0; Up to 35 metabolites[d]	Supplementary
85-2	Dermal Absorption	Rat	426649-44	-	-	-	-	At 0.2 mg/rat (0.02 mg/cm^2) 2.3% was absorbed.	Minimum

[a] Actual administered dose unless indicated otherwise.
[b] Values are mean compound intake reported in the study.
[c] Particularly ventricular septal defect.
[d] There was some binding of radioactivity to red blood cells.

Flumioxazin **Acute Inhalation Study (81-3)**

EPA Reviewer: Alberto Protzel Ph.D. , Date 4/8/96
Review Section III, Toxicology Branch II (7509C)
EPA Secondary Reviewer: James N. Rowe Ph. D , Date 4/8/96
Review Section III, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity - Rat
OPPTS 870.1300 [§81-3]

DP BARCODE: D194595
P.C. CODE: 129034

SUBMISSION CODE: S446973
TOX. CHEM. NO.: -

TEST MATERIAL (PURITY): V-53482 50 WDG

SYNONYMS: Flumioxazin

CITATION: G.C. Jackson, C.J. Hardy, R.L. Gregson and C. Gopinath (1993). V-53482 50 WDG: Acute Inhalation Toxicity in Rats, 4-Hour Exposure. Huntingdon Research Centre Ltd. P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES, England. Laboratory Project Identification VLT 15/920416. July 6, 1993. MRID 42884002. Unpublished.

SPONSOR: Valent U.S.A. Corporation, Walnut Creek, CA.

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 42884002), groups of young adult Sprague-Dawley rats (5/sex/dose) were exposed by the inhalation route to V-53482 50 WDG (50% a.i. formulation of flumioxazin) in distilled water for 4 hours (whole body) at concentrations of 0.037, 0.051, 0.173, or 0.969 mg/L. Additionally, the rats were exposed to a blank V-53482 50 WDG formulation (i.e. no a.i.) for 4 hours (whole body) at a concentration of 1.35 mg/L. Animals then were observed for 14 days.

The LC_{50} for both sexes was greater than 0.969 mg/L (No mortality, the highest dose was a Maximum Attainable Concentration). V-53482 50 WDG is TOXICITY CATEGORY III based on a 4hr-LC_{50} greater than 0.969 mg/L for both sexes. The following signs were observed at the high dose (0.969 mg/L) in all rats, and both sexes, starting at the following times and continuing through the end of exposure: eyes partially closed and fluid discharge from mouth (equilibration period), wet around the eyes and exaggerated respiratory movements (0.25 hours), and pilo-erection (2.0 hours). Exaggerated respiratory movements were still observed at the high dose through day 3 of the observation period. No clinical signs were observed at 0.037 and 0.051 mg/L during or after exposure.

Microscopic examination of the larynx at the end of the 14-day observation period revealed dose-related increases in mineralization, partial resorption, and focal necrosis of the ventral cartilage of the larynx at 0.173 and 0.969 mg/L. Similar effects on the larynx were found with the blank formulation (i.e. containing all ingredients except the a.i.). No effects on the larynx were found with the water aerosol (control) or the two lower doses 0.037 and 0.051 mg/L. Although based on lethality V-53482 50 WDG is placed in Category III or greater for acute inhalation, it is recommended that a respiratory

protection device be required as follows. Based on the potential for lesions of the larynx upon inhalation of V-53482 50 WDG, it is recommended that the use of a dust/mist filtering respirator be required under use conditions that may result in inhalation of aerosols/dusts of V-53482 50 WDG.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (81-3) in the rat for V-53482 50 WDG.

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:
   Description: A brown granular solid (V-53482 50 WDG). Additionally, the effect of the blank formulation (i. e. the vehicle used in the formulation) was tested. The blank formulation was also identified as a brown granular solid.
   Lot/Batch #: UA 05L11 (for the V-53482 50 WDG). The lot number for the blank formulation was AC 10L11.
   Purity: 50 % a.i. (See MRID 42684919)
   CAS #: 103361-09-7 (for the a.i.)
   Verification of concentration/homogeneity: no data

2. Vehicle and/or positive control:
   The test samples were used as suspensions in distilled water.

3. Test animals: Species: albino rat
   Strain: Sprague-Dawley
   Age and weight at dosing: Age: ♂: 6 weeks, ♀: 8 weeks. Weight: about 200 g for both sexes on the day of dosing.
   Source: Charles River UK Limited, Manston Road, Margate, Kent, England.
   Acclimation period: At least 5 days
   Diet:Diet from Special Diets Services, P.O. Box 705, Witham, Essex, England ad libitum.
   Water: Tap water ad libitum

B. STUDY DESIGN and METHODS:

1. In life dates - Start (exposure date): 10/8/91 (groups 1 and 6); 10/15/91 (group 2), 10/14/91 (group 3), 10/11/91 (group 4), 10/10/91 (group 5). See Table 1 for definition of groups. End: 14 days of observation after exposure date.

2. Exposure conditions: Rats were exposed by whole body exposure (individual compartments) for 4 hours to the test atmosphere containing a liquid droplet aerosol generated from a suspension of the test material in water. Table 1 gives the concentrations and aerodynamic parameters of the aerosols.

3. Animal assignment and treatment - Animals were assigned to the test groups noted in table 1. Five rats/sex/dose were exposed to V-53482 50 WDG and to the blank formulation (no a.i.) by whole body exposure for 4 hours. Clinical signs were recorded at the end of the chamber equilibration period, and at 0.25, 0.5, 1.0 hours and hourly thereafter. The rats were observed twice daily and weighed daily for 14 days after dosing. All rats were sacrificed and a necropsy was performed. The lungs were removed and weighed to determine organ to bodyweight ratios. The lungs, nasal turbinates, larynx, and trachea were examined microscopically.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated. Data obtained from p. 17 of the Study Report (MRID 42884002).

Group No.	Nominal Conc. (mg/L)	Analytical Conc. (mg/L)	MMAD µm	GSD µm	Males	Females	Combined
1	Water	-	-		0/5	0/5	0/10
2	Blank Formulation	1.35 [1]	- (3.4)[3]	- (2.12)	0/5	0/5	0/10
3	0.03	0.037[2]	2.9 (2.5)	2.24 (2.41)	0/5	0/5	0/10
4	0.06	0.051	2.8 (2.6)	2.06 (2.38)	0/5	0/5	0/10
5	0.19	0.173	3.9 (2.9)	2.28 (2.42)	0/5	0/5	0/10
6	MAC	0.969	4.9 (4.3)	2.13 (2.22)	0/5	0/5	0/10

[1] This value refers to the concentration of blank formulation used for this group. Blank formulation was used at the Maximum Attainable Concentration (MAC). The concentration of airborne particulate was determined gravimetrically.
[2] This value and the remaining values in this column refer to the concentration of V-53482 50 WDG. These values were determined from HPLC-measured concentrations of V-53482 (a.i.) in atmosphere samplings. The following formula was used:
V-53482 50 WDG (mg/l) = V-53482 (mg/l) x 1.9646
[3] Value in parenthesis is the value obtained from gravimetric data. The value not in parenthesis is the value obtained by analysis of V-53482 (a.i.).

4. Generation of the test atmosphere and description of the chamber :

The aerosol was produced from a suspension containing 1 part of V-53482 50 WDG or V-53482 in 2 parts of water.

The test material was delivered as an aerosol by pumping the suspension of test material through a pressure nozzle fitted to the bottom of the exposure chamber. The chambers, made of perspex, had an internal volume of approximately 120 liters; clean air was provided at a flow rate of 25 liters/minute. Each chamber was divided with wire mesh to provide 10 separate whole-body exposure animal compartments.
Time to equilibrium was 11 minutes (i.e. theoretical time required to reach 90% of the final value under the conditions of exposure).

Analytical chemistry:

- Test atmosphere concentration: the chamber atmosphere was sampled through a sampling port at 0.5, 1, 2, 3 and 4 hours after the initiation of exposure to assess concentration of a.i by HPLC and of particulate matter gravimetrically. The concentration of V-53482 50 WDG was determined from HPLC-measured concentrations of V-53482 (a.i.) in atmosphere samplings. The following formula was used: V-53482 50 WDG (mg/l) = V-53482 (mg/l) x 1.9646. Results (in mg/L) are in table 1 above.

- Particle size determination: a Marple cascade impactor was used at 1.5 and 3.5 hours of exposure to collect samples for particle size analysis. The material collected at the various stages of the sampler

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was analyzed to determine particle size distribution. Results (MMAD and Standard Geometric Deviation) are shown in table 1 above.

5. Statistics - There were no deaths, no LD_{50} was calculated.

II. RESULTS AND DISCUSSION:

A. Mortality: There was no mortality.

The LC_{50} for both sexes is greater than 0.969 mg/L

B. Clinical observations -

The following signs were observed during exposure:

- Water-treated (Group 1): Normal appearance and behavior throughout, all rats, both sexes.
- Blank formulation (Group 2): Eyes partially closed and exaggerated respiratory movements, starting at 0.25 hours and continuing through the end of exposure, all rats, both sexes.
- 0.037 and 0.051 mg/L (Groups 3 and 4): Normal appearance, all rats, both sexes.
- 0.173 mg/L (Group 5): exaggerated respiratory movements, starting at 0.25 hours and continuing through the end of exposure, all rats, both sexes.
- 0.969 mg/L (Group 6): the following signs were observed in all rats, both sexes, starting at the following times and continuing through the end of exposure: eyes partially closed and fluid discharge from mouth (equilibration period), wet around the eyes and exaggerated respiratory movements (0.25 hours), and pilo-erection (2.0 hours).

The following signs were observed during the 14-day observation period:

- Water-treated (Group 1): Normal appearance and behavior throughout, all rats, both sexes.
- Blank formulation (Group 2): Brown staining around the snout and nose limited to the day of exposure. Normal appearance and behavior for the rest of the observation period; all rats, both sexes.
- 0.037 and 0.051 mg/L (Groups 3 and 4): Normal appearance and behavior, all rats, both sexes.
- 0.173 mg/L (Group 5): hyperactive limited to the day of exposure. Normal appearance and behavior for the rest of the observation period; all rats, both sexes.
- 0.969 mg/L (Group 6): exaggerated respiratory movements on days 1 and 2 after exposure all rats and on day 3 in 2/5 males and in 4/5 females. Brown staining on snout and jaws was observed in all rats and was limited to the day of exposure. Normal appearance and behavior for the rest of the observation period, all rats, both sexes.

C. Body Weight - There were small decreases in bodyweight or reductions in the rate of bodyweight gain, for 1 day following exposure in rats exposed to the blank formulation or to V-53482 50 WDG at 0.969 mg/L.

D. Necropsy -The lung to bodyweight ratios for treated rats were not significantly different from controls.

A dark-colored fluid was found in the trachea of a rat exposed to test material at 0.051 mg/L. There were no other macroscopic findings in any rat.

Microscopic findings are summarized in Table 2. Because the larynx findings (mineralization, resorption and focal necrosis) were not observed in water aerosol-treated rats or in rats treated with V-53482 50 WDG at 0.037 or 0.051 mg/L, it is concluded that the findings at the higher doses and in the blank formulation are treatment-related.

Table 2. Microscopic findings in rats treated with V-53482 50 WDG or its blank (no a.i.) formulation. Data obtained from Appendix 2, pp. 49-72 of the Study Report (MRID 42884002).

Finding	Number of rats with finding (M/F, 5 rats/sex/dose level)					
	Water aerosol (Control)	0.037 mg/L	0.051 mg/L	0.173 mg/L	0.969 mg/L	Blank[1] Formulation (1.35 mg/L)
Lungs	0/0	0/0	1[1]/0	0/0	0/0	0/0
Trachea	0/0	0/0	0/0	0/0	0/0	0/0
Nasal turbinates	0/0	0/0	0/0	0/0	0/0	0/0
Larynx:						
Mineralization, ventral cartilage	0/0	0/0	0/0	0/0	1/0	2/1
Partial resorption, ventral cartilage	0/0	0/0	0/0	0/0	0/1	2/3
Focal necrosis, ventral cartilage	0/0	0/0	0/0	0/2	1/4	1/3
Ventral cartilage with inflammatory cells	0/0	0/0	0/0	1/1	0/0	0/0
Ventral epithelial hyperplasia (minim.) with occasional inflammatory cell infiltration	0/0	0/0	0/0	1/0	0/0	0/0
Moderate squamous metaplasia in ventral pouch and inflammation assoc. with vegetable material.	0/0	0/0	0/0	0/0	1/0	0/0

[1] Minimal focus of neumonitis in one lung.
[2] Contains all components of V-53482 50 WDG, except that it does not contain the a.i.

E. Deficiencies - No deficiencies were found to impair the acceptability of this study.