

US EPA ARCHIVE DOCUMENT

497E



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

MAR 25 1994

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

**SUBJECT:** Section 18: ID# 94ID0005. Emergency Exemption for Use  
of ADMIRE 2 Flowable (Imidacloprid) on Hops in Idaho

Tox. Chem. No.: 497E  
PC No.: 129099  
Barcode No.: D200408  
Submission No.: S460011

**TO:** Rebecca Cool, Manager, PM Team 41  
Margarita Collantes, Reviewer, PM Team 41  
Emergency Response and Minor Use Section/Registration  
Support Branch  
Registration Division (H7505C)

**FROM:** William Dykstra, Ph.D. *William Dykstra 3/17/94*  
Review Section I, Toxicology Branch I  
Health Effects Division (H7509C)

**THRU:** Myron S. Ottley, Ph.D. *MS Ottley 3/17/94*  
Review Section IV, Toxicology Branch I  
Health Effects Division (H7509C)  
and  
Roger Gardner, Section Head *Roger Gardner 3/18/94*  
Review Section I, Toxicology Branch I  
Health Effects Division (H7509C) *RB*

**I. CONCLUSIONS**

The toxicology data requirements are complete for the issuance of a Section 18 emergency exemption by the State of Idaho for the temporary use of imidacloprid (ADMIRE 2 Flowable) to control aphids on hops. The margins of exposure (MOEs) for acute exposure are greater than 100. Imidacloprid is a "Group E" carcinogen, so there is no cancer risk associated with exposure to this chemical.

Toxicology Branch I has no objection to the issuance of this exemption.

**II. ACTION REQUESTED**

In a letter dated March 1, 1994, the Idaho Department of



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**I. INTRODUCTION:**

**Background/Purpose**

The State of Idaho has requested an emergency exemption to use Admire 2 F, (imidacloprid) to control mites and aphids on hops. The State of Idaho has 4,000 acres of hops that they feel will need treatment.

**II. DETAILED CONSIDERATIONS:**

**A. Use**

Imidacloprid will be applied by ground as a foliar spray at the rate of 6.4 oz product per acre or 0.10 lb ai per acre. A maximum of three applications may be applied per season with a maximum application of 19.2 fl. oz. of product or 0.3 lb ai/acre. Hops are normally grown in rows with 7 ft. centers on trellises that stand approximately 14-18 feet tall. Insecticides are generally applied via ground, air-blast equipment with no less than 100 gallons of water per acre and preferably 400 gallons of water applied per acre for maximum coverage. In discussions with an expert in hops production<sup>1</sup>, it is estimated that the maximum acreage that could be sprayed in one day is 20 acres (spraying 20 A would require > 12 hrs.).

**B. Toxicology concerns**

The tox endpoint of concern is maternal/developmental toxicity with a NOEL of 24 mg/kg/day. Imidacloprid is a tox category III chemical for oral toxicity, dermal and eye irritation; and a tox category IV for inhalation and primary dermal toxicity.

**C. Prior exposure reviews**

Other exposure evaluations have been performed for hops with the same application rate and same PPE required. The table below provides the estimates of worker exposure.

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<sup>1</sup> Personal communications with Dr. Wyatt Cone, Washington State University (IAREC), Prosser, WA (509) 786-2226.

**D. Detailed exposure calculations**

Exposure calculations are based on the following assumptions:

- Average worker has the mass of 60 kg,
- mixer/loader and applicator can be the same person (see combined exposure),
- respiratory exposure is negligible compared to dermal exposure,
- dermal exposure is not adjusted for dermal absorption,
- standard work clothing is worn which includes protective gloves, long sleeved shirts, long pants, shoes, socks, and hat,
- in one day a single person will mix/load and spray a maximum of 20 acres at 0.1 lbs ai per acre.
- the maximum application rate is used during each of three applications (0.1 lb ai/acre times 3 applications = 0.3 lbs ai/acre per year.)

The following table summarizes daily and annual exposures for mixer/loader, applicator, and mixer/loader/applicator, using an open pour loading system.

**WORKER EXPOSURES TO IMIDACLOPRID USING PHED SURROGATE DATA**

<b>OPERATION</b>	<b>UNIT EXPOSURE</b> <i>μg/lb handled</i>	<b>GROSS EXPOSURE<sup>2</sup></b> <b>20 ACRES</b> <i>(μg a.i.)</i>	<b>DAILY EXPOSURE<sup>3</sup></b> <b>(20 ACRES)</b> <i>μg/kg</i>
<b>M/L OPEN LOAD</b>	448.5	897.0	15.0
<b>GROUND A.B. 20 ACRES</b>	325.9	651.8	10.9
<b>M/L/A GROUND</b>	774.4	1,548.8	25.8

**III. CONCLUSIONS:**

Daily exposure estimates for a mixer/loader/applicator spraying 20 acres of hops at 0.1 lb ai per acre is 25.8 μg/kg/day.

The minimum PPE required include long-sleeved shirt, long pants, shoes with socks, and chemical resistant gloves. Other PPE including chemical resistant headgear, coveralls or rain-suit and dust mist respirator may also be used.

cc: Correspondence File  
Imidacloprid File (129099)

<sup>2</sup> Exposure resulting from handling 2 lbs ai; enough to spray 20 acres @ 0.1 lbs ai/acre.

<sup>3</sup> Daily exposure estimate for handling 2 lbs ai. Estimates calculated using the following formula:

$$\frac{\text{Unit Exposure} * (2 \text{ lbs ai})}{60 \text{ kg. bw.}} = \text{Daily Exposure}$$



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MAR 17 1994

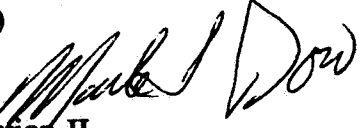
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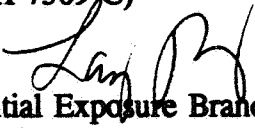
**MEMORANDUM**

**SUBJECT:** Section 18, Idaho State Request to Use Imidacloprid on Hops

**FROM:** John Tice   
Occupational and Residential Exposure Branch  
Health Effects Division (H-7509-C)

**TO:** Bill Dykstra, Ph.D, D.A.B.T.  
Toxicology Branch I  
Health Effects Division (H-7509-C)

**THRU:** Mark I. Dow, Ph.D., Section Head   
Special Review and Registration Section II  
Occupational and Residential Exposure Branch  
Health Effects Division (H-7509-C)

Larry Dorsey, Chief   
Occupational and Residential Exposure Branch  
Health Effects Division (H-7509-C)

Please find below, the OREB review of:

DP Barcode: D-200407

Pesticide Chemical Code: 129099, Imidacloprid

EPA Reg. No.: 3125-UEE, Admire 2 Flowable

EPA MRID No.: N/A

PHED: PHED version 1.01 used for exposure estimates  
mixer/loader exposures from run # 7  
Air-blast (long-sleeves, pants and gloves) run # 2

**REFERRED TO TOX II FOR RISK ASSESSMENT**



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Agriculture requested an emergency exemption under Section 18 for the use of imidacloprid to control aphids (Phorondom humuli) which affects 4,000 acres of hops grown in Canyon and Boundary counties. This is the first request made by Idaho for this use.

ADMIRE -2 Flowable (Miles, Inc.) is the formulation for the active ingredient. The pesticide will be used three times per growing season. Each application may be made at rates not to exceed 0.1 lb ai in sufficient water for coverage using ground equipment, at recommended intervals of at least 21 days. These applications would result in a maximum application of 600 gallons of Admire (1200 lbs of ai imidacloprid). A restricted entry interval of 12 hours would be observed for this product.

### III. TOXICOLOGY BRANCH I COMMENTS

The toxicology data base for imidacloprid is sufficient to support the proposed Section 18 exemption.

### IV. RISK/EXPOSURE ASSESSMENT

This action was submitted to OREB (Occupational and Residential Exposure Branch) for determination of exposure estimates (see attached memo from J. Tice to W. Dykstra, dated March 17, 1994). Therefore, the OREB exposure estimates and the rabbit maternal and developmental NOEL of 24 mg/kg/d (see One Liners, below) were used to determine the Acute MOEs. Calculations were based on a dermal absorption of 100%, because no dermal absorption data is available for imidacloprid. However, dermal penetration is not extensive, since the 21 day dermal toxicity study in rabbits had a NOEL of 1000 mg/kg/day. Cancer risk is not quantitated, since imidacloprid is a group E carcinogen, and there is no Q<sub>1</sub>\* for this chemical.

Formula used in calculations:

$$\text{Acute MOE} = \text{NOEL (24 mg/kg BW/d)} \div \text{Exposure (mg/kg BW/d)}$$

OPERATION*	EXPOSURE (mg/kg/d)	ACUTE MOE
Mixer/Loaders, open pour	0.015	1,600
Applicator, air blast	0.011	2,182

\* Minimum clothing requirements for Applicators are long pants, long-sleeved shirt, and chemical resistant gloves; Mixer/Loader exposure is based on wearing long pants, long sleeves, and gloves (Worker Protection Standard for Agricultural Pesticides).

### V. SPECIAL TOXICOLOGY ISSUES AND PROBLEMS

1. Labelling. The labelling precautionary statements for ADMIRE 2 Flowable are governed by toxicity studies on the active

ingredient.

2. Carcinogenicity. There is no cancer risk associated with exposure to this chemical, because the HED RfD Review Committee has determined that the test compound is a "Group E" carcinogen.
3. RfD. The RfD/Quality Assurance Peer Review Committee met on April 22, 1993 to assess the reference dose for this chemical. The Committee recommended that an RfD of 0.057 mg/kg/day should be established, based upon a NOEL of 5.7 mg/kg/d in a chronic toxicity study in rats. An uncertainty factor of 100 was used to account for interspecies extrapolation and intraspecies variability.
4. Non-carcinogenic risk assessment. In a chronic/oncogenicity study, male rats exhibited increased thyroid lesions at 16.9 mg/kg/day and above, and females at 73 mg/kg/day (see attached Toxicology Profile, study # 100652/101931). In a developmental study in rabbits, 72 mg/kg/d of technical imidacloprid (administered on days 6-19 of gestation) increased the number of resorptions and abortions in the dams, and increased skeletal abnormalities and decreased body weight in the pups.
5. Mutagenicity/genetic toxicity comments. Most of the genotoxicity studies for imidacloprid were negative, although an in vitro chromosome aberration study (human lymphocytes) was positive at cytotoxic concentrations (Tox. Doc. #099262), and an in vitro sister chromatid exchange mutagenicity study (CHO cells) was positive at cytotoxic doses (Tox. Doc. 102655).
6. Dermal Penetration. There are no available dermal penetration data for imidacloprid. However, a 21 day dermal toxicity study in rabbits has a systemic NOEL of 1000 mg/kg/day (HDT).



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OFFICE OF PESTICIDES/HED/TB-1  
TOX ONELINERS**

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CASWELL#: 497E  
CAS-RBG#: 105827-78-**

P.C. CODE 129099- Imidacloprid FILE LAST PRINTED: 03/14/94

CITATION MATERIAL RESULTS ACCESSION/ NRID NO. TOX CAT COREGRADE/ DOCUMENT#

83-2(b)  
Carcinogenic  
Species: mice  
Bayer AG Institut. Fur Tox. Germ  
T5025710 814029986; 01/28/91

Imidacloprid (MTN 33893)  
95% pure; batch# 180587

422563-35  
422563-36

In the main study, the test material was admin. in the diet at levels of 0, 100, 330, or 1000 ppm (0, 20, 66 or 208 mg/kg/day for males; 0, 30, 104, 274 mg/kg/day for females). In the supplementary MTD study, diet levels were 0 or 2000 ppm (0 or 414 mg/kg/d for males; 0 or 424 mg/kg/d for females). The NOEL was 1000 ppm. The LOEL was 2000 ppm based on decr. body weight, food consumption, and water intake in both sexes. Treatment had no effect on tumor incidence. Strain used: B6C3F1 mice.

Guideline  
010537

83-1(a) and 83-2(a)  
Feeding/carcinogenic-2 year  
Species: rat  
Bayer AG Institut. Fur Tox. Germ  
100652; 101931; 07/14/89

MTN 33893 Tech. 94.3% -  
95.3%

422563-31  
422563-32

MTN 33893 tech. was admin. in the diet to 50 male & 50 female Bor WISU (SPF Cpb) rats per group at: 0, 100, 300, 900 and 1800 ppm for 104 weeks. The 1800 ppm dose group tested in a separate study with its own con- current controls.

Minimum  
009960

83-1(b)  
Feeding-1 year  
Species: dog  
Res. and Consulting Co.; Switz  
100015; 10/19/89

MTN 33893 Tech. 94.9%  
(Imidacloprid)

422730-02

Chronic NOEL = 100 ppm (5.7 mg/kg/d in male; 7.6 mg/kg/day female) in males and in females at 900 ppm (73 mg/kg/d) and above. Decr. body wt. gain in females at 300 ppm (24.9 mg/kg/d) and above; weight changes in liver, kidney, lung, heart, spleen, adrenals, brain and gonads in males and/or females at 900 ppm (51.3 mg/kg/d in males, 73.0 mg/kg/d in females) or 1800 ppm.  
Oncogenicity: No apparent treatment-related effect at any dose.

Minimum  
009960

83-3(a)  
Developmental Toxicity Study  
Species: rat  
Res. and Consulting Co.; Switz  
083496; 01/08/92

MTN 33893 tech., 94.2%  
Batch# 17001/87

422563-38

MTN 33893 tech. was admin. by gavage to HSD(SD) rats at: 0, 10, 30, and 100 mg/kg/d during gestational days 6 - 16.  
Maternal NOEL <= 10 mg/kg/d. Maternal LOEL = 10 mg/kg/d; decr. body wt. gain. At 100 mg/kg/d; decr. food consumption.  
Developmental NOEL = 30 mg/kg/d. Developmental LOEL = 100 mg/kg/d; increased wavy ribs.

Minimum  
010537

83-3(b)  
Developmental Toxicity Study  
Species: rabbit  
Res. and Consulting Co.; Switz  
083518; 01/08/92

MTN 33893 tech. 94.2%

422563-38

MTN 33893 tech was admin. to 16 pregnant Chincilla rabbits/group at: 0, 8, 24, and 72 mg/kg/d during gestation days 6-19.  
Maternal NOEL = 24 mg/kg/d. Maternal LOEL = 72 mg/kg/d, based on decr. food consumption at 72 mg/kg/d; decr. body weight, increased resorption, increased abortion and death.  
Developmental NOEL = 24 mg/kg/d. Developmental LOEL = 72 mg/kg/d; decr. body weight, increased skeletal abnormalities.

Minimum  
009960  
010537

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TOX ONELINERS**

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**CASWELL#: 497E**

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CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
83-4 Reproduction Species: rat Res. and Consulting Co.; Switz 100647; 07/21/90	NTN 33893 tech., 95.3% batch# 180587	422563-40	NTN 33893 tech. was admin. in the diet to 30 male & 350 female Wistar/ Han rate per group at: 0, 100, 250, or 700 ppm. Parental NOEL = 700 ppm (approx 55 mg/kg/d). Parental LOEL = not determ. Reprod. NOEL = 100 ppm (8 mg/kg/d). Reprod LOEL = 250 ppm (19 mg/kg/d) based on decr. pup weight in both generations.		Minimum 010537
82-4 Inhalation-subacute Species: rat Bayer AG Instit. Fur Tox. Germ 16771; 02/26/90	NTN 33893 Tech.	420553-33	Inhalation exposure 6 hr. daily for 5 days to Wistar rats at 20, 109, and 505 mg/m <sup>3</sup> dust. Controls received conditioned air. All animals were observed for 14 days post treatment. LC50 > 505 mg/m <sup>3</sup> - Tentative. Necropsy observations: Dark spleen & isolated hepatic foci in high- dose (M) & (F) (high not assayed). Elevated triglycerides in high dose M. Decreased absolute liver weight in mid and high dose M & F. Maximum dust particle size was exceeded. Data submission is incomplete. Verification of particle size and distribution in chamber not possible due to absence of equipment calibration data.		Unacceptable 009375
82-2 Dermal-3 week Species: rabbit Bayer AG Instit. Fur Tox. Germ 17029592; 06/11/90	NTN 33893 Tech. 95.0%	422563-29	NTN 33893 tech. was admin. at 1000 mg/kg to shorn backs of 5 male & 5 female NZJ rabbits for 6 hrs/day, 5 days/week for 3 weeks. Systemic and Dermal NOEL = 1000 mg/kg. Sys & Dermal LOEL > 1000 mg/kg/d.		Minimum 009960
Inhalation-28 day Species: rat Bayer AG Instit. Fur Tox. Germ 13027365; 07/18/89	NTN 33893 tech., 95.2% batch# 180587	422730-01	NTN 33893 tech. was administered by inhalation (nose only) at: 0.006, 0.031, or 0.191 mg/L to 10 male and 10 female Wistar rats for 6 hrs/d, 5 d/wk, for 4 weeks. NOEL = 0.191 mg/L. LOEL > 0.191 mg/L.		Minimum 010537
84-2(a) Mutagenic-Ames Species: salmonella Bayer AG Instit. Fur Tox. Germ 80AC15; 11/26/90	NTN 33893 tech.	422563-63	Negative up to 5500 ug/plate.		Acceptable 010128
84-2(b) Mutagenic- in vitro cytogen. Species: mammalian cells Bayer AG Instit. Fur Tox. Germ 18030618; 08/15/89	NTN 33893 tech.	422563-64	Negative up to 2000 ug/mL.		Acceptable 010128

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CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(b) Mutagenic- in vitro cytogen. Species: mammalian cells Bayer AG Instit. Fur Tox. Germ 1703-167; 02/22/89	MTN 33893 tech.	422563-65	Negative up to 2000 ug/mL		Acceptable 010128
84-2(b) Mut- Chrom. aberr. in vitro Species: mice MT Bayer AG Instit. Fur Tox. Germ 10032852; 10/03/89	MTN 33893 tech.	422563-66	Negative up to (toxic) 50 mg/kg (i.p).		Acceptable 010128
84-2(b) Mutagenic-chromosome aberr. Species: mice MT Nihon Dobutsu Co. Japan 88S032; 11/29/88	MTN 33893 tech.	422563-67	Negative up to (toxic) 80 mg/kg (ip), a NON-TOXIC dose.		Unacceptable 010128
84-2(b) Mutagenic-chromosome aberr. Species: mice MT Bayer AG Instit. Fur Tox. Germ 11032853; 10/03/89	MTN 33893 tech.	422563-68	Negative up to 100 mg/kg (oral), a non-toxic dose.		Unacceptable 010128
84-2(b) Mutagenic-chromosome aberr. Species: mice MT Nihon Dobutsu Co. Japan 88S031; 11/29/88	MTN 33893 tech.	422563-69	Negative up to oral 160 mg/kg, toxic dose.		Acceptable 010128
84-2(b) Mut- Chrom. aberr. in vitro Species: Cytotest# T1032773 09/27/89	MTN 33893 tech.	422563-70	Negative up to 1000 ug/mL.		Acceptable 010128
84-2(b) Mut- Chrom. aberr. in vitro Species: Nihon Dobutsu Co. Japan 88P016; 11/05/88	MTN 33893 tech.	422563-71	Negative up to 1000 ug/mL.		Acceptable 010128

P.C. CODE 129099- Imidacloprid FILE LAST PRINTED: 03/14/94

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CITATION	MATERIAL	ACCESSION/ MRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-4 Mutagenic-DNA repair test Species: Hino # T40300 04/24/89	MTN 33893 tech.	422563-62	Negative up to 1333 ug/mL		Acceptable 010128
84-2(a) Mutagenic-Ames Species: salmonella Hino # 90A032 01/17/91	MTN 33893 tech.	422563-41	Negative for inducing reverse mutation in bacteria exposed to doses up to 5000 ug/plate.		Acceptable 010128
84-2(b) Mutagenic- in vitro cytogen. Species: CHO cells Bayer AG Instit. Fur Tox. Germ T5029536; 01/06/89	MTN 33893 tech.	422563-42	Negative for inducing forward mutation in CHO (mammalian cells) treated up to 1222 ug/mL.		Acceptable 010128
84-2(a) Mutagenic-Ames Species: salmonella Bayer AG Instit. Fur Tox. Germ T6030111; 01/06/89	MTN 33893 tech.	422563-43	Negative up to 12,500 ug/plate.		Acceptable 010128
84-2(b) Mut-Chrom aberr. in vivo Species: Bayer AG Instit. Fur Tox. Germ T8032562; 11/24/89	MTN 33893 tech.	422563-44	Negative for chromosome breakage up to 2000 mg/kg.		Acceptable 010128
84-2(b) Mut-Chrom. aberr. in vitro Species: Bayer AG Instit. Fur Tox. Germ T6029654; 06/16/89	MTN 33893 tech.	422563-45	Positive at 500 ug/mL - S9 and 1300 ug/mL +S9, both toxic doses.		Acceptable 010128
84-2(b) Mut- sister chrom ex; in vivo Species: Bayer AG Instit. Fur Tox. Germ T80303029; 06/16/89	MTN 33893 tech.	422563-46	Negative up to 2000 ug/kg.		Acceptable 010128

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CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(b) Mutagenic-chromosome aberr. Species: mice MT Bayer AG Instit. Fur Tox. Germ T7027161; 05/27/88	MTN 33893 tech.	422563-47	Negative, but only tested up to 80 mg/kg, a NON-TOXIC dose. Study unacceptable but a repeat not required at this time.		Unacceptable 010128
84-2(b) Mut- Chrom aberr. in vivo Species: Cytotest# T5032695 05/22/90	MTN 33893 tech.	422563-48	Negative, but only tested up to 80 mg/kg. Study is unacceptable, but a repeat not required at this time.		Unacceptable 010128
84-4 Species: Hazleton R4407; 04/21/88	MTN 33893 tech.	422563-49	Positive at 500 mg/mL -S9 and 2000 mg/mL +S9, both toxic doses.		Acceptable 010128
84-4 Species: 09/12/89 MA# T8302.334	MTN 33893 tech.	422563-50	Negative, but only tested up to 400 ug/mL -S9, 1250 ug/mL/+S9.		Acceptable 010128
84-4 Mutagenic-DNA repair test Species: 06/18/90 Hino# 90A013	MTN 33893 tech.	422563-51	Negative up to 5000 ug/disc.		Acceptable 010128
84-4 Mutagenic-DNA repair test Species: Hazleton Lab America HLA 10237-0-447; 12/21/88	MTN 33893 tech.	422563-52	Negative up to 750 ug/mL, a toxic dose.		Acceptable 010128
84-2(b) Mutagenic-recomb/converters assay Species: yeast Bayer AG Instit. Fur Tox. Germ T5025954; 06/27/88	MTN 33893 tech.	422563-53	Negative for crossing over in yeast up to 10,000 ug/plate.		Acceptable 010128

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CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(a) Mutagenic-Ames Species: salmonella Hino 90A015; 11/26/90	WAK-3839 (98.3%); batch TX 020390	422563-63	Negative for gene mutation in bacterial cultures exposed up to 5000 ug/pl		Acceptable 010537
84-4 Mutagenic-(NGPRT) Species: V79 cells Bayer AG Instit. Fur Tox. Germ T8030618; 11/15/89	WAK-3839 (98.3%); batch TX 020390	422563-64	Negative for forward mutation in Chinese hamster cells exposed to solubility limits (2000 ug/mL).		Acceptable 010537
84-4 Mutagenic-(NGPRT) Species: CHO cells Bayer AG Instit. Fur Tox. Germ T7030167; 02/22/89	WAK-3839 (94.3%); batch C-E	422563-65	Negative for mutation in Chinese hamster cells exposed to cytotoxic doses (2000 ug/mL).		Acceptable 010537
84-2(b) Mutagenic-micronucleus assay Species: mice Bayer AG Instit. Fur Tox. Germ T0032852; 10/03/89	WAK-3839 (98.9%); batch C-E	422563-66	Negative for inducing micronuclei in mice treated i.p. at the MTD, 50 mg/kg.		Acceptable 010537
84-2(b) Mut- Chrom aberr. in vivo Species: mice (Pilot) Mikon Shering 88S032; 11/29/88	MTN 37511 (96.5%); batch TX-19088	422563-67	Severely toxic at 100 mg/kg and above; no clastogenicity at doses up to 80 mg/kg. Pilot only. Not evaluated.		010537
84-2(b) Mutagenic-micronucleus assay Species: mice Bayer AG Instit. Fur Tox. Germ T1032853; 10/03/89	WAK 3839 (98.9%); batch C-E	422563-68	Negative for micronuclei in mice treated orally up to 100 mg/kg, a toxic dose.		Acceptable 010537
84-2(b) Mut- Chrom aberr. in vivo Species: 777777 Mikon Shering 88S031; 11/29/88	MTN 37571 (96.4%); batch# TX-19088	422563-69	Tested orally up to 160 mg/kg. Not evaluated; Pilot only.		010537

CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
81-1 Acute oral LD50 Species: rat Mobay Chem. 02/20/90	MTN 0.62% granular	420553-23	Study waived. Use data from study #89-012-DY (NRID 420553-24).		Waiver 009375

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CITATION	MATERIAL	ACCESSION/ NRID NO.	RESULTS	TOX CAT	COREGRADE/ DOCUMENT#
84-2(b) Mut- Chrom. aberr. in vitro Species: V79 hamster cells Cytotest; T103272 09/27/88	WAK 3389 (98.8%); batch# C-E	422563-70	Negative for chromosome aberrations in V79 hamster cells exposed to precipitating doses (1300 ug/mL).		Acceptable 010537
84-2(b) Mut- Chrom. aberr. in vitro Species: CHO cells Nikon Shering 88P016; 11/05/88	MTN 37571 (98.8%)	422563-71	Negative for inducing aberrations in CHO cells exposed to toxic levels (1000 ug/mL).		Acceptable 010537
84-4 Mutagenic-unscheduled DNA synt Species: rat hepatocytes Cytotest; T4030074 04/24/89	WAK 3839 (98.9%)	422563-72	Negative for DNA repair (UDS) in rat hepatocytes exposed to cytotoxic doses (1333 ug/mL).		Acceptable 010537
85-1 Metabolism Species: rat Bayer AG Instit. Fur Tox. Germ M1820175&M1810175; 11/20/87	MTN 33893 tech.	422563-54 422563-55 422563-56 422563-57 422563-73 422563-59 422563-58	MTN 33893 was rapidly absorbed & eliminated in the excreta (90% of the dose within 24 hrs) demonstrating no biologically significant differences between sexes, dose levels or route of administration. Elimination was mainly renal (70-80% of the dose) and fecal (17-25%). The major part of the fecal radioactivity originated in the bile. Total body accumulation after 48 hrs constituted 0.5% of the radioactivity with the liver, kidney, lung, skin and plasma being the major sites of accumulation. Therefore, bioaccumulation is slow in rats. Max. plasma conc. was reached between 1.1 & 2.5 hrs. Comparison between MTN 33893 and its major metabolite WAK 3389, showed that the total elimination was the same for both compounds.		Acceptable 010537
81-1 Acute oral LD50 Species: rat Mobay Chem. 89-012-DY; 02/26/90	MTN 33893, 2.5% granular	420553-24	LD50 > 4820 mg/kg (5000 mg/kg nominal, limit test) Necropsy Observations: None.	4	Acceptable 009375
81-1	MTN 33893 Tech.	420553-31	Male Sprague-Dawley rats dosed at: 0, 50, 100, 250, 315, 400, 450, 500 &	2	Acceptable

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81-1 Acute oral LD50 Species: rat Mobay Chem. 09/30/91	NTN 0.62% Granular	420553-23	Study waived. Use data from study #89-012-DY (NRID 420553-24).		Waiver 009375
81-1 Acute oral LD50 Species: rat Mobay Chem. 89-012-DV; 02/26/90	NTN 33893 240 F.S., 21% a.i.	422563-13	NTN 33893 240 F.S. was administered once by gavage to Sprague-Dawley rats (5/sex/dose) at: 0, 1030, 2100, 3595 and 4870 mg/kg for males, and 0, 2100, 3595 and 4870 mg/kg (F). Animals were observed for 14 days. LD50 (M) > 4870 mg/kg. LD50 (F) = 4143 mg/kg.	3	Acceptable 010079
81-1 Acute oral LD50 Species: rat Mobay Chem. 91-012-JJ; 08/27/91	NTN 33893, 75 WP-US, batch# 003-3005	422563-12	NTN 33893 75 WP-US was admin. once orally to 5 male & 5 female Sprague-Dawley rats per group at 1063, 2180, 2570 (females only) and 3170 mg/kg and observed for 14 days. LD50 (M) = 2591 mg/kg; slope = 2.3 LD50 (F) = 1858 mg/kg, slope = 5.4. NOEL < 1063 mg/kg.	3	Acceptable 010128
81-2 Acute Dermal LD50 Species: rat Mobay Chem. 09/30/91	NTN 33893 0.62% Granular	420553-23	Study waived. Use data from study #89-025-DS (NRID 420553-25).		Waiver 009375
81-2 Acute Dermal LD50 Species: rabbit Mobay Chem. 89-025-DS; 01/15/90	NTN 33893 2.5% Granular	420553-25	NZM rabbits dose at 0 and 2000 mg/kg. LD50 > 2000 mg/kg. Necropsy: None	3	Acceptable 009375
81-2 Acute Dermal LD50 Species: rat Mobay Chem. T 5033063; 11/15/89	NTN 33893 Tech.	420553-32	Sprague-Dawley rats dosed at 0 and 5000 mg/kg. LD50 > 5000 mg/kg (limit test). Necropsy Observations: None	4	Acceptable 009375
81-2 Acute Dermal LD50 Species: rat Mobay Chem. 89-025-EB; 02/22/90	NTN 33893 240 F.S., 21% a.i.	422563-15	NTN 33893 240 F.S. was administered once dermally for 24 hrs to NZM rabbits (5/sex/dose) at: 0 and 2000 mg/kg. Animals were observed for 14 days. LD50 > 2000 mg/kg.	3	Acceptable 010079



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81-2 Acute Dermal LD50 Species: rat Mobay Chem. 91-012-JH; 08/21/91	MTN 33893, 75 WP-US, batch# 003-3005	422563-14	MTN 33893 75 WP-US was admin. once dermally to 5 male & 5 female Sprague-rats per group at 2000 mg/kg and observed for 14 days. LD50 < 50 mg/kg. NOEL (local & systemic): < 2000 mg/kg (limit test). LOEL (local & systemic): 2000 mg/kg - urine stains; alopecia.		Acceptable 010128
81-3 Acute inhalation LC50 Species: rat Mobay Chem. 89-042-DX; 02/26/90	MTN 33893, 2.5% granular	420553-26	Sprague-Dawley rats dosed at 0 and 5092 mg/m <sup>3</sup> . LC50 > 5092 mg/m <sup>3</sup> (95% C.I. intervals) Tentative. Necropsy: None Data submission is incomplete. Verification of particle size & distribution in exposure chamber not possible. See deficiencies section.		Not Acceptable 009375
81-3 Acute inhalation LC50 Species: rat Bayer AG Instit. Fur Tox. Germ 16777; 06/06/88	MTN 33893 Tech.	420553-33	Wistar rats dosed at 69 mg/m <sup>3</sup> aerosol, 1220, 2577, and 5323 dust. Control received conditioned air or 20,000 µl Lutrol vehicle. LC50 > 5323 mg/m <sup>3</sup> (Tentative).		Unacceptable 009375
81-3 Acute inhalation LC50 Species: rat Mobay Chem. 89-042-EG; 02/27/90	MTN 33893 240 F.S., 21% a.i.	422563-17	MTN 33893 240 F.S. was administered as a liquid aerosol by inhalation once for 4 hrs to Sprague-Dawley rats (6/sex/dose) at: 0, 5060, and 5330 mg/m <sup>3</sup> . Animals were observed for 14 days. LC50 > 5330 mg/m <sup>3</sup> . NOEL < 5060 mg/m <sup>3</sup> . LOEL 5060 mg/m <sup>3</sup>	4	Acceptable 010079
81-3 Acute inhalation LC50 Species: rat Mobay Chem. 91-042-JZ; 09/25/91	MTN 33893, 75 WP-US, batch# 003-3005	422563-16	MTN 33893 75 WP-US was admin. for 4 hrs by inhalation to six male & six female Sprague-Dawley rats per group at analytically confirmed doses of: 0, 2.110, 2.810 or 2.990 mg/L & observed for 14 days. LC50 (M) = 2.650 mg/L. LC50 (F) = 2.750 mg/L.	3	Acceptable 010128
81-3 Acute inhalation LC50 Species: rat Mobay Chem. T202 5951& T402593; 06/06/88	MTN 33893 tech.	420553-33	MTN 33893 tech. was admin. by inhalation to 6 male & 6 female WISW (SPF-Cpb) Wistar rats for 4 hrs at 0.02, 0.100, 0.500, 1.220, 2.577, or 5.323 mg/L. LC50 (M&F): one 4 hr dose > 5.323 mg/L; five 6 hr doses: LC50 > .505 mg/L		Not Acceptable 009960
81-3 Acute inhalation LC50 Species: rat Mobay Chem. 16777; 06/06/88	MTN 33893 Tech.	422861-01	MTN 33893 tech. was admin. by inhalation to 6 male & 6 female WISW *SPF-Cpb) Wistar rats for 4 hrs at 0.02, 0.100, 0.500, 1.22, 2.577, or 5.323 mg/L. LC50 (M&F): one 4 hr. dose > 5.323 mg/L; 5 6-hr doses: > .505 mg/L	4	Acceptable 009960

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81-3 Acute Inhalation LC50 Species: rat Hobay Chem. 89-042-EG; 02/27/90	MTN 33893 Tech. 240 F.S	422563-17	NTN 33893 240 F.S. was admin by inhalation to 6 male & 6 female Sas(CD) BR rats for 4 hr. AT 5.06 at 5.33 mg/L. LC50 > 5.33 mg/L.	4	Acceptable 009960
81-3 Acute Inhalation LC50 Species: rat Hobay Chem. 91-042-JZ; 02/27/90	MTN 33893 Tech. 75 WP-US	422563-16	NTN 33893 75 WP-US was admin. by inhalation to 6 male & 6 female Sas(CD) BR rats for 4 hr AT 2.11, 2.99 or 2.81 mg/L. LC50 (M) = 2.65 mg/L. LC50 (F) = 2.75 mg/L	3	Acceptable 009960
81-4 Primary eye irritation Species: rabbit Hobay Chem. 92-335-PX; 10/12/92	MTN Granular 0.71% a.i. batch 233005 and 2030071	426744-02	Mild irritation.	3	Acceptable 010423
81-4 Primary eye irritation Species: rabbit Bayer AG Instat. Fur Tox. Germ T 802515; 02/25/89	MTN 33893 Tech. 94.2%	420553-34	NZW rabbits given 0.1 mL of test substance in one eye. TIS: Primary Irrit. Index = 0. Non-irritating. Minimal redness (1 animal & swelling (1 animal) observed 1 hr. post-dosing; was completely gone at 24 hrs.	4	Acceptable 009375
81-4 Primary eye irritation Species: rabbit Hobay Chem. 89-335-DT; 01/15/90	MTN 33893 2.5% granular	420553-27	NZW rabbits received 0.1 mL of pulverized test substance/animal. Reversible irritation by 14 days. TIS Time 1 hr 24 hr 48 hr 72 hr 7 d 14 d Iris Irrit Score 2.3 1.2 1.0 0.5 0.2 0.0 After reevaluation, the 72 hr. and 7 day effects are not considered positive effects (DER 010423).	3	Acceptable 009375 010423
81-4 Primary eye irritation Species: rabbit Hobay Chem. 89-335-IG; 12/11/90	MTN 33893 0.5% granular	420553-30	NZW rabbits received 0.1 mL of test substance. Moderate conjunctival irritation reversible by 7 days. TIS: Time 1 hr 24 hr 48 hr 72 hr 7 d Irrit. Score: 2.5 1.3 1.0 0.7 0.0	3	Acceptable 009375
81-4 Primary eye irritation Species: rabbit Hobay Chem. 89-335-DZ; 01/15/90	MTN 33893 240 F.S., 21% a.i.	422563-19	NTN 33893 240 F.S. was introduced into the conjunctival sac of one eye of 6 NZW rabbits (3/sex) at 0.1 mL. The other eye served as a control. Animals were observed for 14 days. TIS: TIME 1 hr. 24 hr. 48 hr. 72 hr. 7 d 14 d IRRITATION Score 1.0 0.3 0.2 0.0 0.0 0.0	3	Acceptable 010079

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81-4 Primary eye irritation Species: rabbit Mobay Chem. 91-335-JK; 06/25/91	NTN 33893, 75 WP-US, batch# 003-3005	422563-18	NTN 33893 75 WP-US was introduced into the conjunctival sac of the left eye of six male NZW rabbits at 0.1 ml of pulverized test material/animal. The right eye served as a control in each animal. Animals were observed for 14 days. Minimal irritation, resolved by 7 days.	3	Acceptable 010128
81-5 Primary dermal irritation Species: Mobay Chem. 09/30/91	NTN 33893 0.62% Granular	420553-23	Study waived. Use data from study #89-325-ED (MRID 420553-28)		Waiver 009375
81-5 Primary dermal irritation Species: rabbit Mobay Chem. 89-325-ED; 12/11/90	NTN 33893 2.5% granular	420553-28	4 hr dermal exposure to NZW rabbits at 50 mg/animal & observed for 72 hrs. PIS = 0.0. Nonirritating.	4	Acceptable 009375
81-5 Primary dermal irritation Species: rabbit Bayer AG Instit. Fur Tox. Germ T 8025515; 02/25/88	NTN 33893 Tech.	420553-35	4 hr dermal exposure to NZWrabbits at 500 mg/kg. PIS = 0.0 (non-irritating).	4	Acceptable 009375
81-5 Primary dermal irritation Species: rabbit Mobay Chem. 89-325-DU; 01/15/90	NTN 33893 240 F.S. 21% a.i.	422563-21	NTN 33893 240 F.S. was administered for 4 hrs. once dermally to shaved backs of 6 NZW rabbits (3/sex) at 500 mg/animal, & observed for 7 days. P.I.S.: = 0.0 Non-irritating.	4	Acceptable 010079
81-5 Primary dermal irritation Species: rabbit Mobay Chem. 91-325-JG; 08/15/91	NTN 33893, 75 WP-US, batch# 003-3005	422563-20	NTN 33893 75 WP-US was admin. for 4 hr. once dermally to shaved backs of six male NZW rabbits at 500 mg/animal, and observed for 7 days. PIS: 1.08 (mildly irritating).	4	Acceptable 010128
81-6 Dermal sensitization Species: Mobay Chem. 09/30/91	NTN 33893 0.62% Granular	420553-23	Study waived. Use data from study #89-324-DN (MRID 420553-29) Not a sensitizer.		Waiver 009375

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B1-6 Dermal sensitization Species: guinea pig Kobay Chem. 89-324-DN; 12/11/90	MTN 33893 2.5% granular	420553-29	Not a sensitizer to Hartley guinea pigs.		Acceptable 009375
B1-6 Dermal sensitization Species: guinea pig Bayer AG Instit. Fur Tox. Germ T 902561; 03/15/88	MTN 33893 Tech.	420553-36	Not a sensitizer to DHPW guinea pigs.		Acceptable 009375
B1-6 Dermal sensitization Species: guinea pig Kobay Chem. 89-324-DO; 02/22/90	MTN 33893 240 F.S. 21% a.i.	422563-23	MTN 33893 240 F.S. was administered, in 3 6 hr. topical induction applications followed by one 24 hr. topical challenge 14 days later, to shaved backs of 15 Hartley albino guinea pigs. Conclusion: Not a sensitizer.		Acceptable 010079
B1-6 Dermal sensitization Species: guinea pig Kobay Chem. 91-324-JC; 08/23/91	MTN 33893, 75 WP-WS, batch# 003-3005	422563-22	MTN 33893 75 WP-WS was admin. to shaved backs of 10 male DHPW guinea pigs at 0.4 mL of 7.5% (w/v) suspension per animal, following the induction/sensitization protocol. One week prior to the topical induction intradermal induction was performed with 3 x 1 mL injections/animal. Not a sensitizer.		Acceptable 010128