UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

5

DATE: October 13, 1978

SUBJECT: Request for a tolerance of 2 PPM of Imazalil in whole bananas and 0.2 PPM in the edible pulp. PP#8E2100 - Caswell ~~333F~~ 497AB pc 111901

FROM: Carlos A. Rodriguez — Carlos A. Rodriguez 11-3-78
TOX/HED TS-769

Doc. Desc. of ?
accn 097134 ?

TO:

Product Manager#21

Petitioner: Chevron Chemical Co.
Ortho Division
Richmond, California

Recommendations:

A complete human hazard assessment is not possible at this time due to the toxicity data gap consisting of at least an oncogenic study in a second species.

Residue Chemistry Considerations:

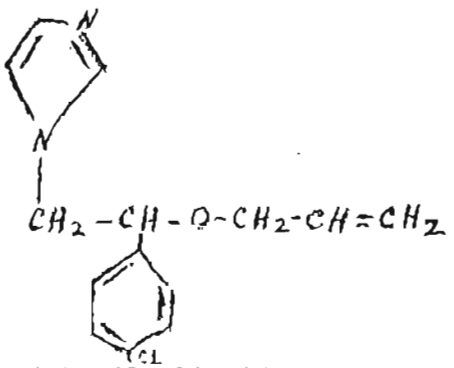
A. Substance Identification:

1. Chemical Name: 1- 2-(2,4-dichlorophenyl)-2-(2-propenyloxy)-ethyl -1H-imidazole.

2. Common Name: Imazalil

3. Alternate Names:
   a) R23979 for Imazalil free base
   b) R27180 for Imazalil sulfate salt
   c) R18531 for Imazalil nitrate

4. Structural Identity:



5. Empirical formula: $C_{14}H_{14}Cl_2N_2O$

6. Molecular Weight: 297.18

7. Physical State: Slightly yellow to brownish oily liquid. The sulfate salt

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is an off-white to beige colored powder.

8. Boiling Point: 347°C

9. Melting Point: 130°C for the sulfate salt

10. Vapor Pressure: 7 X 10^{-8} mm/tg at 20°C

11. Solubility: Freely soluble in lower alcohols and aromatic hydrocarbons. Less soluble paraffinic hydrocarbons and only slightly soluble in water.

    The sulfate salt is freely soluble in water and lower alcohols.

12. Stability: Both Imazalil and its sulfate salt are stable at room temperature in the absence of light. In a light exposure chamber at 30°C., exposed to 25,000 LUX for 15 days, imazalil shows a slight decomposition while the salt does not. Predict shelf life for Imazalil is at least two years.

13. Purity of the technical material.

    A minimum of 97.5% imazalil

    The principal impurities are:

[redacted]

B. Related Petition: None

C. Formulations:

I. Emulsion Concentrate

1. Active Ingredient

Imazalil 1-[2-(2,-4-dichlorophenyl)-2-(propenyloxy)ethyl] -1H-imidazole ----------.46%

Inert Ingredient

[redacted]

Manufacturing process information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment

2. Active Ingredient

Imazalil 1- [2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl] -1H-imidazole--75.2

Inert Ingredient

[redacted]

II. Inert Clearance: cleared by Mr. David Ritter (8-9-78).

(1) [redacted]

(2) [redacted] Cleared.

D. Uses Proposed: Fungicide

(1) Uses: For the control of the Sigatoka, Black Sigatoka and Black Leaf Streak diseases on bananas.

(2) Application: To be applied at the rate of 200-400 ml. per hectare in spray oil or oil-in-water emulsion. For aerial application, a minimum of 10 to 12 liters of the spray mix per hectare is recommended. Depending on the infection conditions the spray intervals recommended are 2 to 3 weeks throughout the complete crop cycle.

E. Toxicological Studies:

The results of these studies are summarized below:

Technical Product (Imazalil Free-Base

Study	Species	LD_{50} mg/kg	95% C.L. mg/kg
I Acute Oral	Rat (M)	320	253-405
II Acute Dermal	Rat (M & F)	4,200 (M) 4,880 (F)	2966-5498 3144-7575
III Acute Oral	Dog (M & F)	640	- -
IV Acute Inhalation (20% E.C.)	Rat (M & F)	>16 g/m^3	- -
V Eye Irritation (1,000 and 2,000 ppm)	Rabbit (M)	Slight Irritation	
VI Eye Irritation (98%)	Rabbit	Severe Irritation	

(continued from page 3)

Study	Species	LD_{50} mg/kg	95% C.L. mg/kg
VII 6 months, 1 & 2 years feeding study	Rat (M & F)	N.E.L. 5.0 mg/kg	
VIII 3-Generation Study (5,20, and 80 mg/kg)	Rat	Reproductive performance not affected	
IX Feeding Study (4 weeks)	Hen	Egg production and reproduction not affected.	
X Cumulative Oral	Rat	N.E.L 200 mg/kg	
XI Mutagenic (dominant lethal) (20 and 120 mg/kg)	Mice (M & F)	Not a mutagenic	
XII Acute Oral (20% E.C.)	Rat (M & F)	LD_{50} 374 (284-488) mg/kg.	
XIII Acute (I.P.)	Rat (M & F)	LD_{50} = 287 mg/kg (M) LD_{50} = 154 mg/kg (F)	
XIV Oral Fertility (5,20 and 80 mg/kg)	Rat (M & F)	Fertility not affected.	
XV Subchronic Oral (2-year) (1.25, 5 and 20 mg/kg)	Dog (M & F)	N.E.L 1.25 mg/kg	
XVI Oral-3 Generation Study	Rat (M & F)	N.E.L 80 mg/kg	
VXII Teratogenic and Embryotoxicity (5, 20 and 80 mg/kg)	Rat (F)	No Teratogenic or embryotoxic effects.	
XVIII Metabolism	Rat	No retention in fatty tissues, little tissue retention.	

Technical (Imazalil nitrate - R18531)

Study	Species	LD_{50} mg/kg	95% C.L. mg/kg
XIX Subacute Dermal (20% Conc.)	Rat	No effects	
XX Oral Dietary (14 weeks)	Rat	N.E.L. = 20 mg/100 g food .	
XXI Acute Oral	Rat	LD_{50} = 376.1 mg/kg.	
XXII Teratogenicity and Embryotoxicity	Rat	Non-teratogenic	

Technical - Imazalil Sulphate - R27180

XXIII Acute Oral	Rat	LD_{50} = 550 (421-719) mg/kg.	

F. Toxicological Review: (Volume I, of 2 Volumes)

1. Acute Oral LD_{50} of Imazalil (R23979) free base, in rats September 1974.

30 male Wistar rats were distributed into 3 groups, each composed of 10 males each. The weight range for the rats was 245 $\pm$ 25 g. The dosages administered by oral gavage were 160, 320, and 640 mg/kg. Behavior, mortalities and toxic signs were recorded - 1, 3, 6, 24, 48, 72 and 168 hours after administration.

Results:

LD_{50}: 320 (253-405) mg/kg. (male rat)

At 160 mg - no abnormal behavior.

At 320 mg - slight tremor and mild clonic seizures. 5 animals died within 72 hours.

At 640 mg - slight tremors and clonic seizures, ataxia and hypotonia. All animals died within 24 hours.

TOX Category: II

Classification: Supplementary Data
(1) rat female not were tested.

2. Acute Dermal Toxicity in Rats, Imazalil free base (R23979), Experiment No.583, Janssen Research Laboratories, Beligium, 4-23-75)

20 male and 20 female albino Wistar rats (average weight 180 g) has their hair removed from the back and flanks. The dosages administered of the test material (placebo and imazalil) were 2, 560 and 5, 120 mg/kg. Control animals, 6 male and 6 female received arachid oil. The test material was in contact with the skin for 24 hours. The material was covered with a plaster sufficiently tightened to prevent the rats wriggling free. At the end of 24 hours the plasters were removed and the animals observed for further 7 days.

Results:

LD_{50} - 4,200 (2966-5948) mg/kg for male rats
LD_{50} - 4,880 (3144-7575) mg/kg for female rats

At 2,560 mg/kg - 1 male and female died.

At 5,120 mg/kg - 5 males out of 10 and 3 females out of 10 died.

All control group of animals survived.

TOX Category: III

Classification: Core-Minimum Data

3. Acute Oral LD_{50} of Imazalil (R23979) in Dogs, March-April 1975, (Janssen Research Labs., Belgium)

Imazalil (R23979) was given orally to 5 dogs (3 male and 2 female) at the dose of 160 mg/kg and to 3 dogs (1 male and 2 female) at a dose of 640 mg/kg Since the dogs at 640 mg/kg vomited within 15 minutes, higher dose were not given. The dogs were individually caged and observed for 7 days.

Results:

LD_{50} > 640 mg/kg

Toxic Signs: vomiting and diarrhea, no other toxic signs observed.

TOX Category: III

Classification: Core-Minimum Data

4. 6 months, 1 year, 2 years rat feeding study with Imazalil (base) R23979, Experiment No.480, 8-30-75, Janssen Research Labs., Belgium)

Protocol: 40 M - 40 F fed 5, 20 and 80 mg/100 g food - 6 months
40 M - 40 F fed 5, 20 and 80 mg/100 g food - 1 year
40 M - 40 F fed 5, 20 and 80 mg/100 g food - 2 years
Control - Dosed basic laboratory diet.
Observations and tests included mortality, behavior, appearance,

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food consumption, body weight, haemotology, urinalysis, serum analysis, gross pathology, organ weight and histopathology. (Rat age - 6-8 weeks and weight 160 - 198 g).

Results:

Mortality - 42 animals died during the 6, 12 and 24 month study - No dose related was evidenced.

Behavior & appearance - divergent observations in both dosed and control animals, but no drug related effects seen.

Haematology - normal value in all groups, except a marginal increase of white blood cells count in the 24 month - 80 mg/100 g food dosed, a marginal increase of segmented heterophils and decrease of lymphocytes in the 20 and 80 mg dosed males.

Serum analysis - normal values in all groups.

Urinalysis - normal values in all groups.

Gross Pathology - divergent necropsy findings in both dosed and undosed animals. No dose related effect seen.

Organ weight - 6-month study-normal values. - 12 month study - a marginal increase weight of the liver, brain and kidneys in the 80 mg dosed males. - 24 month- study - marginal increase of kidney weight in the 80 mg dosed females.

Histology - 6 month study - some centrilobular swelling, fatty surcharge and numerous vacuoles in the liver at 80 mg dose rats particularly the females. Also some heavier amount of glycogen in centrilobular areas. Also some reduction in the outer cortical fat of the adrenals was noted. The 20 mg dosed animals were normal. - 12 month study - same alterations in the liver as in the 6 - month study for the 80 mg dosed animals. Some 20 mg dosed animals showed the same liver alterations whereas the 5 mg dosed animals rats were comparable to controls. - 24 month study, the changes observed were dose normally expected in ageing animals and no difference were seen between controls and the 80 mg dosed animals. All organs and tissues were comparable to the control group, except for a slight liver alteration.

Food Consumption - no adverse effects when rats dosed at 5, 20 or 80 mg/100 g food.

Systemic NEL = 5.0 mg/100 g food providing $\pm$ 5 mg/kg/day in the rat.

5. Acute Inhalation Toxicity Study with R23979, 20% E.C. in Rats, Report#R4806, (Janssen Research Laboratories, Belgium, October 1975).

Protocol: 5 male and 5 female rats (weight of male 213-224g., weight of female 125-136g.) were exposed for four hours to a fine dispersion of R23979-20% E.C. at a concentration of 16 g/m^3 of air. The animals were observed for 14 days. Autopsy, macroscopic observations done on all animals.

Results:

It appeared that a four-hour exposure to a fine dispension of R23979 - 20% E.C. at concentrations of 16 g/m^3 of air produced no mortality or grossly visible injury. It is unlikely that the substance will occur at higher concentrations in practive, this result indicates that the product presents little acute inhalation hazard.

6. Eye Irritation Study with Imazalil base: R23979, Experiment No.611 (10-31-75), (Janssen Research Laboratories, Belgium)

4 groups each consisting of 6 adult healthy male New Zealand White rabbits, were selected for this study. One group received placebo (control) for 7 consecutive days and the other groups received respectively 1 drop once of R23979 as a technical 98% formulation, 0.1 ml R23979 (2000 ppm) in arachid oil 7 days, 0.1 ml R23979 (1000 ppm) as a water-soluble sulfate form (27180) 7 days. The formulations were instilled into the left eyesac of each rabbit. The right eye served as a control. The animals were kept in restraining boxes for one hour to prevent them fron scratching their eyes.

Results:

1000 ppm R23979 - 0.1 ml. 7 days - One hour after treatment only one rabbit had grade 1 for conjunctivae redness.

2000 ppm R23979 - 0.1 ml 7 days - One hour after treatment 5 rabbits out of 6 had grade 1 for conjunctivae redness and this persisted in 3 rabbits up to 24 hours.

98% R23979 - One drop once - ocular lesions were observed in the treated eyes of all rabbits. The effects lasted for several days. One rabbit exhibited corneal opacity (1) at 7 days observation period. Another rabbits exhibited iritis (1) at 7 days observation period, the same two rabbits exhibited discharged (1) at 7 days observation period. 4 rabbits the readings were (0) at the 7 day observation period.

TOX Category: I

Classification: Core-Minimum Data

7. 3-Generation Wistar Rat Reproduction Study: R23979, Experiment No.616, 11-18-75, (Janssen Research Laboratories, Belgium)

Protocol: 80 virgin female rats, 3-4 months old and weighing 181-220 g were divided into four comparable groups. They were kept in a acclimatize room for at least one week before the start of the experiment and coupled with bleeding males. From day 6 through day 15 of pregnancy, the females were treated with Imazalil (R23979) at doses of 0, 5, 20 and 80 mg/kg. Eighty virgin females born from treated mothers were mated with 40 males also born from mothers treated in the first generation study. Treatment was the same dose levels as their mother In the third generation study, 80 females and 40 males were chosen among the young animals born in the second generation. (continue on next page)

The females were treated daily at the same dose-levels as the second generation; from weaning until 3 months of age and further from day 1-21 after mating; they were killed the morning of the 22nd day after insemination. Observations included:

1. Dams : body weight, food consumption, mortality, pregancy and gestation period.

2. Litter: cannibalism (I & II generation), size, weight at birth and at 2 and 3 weeks after birth (I & II generation)
no. of live, dead and resorbed fetuses (III generation)survival of pups, 4 days, 2 and 3 weeks after delivery (I & II generation), abnormalities.

Results:

Weight - normal increase in all groups.

Mortality - no mortality occurred except one control female died in the second generation.

Pregnancy and gestation - no differences between groups.

Offspring-no embryotoxic effects.

Abnormalities - Third generation.

Control - 2 fetuses born with waved ribs.

Medium dose - 1 small size fetus born.

High dose - 2 fetuses born with waved ribs.
- 1 fetus showed absence of metatarsal bones of left hind leg.
- 1 fetus showed absence of metatarsal bones of right hind leg.
- 1 fetus showed absence of metacarpal bones of right fore-leg.

Conclusion - Reproductive performance at 5, 20 and 80 mg/kg not affected.

8. Feeding Study with Fodder treated with Imazalil and Imazalil plus Panoctine to domestic hens, (Janssen Research Labs., 10-12-75)

The experiment: (4 weeks feeding)

A pre-period experiment started on April 15, 1975 before the test period experiment started in which all animals consumed commercial egg-laying fodder. The animals were weighed at the beginning and at the end of the period. On May 30, 1975 through June 27, 1975, the real test experiment started. 174 Hisex white egg-laying hens, 26 weeks of age weighing between 1535-1541 g and 20 White Leghorn cocks, 38 weeks of age and weighing between 2065-2022 g were divided into 3 groups (1, 6 and 16). Group 1 consumed commercial egg-laying fodder with Imazalil, group 6 consumed commerical egg-laying fodder with Imazalil plus Panoctine, group 16 consumed commerical egg-laying fodder alone (Control group). All the fodder was in the form of a fine ground meal.

Consumed material:

Group I - 120 g/animal/day.

Group VI - 53 g/animal/day.

Group XVI - 116 g/animal/day.

Results:

Group I - Commercial egg-laying fodder plus Imazalil did not effect the fodder consumption, egg production nor reproduction ability. No gross effects reported.

Group VI - Reduced fodder consumption less than half of the consumption of the other groups, the egg-laying stopped entirely and the animals had lost weight considerably. This was due that Panoctine showed to be strongly repellent. This group gave a decrease in weight of about 22% of the body weight. These animals regained weight within the two following weeks on unmixed fodder. No other gross effects reported. Panoctine does not seem to give any irreversible damage.

Group XVI- The weight increase was higher than group I and VI. This may be due that the fodder in the test groups contained somewhat less energy by adding the seed dressing to the unmixed laying fodder.

No histopathology reported on this experiment.

9. Cumulative Oral Toxicity Study in Wistar Rats with R23979, Experiment No.644 (3-18-76). (4 weeks), (Janssen Research Lans., Belgium)

60 Wistar rats were distributed into 3 groups each composed of 10 male and 10 female animals. The weight ranges were 267-286 g for males and 248-277 g for females. The dosages administered by stomach tube were 0, 100 and 200 mg/kg. The dose animals received the compound 6 days a week for 4 weeks in a volume of 1 ml/300 g rat. Initial and body weights, mortality, toxic and pharmacological response, food consumption, were recorded during test and 8 weeks further.

Results:

Mortality - none, except one high dose died accidentally during a further 2-week observation period.

Behavior and appearance - Control group: slight diarrhea, some temporary hairloss, some crusts on the jaws and behind the ears.

Low Dosage Group: (100 mg/kg) - some crusts on the jaws.

High Dosage Group: (200 mg/kg) - slight diarrhea, some temporary hairloss.

Slit-lamp examination - no abnormalities of the eyes were seen.

Discussion - some diarrhea, some hairloss and crusts on the jaws and ears were seen in the controls as well in the dosed animals, therefore it is concluded that R23979 when administered daily for 4 weeks at doses of 100 and 200 mg/kg does not affect the health, behavior and appearance of Wistar rats.

10. Dominant Lethal Test in Male Mice, Exp. No.649, 4-6-76, Janssen Pharmaceutics, Research Labs., Belgium. (Imazalil-R23979)

Protocol: 30 fertile male mice were divided into 5 groups of 6 males each and were dosed with 0, 10, 40 and 160 mg/kg of R23979 (Imazalil). The test material was administered in arachid oil. Control males received arachid oil only. Positive control males were dosed orally with 210 mg/kg cyclophosphamide (Endoxan Asta). The female mice were left undosed. At weekly intervals for a total of 8 weeks, 4 virgin females and 1 male were arranged to mate. Complete autopsies were performed on all females 15 days after introduction to a male. Mortality, pregnancy, corpora lutea early and late embryomic deaths and total implants were recorded.

Results: Mating frequency, total implantation, early and late dead foetuses compared to controls and no adverse effects could be evidenced. Positive control groups, the number of embryonic deaths was found to be significantly increased compared with the controls. This result occurred in the first three weeks indicating a spermatids, testicular and epididymal spermatozoa were affected.

Evaluation: This experiment did not demonstrate any dominant lethal mutations induced by R23979 (Imazalil) in any stages of the mice germ cells.

11. Dominant Lethal Test in Female Mice, Experiment No.650 (4-8-76), Janssen Pharmaceutica, Research Labs., Belgium.

Protocol: 50 fertile female mice were divided into 5 groups of 10 females each and were dosed 0, 20, 160 mg per kg of R-23979 (Imazalil). The test material was administered in arachid oil. Control females received orally arachid oil only. Positive control female received orally 210 mg/kg cyclophosphamide (Endoxan: Asta). The male mice were left undosed. At weekly intervals for a total of 5 weeks, 50 undosed males were divided into 5 groups of 10 males each and coupled each with one female till mating occurs or for a maximum of 5 days. All females were autopsied between 11-13 days of pregnancy or between 13-17 days of presumed pregnancy when no vaginal plug was seem. Mortality, pregnancy, pseudopregnancy rate were recorded. Counts were done of corpora lutea, early and late embryonic deaths and total implants.

Results: Mortality, incidence of pregnancy and total implantations, early and late dead foetuses, pseudopregnancy, and corpora lutea were not different between control and dosed groups. As a contrast there was a very significant increase of the number of dead implants due to an increase of early deaths in the positive control groups.

Evaluation: This experiment did not demonstrate any lethal mutations induced by R23979 (Imazalil) in the female mice germ cells.

12. Acute Oral Toxicity of R23979-20% E.C. in Rats, Janssen Pharmaceutica, Department of Pharmacology, Belgium, August 1976

30 adult Wistar rat were distributed into 3 groups each composed of 5 male and 5 female animals. The weight range 250 ± 30 g . The dosages administered were 0.25 ml, 0.5 ml. and 1.0 ml. Mortalities and reactions were recorded during 7th day observation period.

Results: LD_{50} = 374 (286-488) mg/kg.

Toxic Signs: (0.25) exophthalmia, ataxia hypotonia, sedation.
(0.5 ml) ptosis, hypnosis hyperaemia, hypothermia and lacrimation.

TOX Category: II

Classification: Core-Minimum Data

13. Acute Intraperitoneal Toxicity of R23979 (Imazalil base), Department of Pharmacology, Janssen Pharmaceutica, Belgium, Jan. 1977

30 adultWistar rat were distributed into 3 groups each composed of 5 male and 5 female animals. The weight range was 262 ± 23 g. The dosage administered were 80, 160 and 320 mg/kg. Observations were made for mortality and toxic signs.

Results:

Toxic Signs: (80 mg/kg) - piloerection, hypertonia, hypotonia and ataxia.

(160 mg/kg) - exophthalmia, ataxia and convulsions.

(320 mg/kg) - salivation, sedation, tremors, exophthalmia, hypotonia, loss of righting reflex, convulsions, lung edema and dyspnea.

LD_{50} = 287 mg/kg (male rat)

LD_{50} = 154 mg/kg (female rat)

14. Oral Male and Female Fertility Study with R23979,(Experiment No.598, 3-3-77, Janssen Pharmaceutica, Research Labs., Belgium)

Protocol: 320 Wistar rats (160 males and 160 females) were distributed into 8 groups each containing 20 male and 20 female animals. The dosage administered were 0, 5, 20 and 80 mg/kg. Animals were sexually mature, males were 60 days old before first administration of the compound and treated for 60 days prior to mating and further will copulation. Females were 3 months old and they were treated for 14 days before being exposed to males and further throughout gestation. Virgin females in the prooestrus stage were coupled with breeding males, a treated animal was mated with a nontreated one. As soon pregnancy was noted, the female was isolated until partunation.

Parameters studied for dams were body weight, food consumption, mortality and pregnancy, and for litter number of implantation, size, and weight at birth, number and distribution of live, dead and resorbed embryos in each uterine horn and abnormalities.

Results:

Weight - increase among all dams of all experimert groups.

Food Consumption - no significant difference between controls and treated animals.

Pregnancy - no difference between the percent pregnancies of the various groups.

Mortality - one mortality occurred (male)

Offspring - an equal distribution of live, dead and resorbed fetuses was noted in each uterine horn for all groups no embryotoxic effects.

Fertility - not affected in male or females

Gross observation - Control group - absence of metataral bones left hind-leg and metacarpal bones of right fore-leg in one animal.

Low dose group - none

Medium dosed group - none

High dosed group - 3 fetus born with waved ribs and 2 animals had absence of metatarsal bones of right hind-leg.

Classification: Core-Minimum Study

15. Oral Toxicity Study in Beagle Dogs with Imazalil - base: R23979, Experiment#370, 04-12-77, (Janssen Pharmaceutica Research Laboratories).

Protocol: 24 young Beagle dogs, aged 189 and 212 days weighing from 6.30 to 14.90 kg were divided into 4 groups of 6 each and consisting of 3M and 3F. They were dosed 1.25, 5.0, and 20 mg/kg of Imazalil base: R23979 in gestation capsules for 2 years. Control groups was fed with arachid oil. Observations and tests included: Mortality, behavior and appearance, food consumption, body weight, E.C.G., blood pressure, complete blood counts serum analysis, urinalysis, gross pathology, organ weight and histopathology.

Results: Mortality - All animals survived the 24 months study.

Behavior and appearance - control group - normal.

1.25 mg/kg group - normal.

At 5 mg/kg group - slight decrease of appetite first 2 months.

At 20 mg/kg group - appetite decreased during entire study, abundant salivation and sporadic emesis.

Food Consumption - not measured accurately because of wastage at 1.25 mg. 5.0 mg and contro groups. At 30 mg/kg was lower than normal.

Body Weight: Control group and 1.25 mg/kg - normal.
At 5.0 mg/kg the weight gain was somewhat lower compared to controls.
At 20 mg/kg - lower during the first 5 weeks of dosing, after this period body weight was reach again followed by weight gain.

E.C.G. heart rate - normal value in all dogs.

Blood pressure - normal values within groups.

Ha ematology - normal values in all groups.

Serum analysis - Control group - normal
1.25 mg/kg group - normal
5.0 mg/kg group - normal
20 mg/kg group - decrease in calcium and increase of alkaline phosphatase.

Urinalysis - normal in all groups.

Gross pathology - no necropsy findings.

Organ Weights - normal in all groups.

Histopathology - Control group - normal
1.25 mg/kg - normal
At 5 and 20 mg - a slight glass aspect of the cytoplasms in the centrilobular areas of the liver.

Evaluation - The no-effect level for this experiment is considered to be 1.25 mg/kg.

Classification: Core-Minimum Data

16. Oral Three-Generation Study with Imazalil:R23979, (Experiment No. 736, Janssen Pharmaceutica, Research Labs., 3-15-78)

Protocol:	Group	F/M	R23979 (Imazalil)
	I	20/10	0.0 mg/100
	II	20/10	5.0 mg/100
	III	20/10	20.0 mg/100
	IV	20/10	80.0 mg/100

M and F parent rats were dosed from day 0 of mating and further till copulation. After copulation was established, the females were isolated until parturation. The F_1a a litter were removed and the parents were remated and the pregnant females were isolated again until three weeks after parturation when the young (F_1b) litter were ready for weaning. The F_2 generation was bred from the F_1b litter, three females and one male per F_1b litter were chosen and mated at the age of 3 months. In the same way an F_3 generation was bred from the F_2 litters. The F_1b and F_2b litter were placed on the same diet at weaning and further during the total period of the study. This was done to assure continous exposure to the substance. Observations included body weight, food consumption, mortality, pregnancy and gestation period for adult rats, litters with cannibalism, litter size, weight at birth and at 2 and 3 weeks after birth, number of live, dead and resorbed fetuses, survival of pups until 3 weeks after delivery and adnomalities.

Results: Reproductive performance was unaffected for all tests groups. No abnormalities and no embryonic effects. Litter size, weight and survival rate were normal. The percentage of live, dead and resorbed fetuses were normal.

Evaluation: No effect on reproductive performance to diets fed at doses of 5, 20, and 80 mg/100g food to the rat.

NEL = 80 mg/100g food.

Classification: Core-Minimum Data

17. Potential of R18531 for Embryotoxicity, and Teratogenic Effects in Rats Orally, Report No.356 (4-10-70), Jansses Research Labs.)

Protocol: 80 pregnant rats were dosed with 0, 5, 20 and 80 mg/100g food of R18531 (Imazalil nitrate) during days 6-15 of gestation. Pups were delivered on day 22nd of gestation by caesarean section. Observations included body weights of dams, food consumption, mortality of dams, pregnancies, offspring and abnormalities.

Results:

Average body weight - increase in weight among all the dams in all the groups.

Food consumption - no significant difference between control and dosed groups.

Pregnancy - comparable in all groups.

Abnormalities - 3 fetuses with waved ribs at 80 mg/kg. Investigator indicates that this is a commonly encounted feature in control pups of Wistar rats.

Offspring - no difference between control and dosed groups.

18. Subacute Dermal Toxicity of R18531 (Imazalil nitrate), Report No,362, 7-12-71, Janssen Pharmaceutica, Research Labs.)

Protocol: 80 adult Wistar rats (40 males and 40 females) were divided into 4 groups each containing 10 males + 10 females. Prior to topical application, the back of all animals was sheared. The compound was administered topically for 5 consecutive days at the following dose levels:

Group - Dosage Rate Applied:

I - Control - 1 ml. of 40g (Atlox 2.5g and Kaolin 37.5g) in 200 ml. of water.

II - Low - 1 ml of a 12.5g (R18531-20%, Atlox-5%, Kaolin 75%) in 200 ml of water.

III - Medium - 1 ml of a 50g (R18531-20%, Atlox-5%, Kaolin 75%) in 200 ml of water.

IV - High - 1g/day of a wettable powder of: R18531 - 20%
Atlox - 5%
Kaolin - 75%

Results: All animals survived the 5 day experiment. The health, behavior and appearance were normal in all animals. Body weight was comparable for control and treated groups. Food consumption was not affected in any of the groups. Serum analyses (phosphorous levels, haptoglobin, cholesterol, sulphydryls) gave normal results.

19. 14-Week Oral Dietary Study with R18531 (Imazalil nitrate) Exp. No.342, (Janssen Research Laboratories, Belgium, 7-20-72.)

Protocol: 80 Wistar rats, 6-8 weeks old, males weighing 166-195g and females 162-290g were divided into 4 groups (20M + 20F) each and dosed 0, 5, 20 and 80 mg/100g food of R18531 (Imazalil nitrate). The control group received the basic laboratory diet. The average daily dosage was: low dosage 4.2-4.4 mg/kg, medium dosage 16-17.4 mg/kg and high dosage 64-69.4 mg/kg. The following observations were made: nortality, behavior and apperance, food consumption, body weight, haematology, serum analysis, urinalysis, gross pathology, organ weight and histopathology.

Results: One control and one low dosed (5 mg/100g food) died accidentally. The 20 mg and 80 mg/100g food groups (male and females) survived the 14 week experiment. Behavior and appearance were normal in all groups, food consumption was not affected. Haemograms were normal in high dosed males somewhat higher values for juvenile forms were recorded. Serum analyses gave normal results in all groups, except in the 20 and 80 mg/100g food dosed males increased value for bilirubin were recorded. Urinalysis were also normal, but in the 80 mg/100g food dosed males a slight decrease of specific gravity and creatinine was recorded. Several differences seen in gross pathology relative to organ weights, however these differences felt within the range of normal values. The histological examination failed to reveal any effect, except the liver with some tendency to fatty surcharge and chronic stimulation of the hepatocytes at the 80 mg/100g food dose.

NEL = 20 mg/100g food.

20. Acute Oral Toxicity in Rats with R18531 (Imazalil nitrate), Janssen Pharmaceutica, May 1973)

Protocol: 30 male Wistar rats weighing 245 $\pm$ 25g were distributed into 3 groups containing 10 animals each. The dosages administered by oral intubation were 160, 320 and 640 mg/kg. Mortality was recorded for seven days after dosing.

Results: 160 mg/kg - no mortality occurred, no abnormal behavior observed.

320 mg/kg - one rat died, no abnormal behavior observed.

640 mg/kg - all rats died 10 of 10, ataxia, hypotonia and hyperthermia occurred within one hour after administration. All rats died within 24 hours after administration.

Calculated LD_{50} - 376.1 mg/kg.

Classification: Supplementary.

21. Oral Embryotoxicity and Teratogenicity Study in Wistar Rats with R18531 (Imazalil nitrate) during the Peri - and Postnatal Study, Experiment No.597, 8-28-75, Janssen Pharmaceutica Research Labs., Belgium.

Protocol: 80 female Wistar rats, 3 months and weighing 200 to 220g, were divided into 4 groups each containing 20 animals. They were coupled with breeding males and after incemination occurred the females were isolated until parturation. The compound was administered at dosages of 0, 5, 20 and 80 mg/kg/day 16 of pregnancy through a 3-week lactation period. Observations included body weight, food consumption, mortality and gestation period for dams, litters observation included cannibalism, number of live and stillborn fetuses, size, weight at birth, and at 2 and 3 weeks after birth, survival of pups and abnormalities.

Results: Normal increase in weight among all dams, at 0, 5, and 20 mg/kg. At 80 mg/kg food consumption decreased during the dosing period. Mortality - 5 out of 20 females died during the experiment at 80 mg/kg. Autopsy did not reveal the cause of death. Pregnancy - no difference between dosed groups and control. Offspring - no embryotoxic effects, except a decrease in litter size and an increased number of stillborn fetuses and the survival rate decreased in the 80 mg/kg high dosage group.

Conclusion: Imazalil (R18531) is not teratogenic to rat at 80 mg/kg.

Classification: Core-Minimum Data

22. Acute Oral Toxicity of Imazalil sulphate in Rats, Serial No.R27180/2, (Janssen Pharmaceutica Research Labs., Belgium, February 1978)

Protocol: 60 inbred Wistar rats, 30 males weighing 256 ± 19g and 30 females weighing 252 ± 18g were distributed into 3 groups composed of 20 animals each, 10 males and 10 females. The dosages administered by oral intubation were 160, 320 and 640 mg/kg. Mortality rate was observed for 14 days.

Results: LD_{50} = 550 (421-719) mg/kg.

Gross behavioral observations:

160 mg/kg - hypotonia, hypothermia, ataxia, tremors, exophthalmia in male and females, piloerection and diarrhea in female only.

320 mg/kg - hypotonia, hypothermia, exophthalmia, ataxia, piloerection, tremors and diarrhea in males and females.

640 mg/kg - hypotonia, hypothermia, exophalmia, ataxia, piloerection, tremors and prelethal loss of the righting reflex in males of the ptosis and sedation in males, and lacrimation, salivation, diarrhea and convulsions in female only.

TOX Category = III Classification: Core-Minimum Data

24. Metabolism of Imazalil (R23979) in rats, Janssen Pharmaceutica Labs., Belgium, December 1975).

Protocol: Two groups of five male and two groups of 5 female Wistar rats weighing 240-260g were fed 20 mg/kg. From each group of rats urine and feces were collected for two or four days. One male and one female group were sacrificed 48 hours after dosing, the two remaining groups after 96 hours. Residues in various animal tissues were analyzed.

Results: Imazalil was rapidly excreted in rats, since more than 80% of the dose was excreted within 48 hours. The amounts were comparable in both urine and feces. Tissue residue were low. Accumulation in fatty tissues did not occur.

Conclusion: There is little tissue retention, and no retention in fatty tissues. The major excretory routes are urinary and fecal. The major urinary metabolite appeared was hydrophilic compounds. Imazalil was metabolized in the rats mainly by oxidative O- and N-dealkylation.

G. Evaluation of ADI.

1. Prior tolerances - none.

2. Pending tolerances - none.

3. Temporary tolerances - none.

4. ADI determination:

(i) 2-year rat feeding study
Systemic NEL - 5.0 mg/kg.

(ii) 2-year dog feeding study
Systemic NEL = 1.25 mg/kg

Using a safety factor of 100 for systemic effect the ADI = 0.0125 mg/kg/day or MPI = 0.75 mg/person/day for a 60 kg person.

The exposure by a human to this chemical by the proposed tolerances will be 0.0043 mg/day. This is only 0.57% MPI. The MPI will not be exceeded. (Please, see attached computer printout).

TOX/HED:th:R.Engler:10-13-78

11/3/78

Chem No. 0 Shaughnessy No. 111 10/3/78

File last updated 10/3/78

ACCEPTABLE DAILY INTAKE DATA

LOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
1.250	50.00	100	0.0125	0.7500

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Bananas (7)	0.200	1.42	0.00426

MPI	TMRC	% ADI
0.7500 mg/day/60kg	0.0043 mg/day/1.5kg	0.57

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