

PACLOBUTRAZOL

(BONZI®)

RISK CHARACTERIZATION DOCUMENT

(8-1-93)

Medical Toxicology and Worker Health and Safety Branches

Department of Pesticide Regulation

California Environmental Protection Agency

PACLOBUTRAZOL

EXECUTIVE SUMMARY

INTRODUCTION

Paclobutrazol is an active ingredient which was developed by ICI Chemicals, and registered by the U.S. Environmental Protection Agency and by the State of California in two formulations (Trade names: Clipper E 20 *ul* and Clipper 20 *ul* Growth Regulator) as an injectable plant growth regulator for ornamental plants. This document concerns a new Section 3 registration for a different formulation (Trade name: Bonzi®) which can be sprayed on plants. Paclobutrazol diminishes plant growth through inhibition of gibberellin. Bonzi® may be used as a concentrate, or a wettable powder, and would be applied primarily in greenhouses. Paclobutrazol is not intended to be used on food products.

RISK ASSESSMENT PROCESS

Paclobutrazol was entered into the risk assessment process because of possible adverse effects identified in developmental toxicity studies and chronic toxicity studies. The risk assessment process consists of four aspects: hazard identification, dose response assessment, exposure evaluation, and risk characterization.

Hazard identification entails review and evaluation of the toxicological properties of each pesticide. The dose-response assessment then considers the toxicological properties and estimates the amount which could potentially cause an adverse effect. The amount which will not result in an observable or measurable effect is called the No-Observed-Effect Level, NOEL. A basic premise of toxicology is that at a high enough dose, virtually all substances will cause some toxic manifestation. Chemicals are often referred to as "dangerous" or "safe", as though these concepts were absolutes. In reality, these terms describe chemicals which require low or high dosages, respectively, to cause toxic effects. Toxicological activity is determined in a battery of experimental studies which define the kinds of toxic effects which can be caused, and the exposure levels (doses) at which effects may be seen. State and federal testing requirements mandate that substances be tested at doses high enough to produce toxic effects, even if such testing involves chemical levels many times higher than those to which people might be exposed.

In addition to the intrinsic toxicological activity of the pesticide, the other parameters critical to determining risk are the exposure level, frequency and duration. The purpose of the exposure evaluation is to determine the potential exposure pathways and the amount of pesticide likely to be delivered through those routes.

The risk characterization then integrates the toxic effects observed in laboratory studies conducted with high dosages of pesticide, to potential human exposures at low dosages. The likelihood of potential, non-oncogenic adverse health effects in people is generally expressed as the margin of safety- a ratio. The dosage which produced no effects in laboratory studies is divided by the human exposure dosage to obtain the margin of safety. For oncogenic effects, the excess lifetime risk of cancer is determined by multiplying the cancer potency of the pesticide times the estimated exposure dosage.

TOXICOLOGY

Based on the currently available toxicity information, DPR concluded that paclobutrazol causes adverse effects on liver function and developmental effects in rodents. DPR has further concluded that, in

the absence of additional data to the contrary, paclobutrazol has the potential to cause similar effects in humans.

WORKER EXPOSURE

Surrogate data were used to estimate potential exposure via dermal contact, and inhalation of mixer/loader/applicators spraying paclobutrazol on greenhouse plants. Exposure through the inhalation route was insignificant compared to potential dermal exposure. Greenhouse workers involved in tending the treated plants have potential occupational exposure through the dermal route.

CONCLUSIONS

Using laboratory animal toxicity data and surrogate worker exposure data, the calculated margins of safety (MOSs) for potential acute exposure of mixer/loader/applicators and greenhouse workers are considered adequate. MOSs for potential chronic occupational exposure to paclobutrazol are also considered adequate.

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I. SUMMARY

Paclobutrazol (Trade name: Bonzi®)((2RS,3RD)-1-[(4-chlorophenyl)methyl]-a-(1,1-dimethyl ethyl)-1H-1,2,4-triazole-1-ethanol) was developed by ICI Chemicals, and registered by the U.S. Environmental Protection Agency and by the State of California as a plant growth regulator for injection into ornamental plants. A new Section 3 registration under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for spraying paclobutrazol on plants has been requested. A risk assessment has been conducted because paclobutrazol induces hepatotoxicity and developmental toxicity in laboratory animals.

Environmental Fate- The half-life of paclobutrazol in soil varied from less than 84 to greater than 140 days under aerobic conditions, depending upon the amount of organic material in the soil. Photolysis did not affect the half-life of paclobutrazol in buffered solutions. The compound did not hydrolyze under acid, base, or neutral conditions. Paclobutrazol had a high octanol:water partition coefficient, had a low mobility in soil, and was degraded relatively slowly in soil.

Pharmacokinetics- Approximately 95% of an oral dose of paclobutrazol was absorbed by rats with an average of 60% excreted in the urine, and 35% excreted in the feces. Virtually all paclobutrazol, regardless of dose, was cleared within 168 hours. Paclobutrazol was converted in rats to diol and carboxylic acid metabolites, which were excreted both conjugated and unconjugated in the urine and bile. The highest tissue concentrations were found in the liver and gastrointestinal system, but paclobutrazol did not bioconcentrate in tissue. Studies with radiolabelled paclobutrazol demonstrated that it was absorbed dermally by rats at rates of between 5 to 28% at 24 hours.

Acute and Subchronic Toxicity- The oral LD50 for paclobutrazol for rats ranged from 1336 to 1954 mg/kg. The No Observed Effect Level (NOEL) for increase in absolute liver weight in rats from a single dose via gavage was 5 mg/kg. The 90 day dietary NOEL in rats for increase in relative liver weights compared to controls, increase in hepatic aminopyrine-N-demethylase activity, and reduction in the prothrombin time was 25 mg/kg-day.

Chronic Toxicity/Oncogenicity- Paclobutrazol was not oncogenic in either the rat or the mouse. In the dog, mouse, and rat the principal target for paclobutrazol was the liver. However, no major histopathological changes in the liver, such as cholestasis or necrosis, were observed. The NOEL for hepatotoxicity (increased absolute liver weight, hepatocellular swelling, elevation of alkaline phosphatase activity and hepatic aminopyrine N-demethylase activity) in the dog was 15 mg/kg-day. The NOEL for hepatotoxicity (increased absolute liver weight, steatosis of the liver) in the mouse was 15.4 mg/kg-day. In the rat, the 104 week NOEL for hepatotoxicity (centrilobular hypertrophy and steatosis), decrement in body weight gain and decreased serum triglyceride values in females was 1.6 mg/kg-day.

Genotoxicity- Paclobutrazol was not mutagenic in either the *Salmonella* or the mouse lymphoma mutagenicity assay. *In vitro* tests showed no effects on chromosomes, and there was no unscheduled DNA synthesis *in vivo*. Chromosomal aberrations were noted in an *in vivo* rat assay, and potentially clastogenic effects were indicated in a mouse micronucleus assay *in vivo*. The adverse effects observed in these *in vivo* cytogenetic assays were not confirmed in a subsequent mouse micronuclear assay, which used a different species and a route of administration different from the earlier mouse micronuclear assay. Based on all available data, the potential genotoxicity of paclobutrazol is equivocal.

Reproductive Toxicity- No adverse reproductive effects were noted in a two-generation rat reproduction study. The parental NOEL was 25 mg/kg-day for body weight gain decrement and hepatic centrilobular fatty change.

Developmental Toxicity- Paclobutrazol was not fetotoxic and caused no fetal abnormalities in two rabbit studies. The NOEL for maternal toxicity (decrement in body weight gain) was 75 mg/kg-day. In the rat, paclobutrazol caused developmental malformations in the urogenital system, cleft palate, and skeletal

abnormalities. The NOEL for developmental anomalies in rats was 10 mg/kg-day. The maternal NOEL (reduced body weight gain and food consumption, and urogenital staining) for rats was 40 mg/kg-day.

Hazard Identification- The acute NOEL, based on developmental abnormalities in the most sensitive species (rat), for the oral exposure route, was 10 mg/kg-day. The chronic NOEL for the oral exposure route, based on hepatotoxicity in rats, was 1.6 mg/kg-day.

Occupational Exposure- Workers involved in paclobutrazol application have potential exposure via dermal contact, and inhalation. Estimates of potential exposure were based on surrogate data from fluvalinate applications. Fluváinate has been applied in greenhouses at rates and label conditions similar to those proposed for paclobutrazol. Estimates of potential acute absorbed dosages from maximum use of paclobutrazol were 67.9 $\mu\text{g}/\text{kg}$ for mixer/loader/applicators, and 9.1 $\mu\text{g}/\text{kg}$ for greenhouse workers. Estimates of potential chronic absorbed dosages from maximum use were 6.5 $\mu\text{g}/\text{kg}\text{-day}$ for mixer/loader/applicators, and 6.0 $\mu\text{g}/\text{kg}\text{-day}$ for greenhouse workers.

Risk Characterization- The margins of safety from potential acute exposure to paclobutrazol were 147 for mixer/loader/applicators, and 1099 for greenhouse workers. Margins of safety for potential chronic exposures were 1538 and 1667 for mixer/loader/applicators and greenhouse workers, respectively.

Conclusions- Using laboratory animal toxicity data and surrogate worker exposure data, the calculated margins of safety (MOSs) for potential acute exposure of mixer/loader/applicators and greenhouse workers exceed 100 and are considered adequate. MOSs for potential chronic occupational exposure to paclobutrazol exceed 1000 and are also considered adequate.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Paclobutrazol ((2RS,3RD)-1-[(4-chlorophenyl)methyl]-a-(1,1-dimethyl ethyl)-1H-1,2,4-triazole-1-ethanol) was developed by ICI Chemicals, and registered by the U.S. EPA and California as a plant growth regulator for ornamental plants. Paclobutrazol diminishes plant growth through inhibition of the plant growth hormone, gibberellin (Lever *et al.*, 1982). It is not used on food crops. The previously registered formulations, Clipper[®] (U.S. EPA #10182-266), and Cultar[®] (U.S. EPA #10182-90) are ready to use liquids containing 2.56% active ingredient (paclobutrazol) injected into ornamental trees under pressure. Under the new Section 3 registration of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), paclobutrazol will come in the form of a liquid concentrate containing 0.4% active ingredient. It may be used for either foliar application or drenching the soil. The maximum application rate will be 0.23 pounds of active ingredient per 100 gallons.

B. FORMULATIONS

Paclobutrazol is the active ingredient in Bonzi[®], Clipper[®], and Cultar[®]. Bonzi[®] ornamental plant growth regulator comes as a liquid containing 0.4% active ingredient, and 99.6% inert ingredients.

C. USAGE

No data are available as the amount of paclobutrazol sold or used in California. No illnesses have been reported associated with the use of paclobutrazol in other formulations.

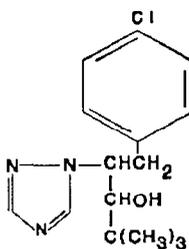
D. PHYSICAL AND CHEMICAL PROPERTIES^a

Chemical Name: (2RS,3RD)-1-[(4-chlorophenyl)methyl]-a-(1,1-dimethyl ethyl)-1H-1,2,4-triazole-1-ethanol

Common Name: paclobutrazol

Empirical Formula: C₁₅H₂₀ClN₃O

Chemical Structure:



Molecular Weight: 293.5
Melting Point: 165-166°C
Vapor Pressure: 8 x 10⁻⁶ mm Hg @ 30°C
Solubility (water): 35 ppm
Octanol:Water Partition Coefficient 1600

^a/ ICI, 1986

E. ENVIRONMENTAL FATE

Summary- The half-life of paclobutrazol in soil varied from less than 84 days to greater than 140 days under aerobic conditions, depending upon the amount of organic material in the soil. Photolysis did not affect the half-life of paclobutrazol in buffered solutions. The compound did not hydrolyze under acid, base, or neutral conditions. Paclobutrazol had a high octanol:water partition coefficient (Ney, 1990), had a low mobility in soil, and was degraded relatively slowly in soil.

Hydrolysis

The hydrolysis of ¹⁴[C]-paclobutrazol was studied in sterile distilled water in the dark (Woods and Leahey, 1983b). Hydrolysis was attempted at a concentration of 10 µg/ml at pH 4, 7, or 9 at 25°C. Following 30 days of incubation, analysis of the solutions indicated no discernible hydrolysis.

Photodegradation

Paclobutrazol at a concentration of 10 µg/ml in an aqueous pH 7 buffer solution was continuously irradiated for 10 days with light from a xenon arc lamp filtered through borosilicate glass to mimic sunlight (Woods and Leahey, 1983a). No statistically significant degradation of paclobutrazol occurred under these conditions.

Soil Metabolism

¹⁴[C]-triazole labelled paclobutrazol was applied to coarse sandy loam (18A) or a calcareous clay loam (Gore) at a concentration equivalent to 0.5 kg/ha, and incubated at 25°C with a 40% moisture holding capacity (Harvey *et al.*, 1982). Paclobutrazol degraded in Gore soil, with a half-life less than 84 days. In the 18A soil, only about 30% degraded in 140 days. Approximately 11% of the radiolabel was lost as ¹⁴CO₂ from the Gore soil in 140 days. Only 1% was evolved as ¹⁴CO₂ from the 18A soil during the same period. After 140 days 37% of the radiolabel was not extractable from the Gore soil and 17% was not extractable from the 18A soil by either methanol soxhlet or n-hexane:acetone reflux. This seems to indicate a substantial amount of paclobutrazol (and/or metabolites) are bound irreversibly to the soil.

Soil Mobility

The mobility of ¹⁴[C]-triazole labelled paclobutrazol was determined by thick layer descending chromatography using 4 different soil types: Lilyfield (coarse sand with 0.7% organic matter), Frensham (loamy sand with 2.2% organic matter), 18A (sandy loam with 5.2% organic matter) and Gore (calcareous silt loam with 12.1% organic matter) (Hill and Prashad, 1982). Thirty centimeter long soil plates were treated with the equivalent of either 0.125 or 1.25 kg paclobutrazol per hectare, and then eluted with an equivalent of 32 cm of rain. The distances to the peak of radioactivity from the application point in coarse sand, loamy sand, calcareous silt loam, and sandy loam were: 5,2,2, or 3 cm respectively for the 0.125 kg/ha; and 1,5,3, or 5 cm respectively for the 1.25 kg/ha. Less than 10% (ranging from <2% - 9.6%) of the applied radioactivity was present in the leachates from the coarse sand, and less than 0.3% in the leachates from other soils. The concentration of paclobutrazol in the leachates was less than 0.006 µg/ml except for the 1.25 kg/ha rate applied to the coarse sand (0.5 µg/ml).

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

Summary- Approximately 95% of an oral dose of paclobutrazol was absorbed by rats. An average of 60% of the rats' oral dose was excreted in the urine, and 35% in the feces. Virtually all paclobutrazol, regardless of dose, was cleared within 168 hours. Paclobutrazol was converted in rats to diol and carboxylic acid metabolites, which were excreted both conjugated and unconjugated in the urine and bile. The highest tissue concentrations were found in the liver and gastrointestinal system, but paclobutrazol did not bioconcentrate in tissue. Radiolabelled paclobutrazol was absorbed dermally by rats at rates of between 5 to 28% at 24 hours.

Oral- rat

Wistar rats (3/sex) were given a single dose (10 mg/kg) of ^{14}C -paclobutrazol (99% purity, 1.76 GBq/mg) by gavage (Jones *et al.*, 1983). From 75 to 87% of the dose was eliminated within 48 hours. Males eliminated 32-48% in the urine and 44-61% in the feces. Females eliminated 48-56% in the urine and 34-41% in the feces. Tissue retention of radiolabel was minimal, and the pattern was the same in both sexes.

Sprague-Dawley rats (4/sex) were given a single dose (5 mg/kg) of ^{14}C -paclobutrazol (98% purity, specific activity = 158.6 $\mu\text{Ci}/\text{mg}$) by gavage (Cresswell *et al.*, 1983). Within 48 hours, 80% of the radiolabel in males had been eliminated (52.4% in urine and 27.7% in feces), and 74% of the radiolabel in females had been eliminated (57.7% in the urine and 16.2% in the feces). After 168 hours, 96.4% had been eliminated from males, 58% in the urine and 37% in the feces. Females excreted 97.3%, 65% in the urine and 28% in the feces. Residual radioactivity was associated with the gastrointestinal tract and the liver.

Sprague-Dawley rats were given a single dose (250 mg/kg) of ^{14}C -paclobutrazol (97.5% purity, 158.6 $\mu\text{Ci}/\text{mg}$) by gavage (Cresswell *et al.*, 1984). No toxic or pharmacologic effects attributable to paclobutrazol were observed. There was no discernible difference between males and females in the routes of elimination. The overall elimination rate at this dose level, when compared to the 5 mg/kg dose level was substantially slower in the first 24 hours. However, 98% of the administered radioactivity was eliminated by 168 hours. Males and females excreted 51-54% in the urine, and 43-45% in the feces. Minor amounts of residual radiolabel were found associated with the gastrointestinal tract and the liver.

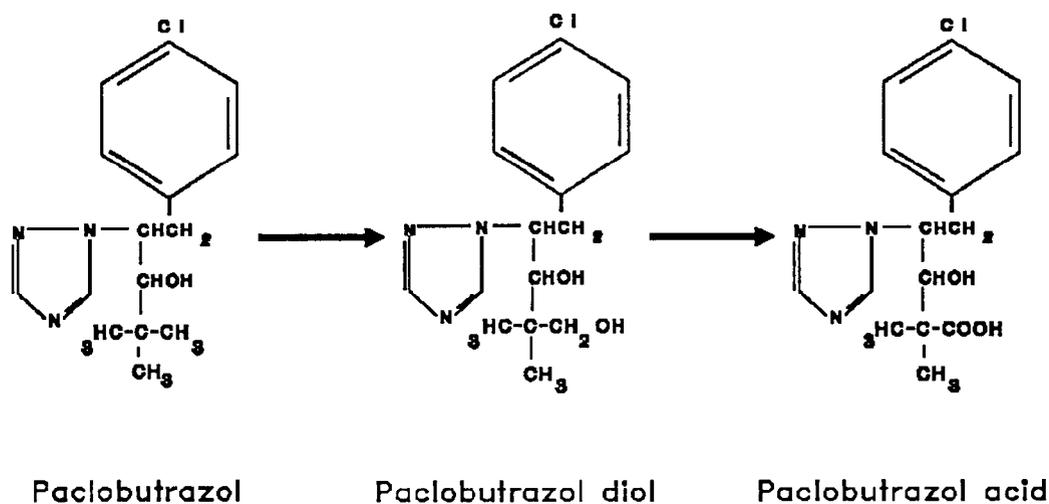
Male Sprague-Dawley rats were given repeated, single, daily oral doses (5 mg/kg-day) of ^{14}C -paclobutrazol (96.9% purity, 158.6 $\mu\text{Ci}/\text{mg}$) for 49 days with interim sacrifices for tissue sampling (Greenslade *et al.*, 1984). Levels of radioactivity in the liver and kidney appeared to plateau after the 28th day. A gradual increase of radiolabel in the blood was observed, but its mean peak level was lower than those in the liver and kidney. The tissue concentrations of radioactivity, expressed as μg equivalents of ^{14}C -paclobutrazol/g tissue, were 0.106 (blood), 0.116 (fat), 1.05 (kidney), and 2.22 (liver). After cessation of dosing, levels of radioactivity in the liver and kidney declined exponentially. Terminal half-lives in the liver and kidney were 6.7 and 9.3 days, respectively. No detectable residues were present in any tissues 28 days after the final dose.

The body tissues of Alpk/AP male and female rats were examined autoradiographically following a single oral dose (250 mg/kg) of ^{14}C -paclobutrazol (98% purity, 1.68 MBq/mg) by gavage (Jones *et al.*, 1984a). Autoradiographs from male and female rats revealed the majority of radiolabel associated with gut contents. Some radiolabel was detected in the liver, kidneys, and peri-renal fat. However, no radiolabel appeared in any other tissues.

Alpk/AP rats were given ^{14}C -paclobutrazol (98% purity, 1.68 MBq/mg) by gavage in a single oral dose of 5 or 250 mg/kg (Jones *et al.*, 1984b). In cannulated animals at the higher dose, 5% of the dose

was not excreted in the bile or the urine, but was eliminated unchanged in the feces. This indicates that 95% of the oral dose of paclobutrazol was absorbed. Biotransformation in the rat is apparently limited to the tertiary butyl moiety, with no metabolism in either the triazole or halogenated phenyl ring (Figure 1). The two main metabolites, paclobutrazol diol and acid, were eliminated in the conjugated and unconjugated forms in the urine, bile and feces. All other metabolites were minor, and each amounted to less than 5% of the dose. Irrespective of the dose, male rats oxidized a greater proportion of paclobutrazol to the carboxylic acid metabolite (39-44% of the oral dose) than did the females (32% of a 5 mg/kg dose; 28% of a 250 mg/kg dose). The second oxidation step to the acid metabolite is saturable in the females, as shown by the greater proportion of the conjugated diol metabolite excreted in the urine (17% at 250 mg/kg compared to 25% at 5 mg/kg).

Figure 1 - Metabolism of paclobutrazol in the rat.



Dermal- Rat

¹⁴C-paclobutrazol (1.25, 0.12, 0.013, 0.003 or 0.001 mg/cm²) was applied to a 10 cm² area of exposed skin on male Wistar rats (10/dose) and covered with a protective non-occlusive device for either 10 or 24 hours (Jones, 1988). Five rats at each dose level were killed 10 hours after dosing, and the remainder were killed at 24 hours. The amount of radioactivity present in the protective device plus the amount removed by washing was considered to represent the unabsorbed dose. The percent absorbed dose, *ie.*, the applied amount divided by the radioactivity remaining in the skin, plus the amount in the excreta and carcass, is presented in Table 1. For risk assessment purposes, the percentage dermal absorption of paclobutrazol by humans was assumed to be the same as the highest percentage observed in the rat- 27.8%.

Table 1 - Percent of ¹⁴C-paclobutrazol absorbed dermally by male rats at different doses and time periods.

Dose (mg/cm ²)	Percent Absorbed	
	10 hr	24 hr
1.25	3.8	5.2
0.12	4.9	5.1
0.013	11.8	12.5
0.003	19.5	24.8
0.001	18.2	27.8

B. ACUTE TOXICITY

The acute oral toxicity data for technical grade paclobutrazol, and formulations of paclobutrazol are summarized in Table 2. The formulation being registered under Section 3 contains 0.4% (4 g/L) paclobutrazol.

Table 2 - The Acute Toxicity of Technical Grade Paclobutrazol

Species	Sex	Dose/Result	References ^a
<u>Oral LD₅₀</u>			
Rat	M	1954 (1147-4985)(mg/kg)	1
	F	1336 (837-1969)(mg/kg)	1
Mouse	M	490 (394-642)(mg/kg)	1
	F	1219(mg/kg)	1
Guinea Pig	M	542 (432-717)(mg/kg)	1
	F	(400-640)(mg/kg)	1
Rabbit	M	835 (250-2500)(mg/kg)	1
	F	937 (555-2026)(mg/kg)	1
<u>Dermal LD₅₀</u>			
Rat	M	>1000(mg/kg)	1
	F	>1000(mg/kg)	1
Rabbit	M	>1000(mg/kg)	1
	F	>1000(mg/kg)	1
<u>Skin Irritation</u>			
Rabbit		mild	2
<u>Dermal Sensitization</u>			
Guinea Pig		negative	3

a/ Reference: 1. Oliver *et al.*, 1982a; 2. Oliver *et al.*, 1982b; 3. Parkinson, 1982.

Table 2 (cont.) - The Acute Toxicity of Paclobutrazol Formulations

Species	% A.I.	Sex	Dose/Result	References ^a
LIQUID FORMULATIONS (0.4-23.8%)				
<u>Oral LD₅₀</u>				
Rat	0.4%	M/F	> 5000 mg/kg	1
Rat	2.8%	M/F	> 5000 mg/kg	2
Rat	24%	F	536 mg/kg	3
<u>Dermal LD₅₀</u>				
Rat	0.4%	M/F	> 2100 mg/kg	1
Rat	2.8%	M/F	> 2043 mg/kg	4
Rat	24%	M/F	> 1000 mg/kg	3
<u>Inhalation LC₅₀</u>				
Rat	24%	M/F	> 0.25 mg/L	6
Rat	2.8%	M/F	> 4.1 mg/L	5
<u>Irritation</u>				
Rabbit	0.4%	eye	mild	8
	2.8%	eye	corrosive ^b	7
	24%	eye	mild	3
	0.4%	skin	mild	8
	2.8%	skin	mild	9
	24%	skin	mild	3

a/ References: 1. Southwood *et al.*, 1984; 2. Southwood *et al.*, 1987a; 3. Truman *et al.*, 1983; 4. Southwood *et al.*, 1987b; 5. Hext *et al.*, 1987; 6. McLean *et al.*, 1985; 7. Reagan and Laveglia, 1987; 8. Southwood, 1984; 9. Southwood, 1987.

b/ The effect was attributed to the "inert" ingredients in the formulation.

Oral- rat

In a range-finding study to determine appropriate doses for pharmacokinetic studies, Alpk/AP rats (5/sex/dose) were given a single dose of paclobutrazol (99% purity) at 0, 5, or 250 mg/kg by gavage (Jones *et al.*, 1984c). After 72 hours, males at the high dose (250 mg/kg) exhibited a statistically significant ($P < 0.01$) increase in the ratio of liver weight to body weight when compared to control animals. The effect in females at the high dose was less pronounced, but still significant ($P < 0.05$). The acute No Observed Effect Level (NOEL) for an increase in relative liver weight was 5 mg/kg.

C. SUBCHRONIC TOXICITY

Oral- rat

Wistar rats (20/sex/group) were fed a diet containing paclobutrazol (92.4% purity) at 0, 48, 232, or 1180 ppm for 90 days (Litchfield *et al.*, 1983). At the highest dose in females there was a decrement in body weight gain (7%) and food consumption (5%). Both males and females exhibited a significant

($P < 0.01$) increase (11% and 12%, respectively) in relative liver weights, an 11-12% increase in hepatic aminopyrine-N-demethylase activity (indicating P-450 enzyme induction), and a reduction in the prothrombin time at the highest dose. Females appeared to be more sensitive, as a significant ($P < 0.05$) decrease in prothrombin time, and increases in relative liver weight and in hepatic aminopyrine-N-demethylase activity were seen at 232 ppm. The NOEL in females for these systemic effects was 48 ppm (calculated from the food consumption data as 3.4 mg/kg-day).

Dermal- rabbit

In a subchronic study, paclobutrazol (97% purity) was applied to intact (5M/5F) and abraded skin (5M/5F) of New Zealand White rabbits at 0 (1% aqueous methylcellulose), 10, 100, or 1000 mg/kg-day for 6 hours/day, 5 days/week, for 3 consecutive weeks (Kynoch *et al.*, 1980). The material caused a slight, not well defined erythema, slight edema, and persistent, well defined to moderate, dermal irritation at all doses. There were varying degrees of hyperkeratosis, acanthosis and inflammatory changes of the superficial dermis present in the majority of animals at the highest dose. No systemic effects were noted at any dose.

D. CHRONIC TOXICITY/ONCOGENICITY

Summary: Paclobutrazol was not oncogenic in either the rat or the mouse. In the dog, mouse, and rat the principal target for paclobutrazol was the liver. However, no major histopathological changes in the liver, such as cholestasis or necrosis, were observed. The NOEL for hepatotoxicity (increased absolute liver weight, hepatocellular swelling, elevation of alkaline phosphatase activity and hepatic aminopyrine N-demethylase activity) in the dog was 15 mg/kg-day. The NOEL for hepatotoxicity (increased absolute liver weight, steatosis of the liver) in the mouse was 15.4 mg/kg-day. In the rat, the 104 week NOEL for hepatotoxicity (centrilobular hypertrophy and steatosis), decrement in body weight gain and decreased serum triglyceride values in females was 1.6 mg/kg-day.

Diet- rat

Sprague-Dawley derived Crl:CD(SD)BR rats (60/sex/dose with 10/sex/dose scheduled for sacrifice at 52 weeks) were fed on a diet containing paclobutrazol (92.4% purity) at 0, 50, 250, or 1250 ppm (approximately 0, 1.4, 6.8, or 33.8 mg/kg-day for males; 0, 1.6, 8.8, or 48.8 mg/kg-day for females; based on reported food consumption) for 104 weeks (Shaw, 1986b). Females exhibited a significant ($P < 0.05$) decrement in body weight gain at doses of 250 and 1250 ppm (Table 3). At the highest dose (1250 ppm), liver weights, adjusted for body weight, were significantly increased ($P < 0.01$) for both males and females. Centrilobular hypertrophy accompanied by steatosis were seen in the livers at the highest dose at both 52 and 104 weeks. At 104 weeks, steatosis was also noted in some males dosed at 250 ppm. No major histopathological changes in the liver, such as cholestasis or necrosis, were reported. No overall treatment effects were observed in glutamate oxaloacetate transaminase (SGOT), glutamate pyruvate transaminase (SGPT), alkaline phosphatase, glucose, cholesterol, total protein, albumin, or albumin/globulin ratio. Serum triglyceride values were significantly reduced compared to controls in females at 250 and 1250 ppm at 39 weeks, and at 1250 ppm at 52 weeks. [The change in the serum triglycerides may indicate an alteration in lipid metabolism which leads to the observed steatosis.] Also, blood urea nitrogen (BUN) was significantly increased in 1250 ppm females at 39 and 52 weeks. The NOEL for hepatocellular effects, decrement in body weight gain, and decreased serum triglyceride values in females was 1.6 mg/kg-day at 104 weeks. This study was acceptable according to the Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA) guidelines.

Table 3 - Chronic effects of paclobutrazol in the livers of rats^a.

	Male Dose (mg/kg-day)				Female Dose (mg/kg-day)			
	0	1.4	6.8	33.8	0	1.6	8.8	48.8
Body wts (g)	676	665	668	691	453	431	409	381**
Relative Liver wts (g)	15.0	15.3	15.2	16.9**	10.4	10.9	10.7	12.8**
BUN (mg/dl)								
(39 wks)					15	16	15	18**
(52 wks)					12	13	13	16**
Serum triglyceride (mg/dl)								
(39 wks)					188	167	88**	68**
(52 wks)					210	255	195	132*

a/ Mean values of 60 rats of each sex at each dose.

* Significantly different from control by two-sided t test, $p < 0.05$

** Significantly different from control by two-sided t test, $p < 0.01$

Diet- mouse

Crl:CD-1(ICR)BR mice (63/sex/dose with 12/sex/dose scheduled for sacrifice at 52 weeks) were fed on a diet containing paclobutrazol (92.4% purity) at 0, 25, 125, or 750 ppm (approximately 0, 3, 15.4, or 93.2 mg/kg-day for males; 0, 3, 15.7 or 122 mg/kg-day for females; based on reported food consumption) for 104 weeks (Shaw, 1986a). There was no indication of oncogenicity. No significant effect on food consumption or body weight gain was noted. At the high dose, absolute liver weights were significantly ($P < 0.01$) increased in males (12%) and females (22%). No major histopathological changes in the liver, such as cholestasis or necrosis, were reported. The severity of steatosis of the liver was significantly increased at the high dose in males. Also at the high dose, serum triglyceride levels were significantly reduced for both sexes at 52 weeks, and in males at 104 weeks (32%). At 750 ppm, female kidney weights were significantly ($P < 0.01$) increased (8%). The NOEL for hepatotoxicity (steatosis of the liver, increased absolute liver weight) was 125 ppm (approximately 15.4 mg/kg-day in males). This study was not acceptable under FIFRA guidelines because the dose levels were not justified, and the maximum tolerated dose was not reached. An additional mouse oncogenicity study was not required because collective evidence from the rat and dog studies had identified the liver as the target organ, and did not indicate an oncogenic potential. An additional mouse oncogenicity study was not expected to provide new, significant information (Appendix A).

Oral- dog

Beagles (6/sex/dose) were given capsules containing paclobutrazol (92.4% purity) at doses of 0, 15, 75, or 300 mg/kg-day for one year (Clapp *et al.*, 1984). No mortality was seen at any dose level. Absolute liver weights in both sexes were significantly increased in a dose dependent fashion (Table 4). Hepatocellular swelling was noted in females at the two highest doses [75 mg/kg-day (2/6); and 300 mg/kg-day (3/6)], and in males at 300 mg/kg-day (2/6). No other histopathological changes were observed in males or females. The lack of overall changes in plasma creatine kinase, SGPT, SGOT, urea, glucose, or cholesterol indicated no major liver injury was occurring. However, some blood chemistry parameters indicated that the liver was responding to paclobutrazol. Plasma total protein and albumin

were significantly ($P < 0.01$) reduced (6-10% and 12%, respectively) in males treated with 300 mg/kg-day from week 12 onwards. Plasma albumin was also variably depressed (1-12%) in females at 300 mg/kg-day from week 12 onwards. There were dose-related increases in the plasma alkaline phosphatase activities of males and females at 75 and 300 mg/kg-day throughout the study. Plasma triglyceride levels were elevated in both males and females treated with 300 mg/kg throughout the treatment period. Alkaline phosphatase activity in the blood and plasma triglyceride levels at the end of the study are shown in Table 4. Hepatic aminopyrine N-demethylase activity was elevated in both sexes in a dose dependent fashion (Table 4), indicating an induction of mixed function oxidases. The NOEL for hepatotoxicity (hepatocellular swelling, elevation of alkaline phosphatase and aminopyrine N-demethylase levels in both sexes) was 15 mg/kg-day. This study was acceptable under FIFRA guidelines.

Table 4 - Chronic effects of paclobutrazol in the livers of dogs^a.

	Dose (mg/kg-day)			
	0	15	75	300
Absolute Liver wts (g)				
Male	362	409*	450**	502**
Female	395	382	434	511**
Alkaline Phosphatase (mU/ml)^b				
Male	4.33	4.37	4.90**	6.11**
Female	4.40	4.67	5.16**	6.35**
Plasma Triglycerides (mg/100ml)				
Male	23.7	27.0	30.2	41.2**
Female	28.7	36.2	38.7	51.7**
Aminopyrine N-demethylase (μmol formaldehyde/hr-g liver)				
Male	12.6	14.6**	19.4**	30.1**
Female	12.1	13.6	17.8**	24.0**

a/ Mean values of 6 dogs of each sex at each dose.

b/ Data transformed by natural log to stabilize the variance.

* Significantly different from control by two-sided t test, $p < 0.05$

** Significantly different from control by two-sided t test, $p < 0.01$

E. GENOTOXICITY

Summary. Paclobutrazol was not mutagenic in either the *Salmonella* or the mouse lymphoma mutagenicity assay. *In vitro* tests showed no effects on chromosomes, and there was no unscheduled DNA synthesis *in vivo*. Chromosomal aberrations were noted in an *in vivo* rat assay, and potentially clastogenic effects were indicated in a mouse micronucleus assay *in vivo*. The adverse effects observed in these *in vivo* cytogenetic assays were not confirmed in a subsequent mouse micronuclear assay, which used a different species and a route of administration different from the earlier mouse micronuclear assay. Based on all available data, the potential genotoxicity of paclobutrazol is equivocal.

Gene Mutation

Paclobutrazol (92.4% purity) was tested on *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100, with and without metabolic (S-9) activation (Callander *et al.*, 1982). Test doses included vehicle (DMSO) and a dose range of 1.6 to 5000 $\mu\text{g}/\text{plate}$, 3 plates/dose and confirmatory assays for all strains. There was no increase in revertant colonies. This study was acceptable to DPR (DPR, 1992).

A mammalian cell gene mutation assay was conducted (MacGregor *et al.*, 1983). L5172Y TK⁺/⁻ Mouse lymphoma cells were exposed for 3 hours *in vitro* to paclobutrazol (92.4% purity) over a dose range of 1 to 100 $\mu\text{g}/\text{ml}$ (first assay) and 60 to 140 $\mu\text{g}/\text{ml}$ (second assay), 3 plates/dose, with and without S-9 activation. No increase in the number of colonies was noted. This study was acceptable to DPR.

Structural Chromosomal Aberration

Paclobutrazol (92.4% purity) at 0, 87.5 or 140 mg/kg was given in a single intraperitoneal injection to five C57BL-6J mice/sex/termination time/dose (Phillips *et al.*, 1983). Animals were killed at 24, 48, and 72 hours after injection, and bone marrow slides were prepared for examination. Five hundred polychromatic erythrocytes (PCE)/sex/termination time/dose were evaluated. There was a highly significant ($P < 0.01$) elevation of the frequency of micronuclei at 140 mg/kg at 24 hours. This study was acceptable to DPR.

Male CD-1 mice (15/dose) were given paclobutrazol (92.4% purity) by gavage at 0, 25, 100 or 300 mg/kg-day for five consecutive days (Wickramaratne *et al.*, 1983). Each male was then mated to 2 females/week for 8 weeks. At the high dose (300 mg/kg-day), males exhibited piloerection, urinary incontinence, and tremors. However, neither dominant lethal effects, nor effects on reproduction were observed at any dose. This study was acceptable to DPR.

Paclobutrazol (92.4% purity) at 30, 150, or 300 mg/kg was given by gavage to 8 Alderley Park rats/sex/dose/kill time (Richardson *et al.*, 1984). Positive and negative (corn oil) controls consisted of 12 rats/sex/dose/kill time. Rats were killed at 24 hr, except animals given 300 mg/kg- which were killed at 12, 24, and 48 hours. A statistically significant ($P < 0.05$) increase in chromosomal aberrations, with or without the inclusion of gaps, was noted in males at 300 mg/kg at 12 hours. Individual treated animals did not have more or different chromosomal aberrations than individual control animals, so the biological significance cannot be addressed. This study was acceptable to DPR.

Human lymphocytes from two donors (1 male and 1 female) were exposed *in vitro* to paclobutrazol (98.8% purity) at 0 (DMSO), 1.6, 8, 40, 200, or 1000 $\mu\text{g}/\text{ml}$ without, or 0, 50, 100, 250, 500, 750, or 1000 $\mu\text{g}/\text{ml}$ with S-9 activation (MacKay, 1991). A statistically significant increase in chromosomal aberrations, associated with cytotoxicity, was seen at 500 $\mu\text{g}/\text{ml}$. Consequently, paclobutrazol was considered negative in this assay. The study was acceptable to DPR.

Paclobutrazol (92% purity) at 0 (corn oil), 233, or 373 mg/kg was given in a single oral dose to 5 C57BL/6JfBL10/Alpk mice/sex/dose/sampling time (James and MacKay, 1991). Bone marrow samples were taken at 24, 48, and 72 hours after dosing. One thousand PCE/animal were scored for incidence of micronuclei. Clinical signs (urinary incontinence, hunched posture, tiptoe gait, eye discharge, piloerection) were noted in some animals at both the low and high dose. At neither dose, however, did paclobutrazol produce any significant increase in the incidence of micronucleated polychromatic erythrocytes. This study was acceptable to DPR.

Other Genotoxic Effects

Paclobutrazol (92.4% purity) at 0 (corn oil), 40, 200 or 400 mg/kg was given by oral gavage to male Alpk:AP rats (2/sex/dose/kill time: Trial 1; 3/sex/dose/kill time: Trial 2), and killed at 4 and 12 hours after dosing (Trueman, 1986). Rat hepatocytes were cultured with ³H-thymidine for four hours, and then

autoradiography was used to determine unscheduled DNA synthesis. No unscheduled DNA synthesis was noted under the conditions of this test. The study was acceptable to DPR.

F. REPRODUCTIVE TOXICITY

Summary- No adverse reproductive effects were noted in a two-generation rat reproduction study. The parental NOEL was 24 mg/kg-day for body weight gain decrement and hepatic centrilobular steatosis.

Dietary- Rat

Alpk/AP rats (15 males/dose, 30 females/dose) were fed continuously for two generations on a diet containing paclobutrazol (92.4% purity) at concentrations of 0, 50, 250, or 1250 ppm (Wickramaratne, 1987). No adverse reproductive effects were noted, so the reproductive NOEL \geq 1250 ppm (approximately 121 mg/kg-day; based on reported food consumption). Mottling, or accentuation of the lobular pattern of the liver was observed in 11/30 F₀ females, and in F₁A, F₁B and F₂A pups of both sexes in the 1250 ppm group. The parental NOEL for marginal reduction in body weight gain (4%) and hepatic centrilobular steatosis was 250 ppm (approximately 24 mg/kg-day; based on reported food consumption). This study was acceptable according to FIFRA guidelines.

G. DEVELOPMENTAL TOXICITY

Summary- Paclobutrazol was not fetotoxic and caused no fetal abnormalities in two rabbit studies. The NOEL for maternal toxicity (decrement in body weight gain) was 75 mg/kg-day. In the rat, paclobutrazol caused developmental malformations in the urogenital system, cleft palate, and skeletal abnormalities. The NOEL for developmental anomalies in rats was 10 mg/kg-day. The maternal NOEL (reduced body weight gain and food consumption, and urogenital staining) for rats was 40 mg/kg-day.

Gavage- Rat

Wistar rats (24 females/dose) were dosed with paclobutrazol (92.4% purity) in corn oil at 0, 40, 100 or 250 mg/kg daily from days 6-15 of gestation, inclusive (Killick *et al.*, 1983a). Five maternal deaths occurred at the high dose. The survivors exhibited urogenital staining, and their food utilization (g body weight gain/100 g food consumed) was only 30% of the control value. No deaths, but similar, less severe effects were noted at 100 mg/kg-day. The maternal NOEL (reduced body weight gain [65%] and food consumption [15%], and urogenital staining) was 40 mg/kg. Three instances of fetal cleft palate were noted at the high dose; none at 100 mg/kg-day; and one instance at 40 mg/kg-day. All groups dosed with paclobutrazol exhibited a significant, dose related increase of minor skeletal abnormalities, indicative of impaired ossification. A NOEL for fetal skeletal abnormalities was not established. This study was not acceptable according to FIFRA guidelines because a developmental NOEL was not established.

Wistar rats (24 females/dose) were dosed with paclobutrazol (92.4% purity) in corn oil at 0, 2.5, 10, 40 or 100 mg/kg daily from days 7-16 of gestation, inclusive (Killick *et al.*, 1984). No adverse effects were noted in the maternal rats. Abnormalities of the urogenital system were noted in fetuses from the two high dose groups (40 or 100 mg/kg-day). The abnormalities consisted of pelvic dilation of the kidney, and dilation and/or kinking of the ureter. There was a toxicologically significant correlation between effects in the kidney and ureter. Eight fetuses from the high dose group exhibited hydroureter. These findings contrast with the first study (Killick *et al.*, 1983a), in which defects of the kidney and ureter were of low incidence, and not treatment related. The author suggested: "This indicates a change in the background incidence and/or an increased sensitivity of detection" (Pigott, 1984). There was also a significant ($P < 0.05$) increase in the number of minor skeletal abnormalities indicative of impaired ossification, and extra thoracic ribs at the two highest doses. However, no instances of cleft palate were observed. The

NOEL for developmental toxicity (urogenital abnormalities, skeletal abnormalities) was 10 mg/kg-day. This study was acceptable according to FIFRA guidelines.

Gavage- Rabbit

New Zealand white rabbits (8 rabbits/dose) were given paclobutrazol (92.4% purity) at doses of 0, 25, 75, or 125 mg/kg in corn oil on days 7-19 of gestation (Killick *et al.*, 1983b). There were no fetotoxic effects, and no compound-related fetal abnormalities. The developmental NOEL was \geq 125 mg/kg. At the highest dose (125 mg/kg), there was a slight decrement in food consumption (7%), and in body weight gain (7%). The maternal NOEL for decrement in body weight gain was 75 mg/kg. This study was acceptable according to FIFRA guidelines.

New Zealand white rabbits (18 rabbits/dose) were given paclobutrazol (92.4% purity) at doses of 0, 25, 75, or 125 mg/kg in corn oil on days 7-19 of gestation (Killick *et al.*, 1986). There were no fetotoxic effects, and no compound-related fetal abnormalities. The developmental NOEL was \geq 125 mg/kg. The maternal NOEL for a transient decrement in maternal body weight gain (2.5%) was 75 mg/kg. This study was acceptable according to FIFRA guidelines.

IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

A risk assessment of potential human health hazards from paclobutrazol exposure has been conducted because of adverse effects in developmental toxicity and chronic toxicity studies submitted in support of a new Section 3 (FIFRA) registration. The results of the toxicity studies are summarized in Table 5.

Table 5 - Summary of Paclobutrazol Toxicology Studies

STUDY	SPECIES	EFFECT	LOEL	NOEL	GENTOX	REF ^a
			(mg/kg-day)			
acute	rat	hepatic hypertrophy	250	5		1
subchronic	rat	hepatotoxicity	125	25		2
chronic	dog	hepatotoxicity	75	15		3
oncogenicity	mouse	hepatotoxicity	93.2	15.4		4
combined	rat	hepatotoxicity	6.8	1.6		5
reproduction	rat	hepatotoxicity	122	25		6
developmental	rat	decr. bdy wt gain	100	40		7
developmental	rat	urogen. & skel. abnormalities	40	10		8
developmental	rabbit	decr. bdy wt gain	125	75		9
gene mutation	bacteria	<i>in vitro</i>			-	10
gene mutation	mammal	<i>in vitro</i>			-	11
cytogenetic	mammal	<i>in vitro</i>			-	12
cytogenetic	mammal	<i>in vivo</i>			+	13
cytogenetic	mammal	<i>in vitro</i>			-	14
DNA damage	mammal	<i>in vivo</i>			-	15,16
cytogenetic	mammal	<i>in vivo</i>			+/-	17

a/ References- 1. Jones *et al.*, 1984c; 2. Litchfield *et al.*, 1983; 3. Clapp *et al.*, 1984; 4. Shaw, 1986a; 5. Shaw, 1986b; 6. Wickramaratne, 1987; 7. Killick *et al.*, 1983a; 8. Killick *et al.*, 1984; 9. Killick *et al.*, 1983b; 10. Callander *et al.*, 1982; 11. MacGregor *et al.*, 1983; 12. MacKay, 1991; 13. Phillips *et al.*, 1983; 14. James and MacKay, 1991; 15. Wickramaratne *et al.*, 1983; 16. Trueman, 1986; 17. Richardson *et al.*, 1984.

Paclobutrazol was not oncogenic in rats or mice. Examination of the toxicological profile, as summarized in Table 5, indicates that the principal systemic target of paclobutrazol is the liver. Several biochemical parameters, gross organ and microscopic observations indicated that there were subtle physiological and morphological alterations resulting from chronic exposure of rodents and dogs to paclobutrazol. Paclobutrazol stimulated the liver's P-450 system (Clapp *et al.*, 1984; Litchfield *et al.*, 1983), altered liver enzyme production (blood alkaline phosphatase- Clapp *et al.*, 1984) and metabolic function (serum levels of triglycerides, BUN- Clapp *et al.*, 1984; Shaw 1986b; Wickramaratne, 1987), caused centrilobular hypertrophy and steatosis in the hepatocytes (Clapp *et al.*, 1984; Shaw 1986b; Wickramaratne, 1987), and, on a gross level, induced a significant increase in absolute and/or relative liver weights (Shaw, 1986a,b; Jones *et al.*, 1984c; Clapp *et al.*, 1984). These effects indicated that the homeostatic mechanisms of the liver were being compromised. However, following one to two years

chronic exposure, there was a complete absence of major histopathological changes, such as clearly defined cholestasis or necrosis, in the livers of rats, mice, and dogs (Clapp *et al.*, 1984; Shaw, 1986a,b).

The lowest NOEL from a single dose, acute exposure to paclobutrazol was 5 mg/kg-day, based on a statistically significant increase in absolute liver weight in rats occurring at the next highest dose, 250 mg/kg-day (Jones *et al.*, 1984c). Although this initial hepatic hypertrophy may presage the hepatotoxicity observed in chronic exposures to paclobutrazol, it was not considered an adverse effect in itself.

The NOEL for developmental effects (urogenital and skeletal abnormalities) in rats, 10 mg/kg-day (Killick *et al.*, 1984), was used for assessment of potential health hazards associated with short-term exposure to paclobutrazol. As developmental toxicity may be manifested as the result of a single dose (Ogata *et al.*, 1984; USEPA, 1991), it is assumed, in the absence of data to the contrary, that the observed effects were elicited from a single dose. Although the use of a developmental endpoint for risk assessment is only relevant in women of child-bearing age, it was assumed that the use of this endpoint(s) would protect all population subgroups from other potential adverse effects which might occur at higher dosages. The NOEL did not need to be adjusted for oral absorption, as a study had indicated that 95% of an oral dose was absorbed (Jones *et al.*, 1984b).

As previously mentioned, the most prevalent systemic effect from chronic exposure of laboratory animals to paclobutrazol was hepatotoxicity. NOELs for hepatotoxicity in dogs or mice were approximately 15 mg/kg-day (Clapp *et al.*, 1984; Shaw, 1986a). However, the rat was apparently more sensitive to paclobutrazol, exhibiting hepatocellular effects (centrilobular hypertrophy accompanied by steatosis), and decreased serum triglyceride values at 33.8 mg/kg-day at 52 weeks, and 6.8 mg/kg-day at 104 weeks (Shaw, 1986b). The NOEL for hepatotoxicity in the rat was 6.8 mg/kg-day at 52 weeks, and 1.6 mg/kg-day at 104 weeks. Although the 104 week NOEL for liver toxicity in the rat (1.6 mg/kg-day) is a lifetime NOEL, it was used as the basis for calculating margins of safety for potential annual occupational exposures to paclobutrazol for three reasons. 1) The same hepatocellular effects (centrilobular hypertrophy accompanied by steatosis) which were significant ($P < 0.05$) at the two high dosages at 104 weeks, were also observed at the highest dosage at 52 weeks. 2) The statistical power to detect significant differences in response to treatment was less at 52 weeks (10 rats/dose terminated) than at the end of the study (40 rats/dose terminated). 3) The liver is clearly the target organ because a single dose of paclobutrazol caused a significant increase in absolute liver weight (Jones *et al.*, 1984c).

B. EXPOSURE ASSESSMENT

No exposure data for paclobutrazol was submitted by the registrant, therefore, potential occupational exposure to paclobutrazol was estimated using surrogate data from a study involving fluvalinate applications (Appendix B). Fluvalinate was used as a surrogate for paclobutrazol because of the similarity in application rates and vapor pressure of the active ingredients. Mixer/loader/applicators are assumed to wear protective clothing, long pants, long-sleeved shirts, and rubber gloves (Appendix B). Greenhouse workers are assumed to not wear gloves while handling treated plants.

Theoretically, worker exposure to paclobutrazol would be via the inhalation and dermal routes. However, inhalation exposure was not calculated as other studies had indicated it would be toxicologically insignificant (less than 1% of the dermal exposure) (Appendix B). Utilizing surrogate data from fluvalinate applications, the geometric mean exposure for mixer/loader/applicators was 25.1 mg/hr for a work day assumed to be 6.8 hours in duration, or 170.8 mg/day per person (Appendix B). It was assumed that clothing provided 90% protection, so that 17.1 mg of paclobutrazol was deposited on the skin each working day (Table 6). The period of applying paclobutrazol was estimated to last 35 days per year.

Greenhouse workers, engaged in cultivating and shifting plants, were assumed to encounter dislodgeable foliar residues (approximately $0.057 \mu\text{g}/\text{cm}^2$) during the 8 hour work day (Appendix B). Assuming a transfer factor of $5000 \text{ cm}^2/\text{h}$, the daily dermal exposure would be 2.3 mg/person/day. It was further assumed that the average greenhouse worker would work 240 days out of the year. However,

studies have shown that extrapolation from short-term exposure measurements to estimates of potential chronic exposure generally lead to overestimations of the latter (U.S. EPA, 1992).

Table 6 - Potential Dermal Exposure to Mixer/Loader/Applicators and Greenhouse Workers from Paclobutrazol in Greenhouses^a.

	Dermal (mg/person/day)	ADD ^b (ug/kg-day)	AADD ^c (ug/kg-day)
Mixer/Loader/Appl. ^d	17.1	67.9	6.5
Greenhouse Worker	2.3	9.1	6.0

- a/ Data obtained from Tables 3 and 4 in Appendix B.
- b/ Absorbed Daily Dosage (ADD) of a 70 kg person, assuming a dermal absorption rate of 27.8% (Appendix B).
- c/ AADD: Annual Average Daily Dosage, assuming 35 spray events per year for mixer/loader/applicators, and 240 days of exposure for greenhouse workers (Appendix B).
- d/ Mixing and Application of 0.1 lbs Active Ingredient per 100 gal water.

C. RISK CHARACTERIZATION

The toxicological effects observed in laboratory animals exposed to paclobutrazol were shown to have an apparent biological threshold. It is assumed that humans would respond to paclobutrazol in a similar fashion (Dourson and Stara, 1985; USEPA, 1986). Consequently, human exposure below a certain level is not expected to cause the adverse effects observed in laboratory animal studies. The margin of safety (MOS) is calculated as the ratio of a NOEL for a toxic endpoint established in laboratory animal studies to the potential exposure dosage estimated for mixer/loader/applicators and greenhouse workers exposed to paclobutrazol.

$$\text{Margin of Safety} = \text{NOEL} / \text{Exposure Dosage}$$

Margins of safety for both potential acute and chronic occupational exposure to paclobutrazol are presented in Table 7. The annual average daily dosage (AADD) was used in the assessment of potential health risk from chronic exposure rather than the lifetime average daily dosage (LADD) because the effects used to characterize the chronic risk were seen at one year in the laboratory animal studies.

Table 7 - Potential Acute and Chronic Dosages, and Corresponding Margins of Safety for Mixer/Loader/Applicators and Greenhouse Workers Associated with the Use of Paclobutrazol

<u>Workers</u>	Potential Exposure Dosage ^a <u>(μg/kg-day)</u>	<u>Margin of Safety^b</u>
<u>Acute</u>		
Mixer/Loader Applicator	67.9	147
Greenhouse Worker	9.1	1099
<u>Chronic</u>		
Mixer/Loader Applicator	6.5	1538
Greenhouse Worker	6.0	1667

a/ The acute (ADDs) and the chronic (AADDs) dosages are from Table 6.

b/ The acute MOSs are based on a NOEL of 10 mg/kg-day for developmental effects (urogenital and skeletal abnormalities) in rats (Killick *et al.*, 1984); the chronic MOSs are based on a NOEL of 1.6 mg/kg-day for hepatotoxicity in rats (Shaw, 1986b).

V. RISK APPRAISAL

Risk assessment is a process used to evaluate the potential for exposure and the likelihood that the toxic effects of a substance, often characterized only in laboratory animals, may occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessment for all chemicals has similar types of uncertainty. However, the degree or magnitude of the uncertainty varies depending on the quality and availability of the toxicological data and the data for the exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for paclobutrazol are delineated in the following discussion.

The margins of safety for potential acute and chronic exposure to paclobutrazol were 147 and 1538 for mixer/loader/applicators, and 1099 and 1667 for greenhouse workers, respectively. A margin of safety of at least 100 would generally be considered adequate for protection against the potential toxicity of paclobutrazol. This benchmark of 100 includes an uncertainty factor of 10 for intraspecies variability in responsiveness, and assumes that humans are 10 times more sensitive to paclobutrazol than are laboratory animals (Davidson *et al.*, 1986; Dourson and Stara, 1983, 1985; U.S. EPA, 1986). In the absence of scientific evidence to the contrary, the effects of paclobutrazol observed in laboratory animals are assumed to occur in humans at similar doses.

Occupational exposure data associated with mixer/loader/applicators and other greenhouse workers were derived from surrogate data. Although the application rates, and the chemical nature of the surrogate are similar to paclobutrazol, the exposure data carry a degree of uncertainty. An additional uncertainty is associated with the assumed work hours and the number of days worked each year. As the formulation is not in use yet, the actual hours toiled may be greater or less than the surrogate estimate.

VI. CONCLUSIONS

Using laboratory animal toxicity data and surrogate worker exposure data, the calculated margins of safety (MOSs) for potential acute exposure of mixer/loader/applicators and greenhouse workers exceed 100 and are considered adequate. MOSs for potential chronic occupational exposure to paclobutrazol exceed 1000 and are also considered adequate.

VII. REFERENCES

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APPENDIX A

Summary of Toxicology Information

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PACLOBUTRAZOL

Chemical Code # 2259, Tolerance # 50583
SB 950 # NA

June 5, 1990, revised May 1, 1991

I. DATA GAP STATUS

Combined, rat:	No data gap, no adverse effect
Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 096620 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T910501

Peter Leung 5/1/91

gler 5/2/91

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

** 030 073313 "Paclobutrazol: 104 Week Oral (Dietary Administration) Combined Toxicity and Carcinogenicity Study in the Rat with a 52 Week Interim Kill" (Hazleton Laboratories Europe Ltd., Harrogate England, Report # 5055-72/273, 10/17/86) Paclobutrazol, Batch # P29 (ICI reference #'s Y00001/001/032, 033, and 037), 92.4% pure, was administered in the feed to 60 Sprague Dawley-derived rats/sex/dose with 10/sex/dose for scheduled sacrifice at 52 weeks, at -0, 50, 250, and 1250 ppm for 104 weeks. No adverse effects noted. NOEL = 50 ppm (decreased body weight gain and decreased triglyceride values in females, hepatocellular fatty degeneration). Acceptable. (Klein and Gee, 6/9/89)

CHRONIC TOXICITY, RAT

See under Combined Rat above.

CHRONIC TOXICITY, DOG

004 033646; interim report for chronic toxicity dog study (# 073310) reviewed by Fred Martz, 4/20/87.

** 027; 073310; "Paclobutrazol: 1 year Oral Dosing Study in Dogs"; ICI PLC Central Toxicology laboratory, Alderley Park, Cheshire, UK, Lab. Report No. CTL/P/958, 5/29/84; paclobutrazol 92.4% pure; 300, 75, 15 or 0 mg/kg/day by oral capsule daily for 1 year; 6 beagle dogs/sex/dose; no mortality at any dose levels throughout the study; males in 300 mg/kg/day group exhibited minor differences (6.94%) in total body weight as compared to control group at the end; no effects on food consumption and hematological indices; increases (p<0.01) in plasma alkaline phosphatase activity at the 300 and 75 mg/kg/day dose level in males (580.0% and 73.4%, respectively) and females (620.5% and 119.3%, respectively); no changes in plasma levels of alanine transaminase or aspartate transaminase; elevated (p<0.01) plasma triglycerides in males (73.8%) and females (80.1%) at the 300 mg/kg/day dose level with a reduction in albumin and calcium from 12 weeks onwards; liver weights were increased (p<0.01) in males at all dose levels (11.1 - 41.6%) and in females at 300 mg/kg/day (31.2%); elevated hepatic aminopyrine N-demethylase were reported in males at all dose levels (15.9 - 138.9%) and in females at 300 mg/kg/day (98.4%); mild hepatocellular swelling in two males and three females at the 300 mg/kg/day dose level and two females at the 75 mg/kg/day dose level and was not considered to be of toxicologic significance at this time; NOAEL (M/F) ≥ 300 mg/kg/day (no adverse effects in dogs were observed when this dose was administered daily for one year); NOEL (M/F) = 15 mg/kg/day (at this dose level, only minimal adaptive changes were observed in male dogs) study acceptable; (Leung, 7/7/89).

ONCOGENICITY, RAT

See under Combined Rat above.

ONCOGENICITY, MOUSE

029 073312 "Paclobutrazol: 104 Week Oral (Dietary Administration) Combined Toxicity and Carcinogenicity Study in the Mouse with a 52 Week Interim Kill" (Hazleton Laboratories Europe Ltd., Harrogate England, Report #

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5014-72/274, 9/86) Paclobutrazol, Batch #P29 (ICI reference #'s Y00001/001/032, 033 and 037), 92.4% pure, was administered in the feed to 63 mice/sex/dose with 12/sex/dose for scheduled sacrifice at 52 weeks, at 0, 0, 25, 125, and 750 ppm for 104 weeks. **No adverse effects noted.** NOEL = 125 ppm (decreased triglyceride levels (M, F), decreased cholesterol levels (M), increased liver weights (M, F), increased kidney weights (F)). NOAEL \geq 750 ppm; **unacceptable** (no dose justification and clinical chemistries and organ weights not adequate to determine if MTD was achieved); originally reviewed as upgradable (with the submission of data to justify dose levels and evidence that MTD was reached). (Klein and Gee, 6/22/89).

033 087665 "Paclobutrazol: 4 Week Oral (Dietary Administration) Dose Range-Finding Study in the Mouse" (Shaw, D.C., Hazleton Laboratories Europe Ltd., Harrogate, UK, Report # 3525-72/272, 5/84) Paclobutrazol, Batch # P29 (ICI reference #'s Y00001/001/032 and 033), 92.4% pure, was administered in the feed to 18 Crl:CD-1(ICR)BR mice/sex/dose at 0, 50, 1000, 1500, and 2000 ppm for four weeks. **No adverse effects were noted.** The NOEL of 50 ppm was based on decreased serum cholesterol and triglyceride levels, increased serum alanine aminotransferase levels, and hepatic hypertrophy and microvacuolation in both males and females, and increased liver weights in males. The NOAEL of 1500 ppm was based on focal hepatocellular necrosis. This supplemental study was submitted as justification for the dose levels selected in Record # 073312. (Klein 6/4/90)

Summary: The supplemental study data (Record #087665) indicate that the highest dose (750 ppm) administered in the mouse oncogenicity study (Record #073312) may not represent the maximum tolerated dose for paclobutrazol. Collectively, data from the chronic toxicity study in dogs and the combined chronic/oncogenicity study in rats indicate that the liver has been identified as the target organ for paclobutrazol and have revealed no evidence of an oncogenic potential. Another mouse oncogenicity study using higher dose levels would probably not provide new significant information.

REPRODUCTION, RAT

** 028 073311 "Paclobutrazol: Two Generation Reproduction Study in Rats Including Individual Animal Data", (ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study # RR0303, Report # CTL/P/1496, 2/27/87); paclobutrazol, 92.4% purity, batch P29, fed continuously in diet for two generations at 0, 50, 250, and 1250 ppm; parental generations 15 males/dose, 30 females/dose, mated each male with 2 females; **No Adverse Effects**; Parental NOEL = 250 ppm (marginal reduction in body weight gain, hepatic centrilobular fatty change), Parental NOAEL \geq 1250 ppm, Reproductive NOEL \geq 1250 ppm; **Acceptable.** (DiBiasio and Patterson, 8/24/89)

TERATOLOGY, RAT

004 033649 033650 "Paclobutrazol: Teratogenicity Study in the Rat" (ICI Central Toxicology Laboratory, Cheshire UK, Report # CTL/P/842, 7/13/83) Paclobutrazol, 92.4% pure, was given by gavage to 24 rats/dose at 0 (corn oil), 40, 100, and 250 mg/kg/day on days 6-15 of gestation. Maternal NOEL = 40 mg/kg (decreased weight gain, increased urogenital staining). Developmental NOEL < 40 mg/kg (increased incidence of minor skeletal defects at all dose levels, cleft palate at 250 mg/kg/day may be related to treatment).

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Possible adverse effect, developmental NOEL < maternal NOEL. Unacceptable (developmental NOEL not established). Shimer and Parker 4/14/87.

** 009 041209 "Paclobutrazol: Second Teratogenicity Study in the Rat" (ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/997, 6/1/84) Paclobutrazol, 92.4% pure, was given by gavage at 0 (corn oil), 2.5, 10, 40, or 100 mg/kg/day to 24 successfully mated female Wistar-derived rats/dose from days 7-16 inclusive of gestation; maternal toxicity NOEL \geq 100 mg/kg/day (no maternal toxicity; prior study [Record #'s 033649, 033650] demonstrated maternal toxicity at 250 mg/kg/day); developmental toxicity NOEL = 10 mg/kg/day (kidney and ureter defects; hydroureter at 100 mg/kg/day); possible adverse effect, developmental NOEL < maternal NOEL. Acceptable. Berliner and Parkar 3/21/86; updated Klein and Patterson 8/15/89.

025 073308 Exact duplicate of 041209.

TERATOLOGY, RABBIT

** 004 033647 033648 "Paclobutrazol: Teratogenicity Study in the Rabbit" (ICI Central Toxicology Laboratory, Cheshire UK, Report # CTL/P/861, 7/14/83) Paclobutrazol, 92.4% pure, was given by gavage at 0 (corn oil), 25, 75, and 125 mg/kg/day to 9, 12, 13, and 8 rabbits, respectively for days 6-18 of gestation; Maternal NOEL = 75 mg/kg (decreased weight gain). Developmental NOEL \geq 125 mg/kg (maximum dose tolerated). No adverse effects (no fetotoxic effects, no fetal defects). Acceptable. Shimer and Parker 4/14/87.

**026 073309 "Paclobutrazol: Second Teratogenicity Study in the Rabbit Including Individual Animal Data", (ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, ID # CTL/P/1460, October 22, 1986), Paclobutrazol (PP333), batch no. P29, CTL reference #'s Y00001/001/017 and Y00001/001/035, 92.4% purity; administered by oral gavage to 18 rabbits/dose at 0 (corn oil), 25, 75, or 125 mg/kg on days 7-19 of gestation (day 1 = day of insemination); No adverse effects indicated; Maternal NOEL = 75 mg/kg (marginal effect on body weight gain); Maternal NOAEL \geq 125 mg/kg; Developmental NOEL \geq 125 mg/kg. Acceptable (DiBiasio and Gee, 8/21/89)

GENE MUTATION

** 006 41734 "PP333 - An Evaluation in the Salmonella/Microsome Mutagenicity Assay" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/722, 9/14/82) Paclobutrazol, Code Name = PP333, CTL reference # Y00001/001/011, 92.4% pure, was tested with Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100, with and without aroclor-stimulated rat liver S9 fraction, at 0 (DMSO) and over a dose range of 1.6 to 5000 ug/plate, 3 plates/dose, confirmatory assays for all strains with a third trial for TA98; no adverse effects noted (no increase in number of revertant colonies); acceptable. Davis 4/7/87, updated Klein and Patterson 7/5/89.

** 004 033652 "PP333 - Assessment of Mutagenic Potential in the Mouse Lymphoma Mutation Assay" (Inveresk Research International, IRI Project # 730415, 3/83) Paclobutrazol, Code Name = PP333 (Y00001/001/011), 92.4% pure, was tested with L5178Y TK⁺ mouse lymphoma cells for 3 hours at 0 (methanol) and over a dose range of 1.0 to 100 ug/ml in the first assay and 60 to 140 ug/ml in the second assay, with and without Aroclor-stimulated rat liver S9 fraction, 3 plates/dose; no adverse effects noted (no increase in number of colonies); acceptable. Davis 4/8/87, updated Klein and Patterson 7/5/89.

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CHROMOSOME EFFECTS

** 004 033651 "An Evaluation of Paclobutrazol in the Mouse Micronucleus Test" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Report # CTL/P/848, 8/4/83) Paclobutrazol, CTL reference # Y00001/001/030, 92.4% pure, was given in a single intraperitoneal injection to 5 C57B1/6j mice/sex/sacrifice time/dose at 0 (corn oil), 87.5 or 140 mg/kg; at 24, 48, and 72 hours animals were sacrificed, bone marrow slides prepared, and 500 polychromatic erythrocytes examined/sex/sacrifice time/dose. **Possible adverse effect**, highly significant elevation of the frequency of micronuclei at 140 mg/kg at 24 hours. **Acceptable**. Davis 4/8/87, updated Klein and Patterson 7/6/89.

** 009 041210 "Paclobutrazol: Dominant Lethal Study in the Mouse" (Imperial Chemical Industries PLC, Central Toxicology Laboratory, Report # CTL/P/922, 12/29/83) Paclobutrazol, CTL reference # Y0001/001/020, Batch P29, 92.4% pure, was given by gavage to 15 male CD-1 mice/dose at 0 (corn oil), 25, 100, and 300 mg/kg/day for 5 consecutive days; each male was mated to 2 females/week for 8 weeks; males dosed with 300 mg/kg/day exhibited piloerection, urinary incontinence, and tremors. **No adverse effects** (no dominant lethal effects, no effect on fertility). **Acceptable**. Remsen 3/5/86, updated Klein and Patterson 7/7/89.

** 009 041211 "Paclobutrazol: A Cytogenetic Study in the Rat" (Imperial Chemical Industries PLC, Central Toxicology Laboratory, Report # CTL/P/891, 5/2/84) Paclobutrazol, CTL reference # Y00001/001/001, Batch P29, 92.4% pure, was given by gavage to 8 Alderley Park rats/sex/dose/sacrifice time at 30, 150, and 300 mg/kg and to 12 rats/sex in negative (corn oil) and positive controls; animals were sacrificed at 24 hr except animals given 300 mg/kg were sacrificed at 12, 24, and 48 hr, chromosome preparations made from bone marrow. **No adverse effect** (statistically significant increase in chromosomal abnormalities at 300mg/kg, 12 hr, considered not biologically significant when compared with control data). **Acceptable**. Remsen 3/5/86, updated Klein and Patterson 7/7/89.

** 036; 88828; "Paclobutrazol: An Evaluation in the In Vitro Cytogenetic Assay in Human Lymphocytes"; ICI Central Toxicology Laboratory, Cheshire, UK; 8/24/90; paclobutrazol (lot# Bx P18, 98.8% (w/w)); 2 donors (1 male, 1 female); cells were exposed in two cytotoxicity tests to either 0 (DMSO), 1.6, 8, 40, 200, or 1000 ug/ml or 0 (DMSO), 50, 100, 250, 500, 750, or 1000 ug/ml of the test compound + S9 fraction. Chromosomal aberrations scored in cells exposed to 50, 250, or 500 ug/ml of test compound; human lymphocytes derived from two donors; too cytotoxic \geq 500 ug/ml (+ S9) (based on mitotic index); no dose dependent increase in chromosomal aberrations, only in the 500 ug/ml cultures was a significant increase reported. Study previously unacceptable, but upgradeable (the study needed 1) documentation of test compound's stability in the vehicle and 2) justification for using only single time points for treatment and harvesting) (Moore, 9/21/90); Requested information submitted (fax, 2/6/91); Test article is not considered to be clastogenic in this assay; Study **acceptable** (Revised, Moore, 3/27/91).

** 037; 96620; "Paclobutrazol: An Evaluation in the Mouse Micronucleus Test" (ICI Central Toxicology Laboratory, Cheshire, UK, Report No. CTL/P/3216, 2/21/91); paclobutrazol technical (Batch # P29 D2517/62, 92% purity); single oral; 0 (corn oil), 233, or 373 mg/kg to 5 mice/sex/dose/sampling time; additional 5 mice/sex were dosed at 373 mg/kg to replace any animals dosed at that level that were found dead or killed in extremis; bone marrow samples taken at 24, 48, and 72 hours after dosing; 1000 PCE/animal scored for

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incidence of micronuclei; positive control functional; **no adverse effects**; clinical signs include urinary incontinence, hunched posture, tiptoe gait, eye discharge and piloerection; 1 male and 3 males at low and high doses, respectively, were killed in extremis, 2 females at the high dose killed in extremis; paclobutrazol did not induce any significant increases in the incidence of micronucleated polychromatic erythrocytes; **acceptable**; (Leung, 5/1/91).

Summary: Five acceptable studies have been submitted in this category. The dominant lethal study was negative, but this assay lacks sensitivity. In the in vitro cytogenetic assay in human lymphocytes, the test article was not considered to be clastogenic. The chromosome aberration study and micronucleus study reports conclude that there is no mutagenicity, but in each there were significantly elevated values at the high dose and early sample time. The most recent chromosomal aberration study (CDFA record # 96620, 2/21/91) submitted did not indicate any significant increases in the incidence of micronucleated polychromatic erythrocytes. Individually, these results might be dismissed as not biologically significant (the CDFA review of the chromosome aberration study on 3/5/86 did so), but taken together they support a possible weak clastogenicity. (B. Davis, 4/8/87; updated, Leung, 5/1/91).

DNA DAMAGE

** 016 053470 "Paclobutrazol: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes In Vivo" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Report # CTL/P/1608, 10/21/86) Paclobutrazol, CTL reference # Y00001/001/017, 92.4% pure, given by oral gavage to male Alpk:AP rats at 0 (corn oil), 40, 200 or 400 mg/kg; animals sacrificed at 4 and 12 hours after test article administration, 2 animals/dose/sacrifice time in Trial 1, 3 animals/dose/sacrifice time in Trial 2; rat hepatocytes into culture with ³H-thymidine for 4 hours, autoradiography for analysis of UDS. **No adverse effect** (no induction of unscheduled DNA synthesis under conditions of the test). **Acceptable**. Gee 4/3/87, updated Klein and Patterson 7/8/89.

024 073307 Exact duplicate of 053470.

NEUROTOXICITY

Not required at this time.

PK 5/1/91

TO: Kathleen A. Wynn, Registration Specialist
Pesticide Registration Branch

FROM: Medical Toxicology Branch

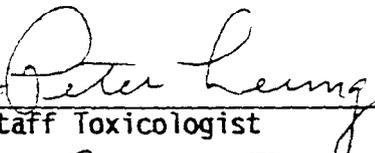
Revised: 5/01/91
Original Date: 3/29/91

PRODUCT REGISTRATION RECOMMENDATION SHEET

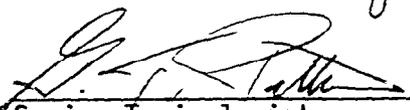
Formulated Product Name: BONZI Ornamental Growth Regulator
SB 950 #: NA ID #: 115551
Document #'s: 50583-4, -5, -021 through -031, EPA #: 10182-92
-033, -036, -037
Company Name: ICI Americas Inc.

RECOMMENDATION:

- 1) Submitted as a Section 3 registration action for greenhouse use on container-grown poinsettias, geraniums, and chrysanthemums and on bedding plants.
- 2) Chronic and SB950 Required Studies - The 4 week oral dose range-finding study in the mouse (Record #087665), submitted as justification for the dose levels selected for the mouse oncogenicity study (Record #073312), indicated that the highest dose administered in the mouse oncogenicity study was probably not at the maximum tolerated dose. Collectively, data from the chronic toxicity study in dogs and the combined chronic/oncogenicity study in rats indicate that the liver has been identified as the target organ for paclobutrazol and have revealed no evidence of an oncogenic potential. For these reasons, the Medical Toxicology Branch will not require another mouse oncogenicity study at this time.
- 3) The Worker, Health and Safety Branch is requested to complete an exposure assessment on the greenhouse use of this product before health assessment considerations can be made by the Medical Toxicology Branch.


Staff Toxicologist

5/1/91
Date


Senior Toxicologist

5/9/91
Date

Senior Toxicologist

Date

50583-003; 033450; Acute Oral Toxicity; 811; mouse; ICI PLC Central Toxicity Laboratory, Alderley Park UK, Report # CTL/P/748, 10/4/82; PP333 (paclobutrazol), 97.0% pure; 5 males/dose at 250, 320, 400, 500, 640, and 800 mg/kg; 10 females/dose at 400, 640, 800, 1000, 1260, and 2000 mg/kg; 5 females/dose at 500, 2500, and 3200 mg/kg; mortalities - male: 0/5, 1/5, 2/5, 1/5, 4/5, 5/5, respectively; females: 1/10, 4/10, 7/10, 5/10, 1/10, 9/10, respectively, and 1/5, 4/5, 2/5, respectively; the material caused subdued behavior, piloerection, unsteady gait, hypothermia and coma; no necropsy performed; most surviving animals gained weight by day 14; LD50 (male) = 490 (394-642) mg/kg, LD50 (female) = 1219 (no confidence limits reported) mg/kg; Toxicity Category II; Acceptable. (Berliner 4/9/87, updated Klein 7/7/89)

50583-003; 033450; Acute Oral Toxicity; 811, guinea pig; ICI PLC Central Toxicity Laboratory, Alderley Park UK, Report # CTL/P/748, 10/4/82; PP333 (paclobutrazol), 97.0% pure; 320, 400, 500, 640, and (males only) 800 mg/kg; 5/sex/dose; mortalities - males: 0/5, 1/5, 3/5, 2/5, 5/5, respectively, females: 0/5, 0/5, 3/5, 5/5, respectively; the material caused subdued behavior and unsteady gait; no necropsy performed; animals increased in body weight by day 14; LD50 (male) = 542 (432-717) mg/kg, LD50 (females) estimated between 400 and 640 mg/kg; Toxicity Category II; Acceptable. (Berliner 4-9-87, updated Klein 7/7/89)

Acute Dermal LD50

50583-003; 033449; Acute Dermal Toxicity; 812; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/748, 10/4/82; PP333 (paclobutrazol), 97.0% pure; 1000mg/kg; 5M/5F per dose; no mortalities; Signs of toxicity-none; Body weight-all animals gained by day 14; Necropsy-not performed; LD50 (M/F) >1000 mg/kg; Toxicity Category not determined; Unacceptable, only one dose used and not a limit test. (Originally reviewed by Berliner 4/9/87, and a Toxicity Category II was assigned; revised to meet current guidelines by Klein, 7/10/89)

50583-003; 033449; Acute Dermal Toxicity; 812; rabbit; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/748, 10/4/82; PP333 (paclobutrazol), 97.0% pure; 1000 mg/kg; 4M/4F; No mortalities; Signs of toxicity-none; Body weights-all animals increased by day 14; no necropsy performed; LD50 (M/F) > 1000 mg/kg; Toxicity Category not determined; Unacceptable, only one dose used and inadequate number of animals used. (Originally reviewed by Berliner, 4/10/87, and a Toxicity Category II was assigned; revised to meet current guidelines by Klein, 7/11/89)

The two acute dermal studies (rat and rabbit) combined will satisfy the data requirement for an acute dermal LD50 study with a Toxicity Category II determination.

Acute Inhalation LC50

None submitted.

Eye Irritation

50583-003; 033446; Eye Irritation; 814; rabbit; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/741, 9/24/82; Technical PP333 (paclobutrazol), 97.0% pure; 100 mg/eye; 9 animals (the eyes of 6 animals were unwashed and the eyes of 3 animals were washed); the material caused slight corneal opacity and conjunctivitis; all unwashed eyes cleared by day 7; CAT. III; Acceptable. (Berliner 4-10-87)

Dermal Irritation

50583-003; 033447; Dermal Irritation; 815; rabbit; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/741, 9/24/82; Technical PP333 (paclobutrazol), 97.0% pure; 500 mg moistened with 0.5 ml of olive oil to 1 intact and 1 abraded skin site/animal, 24-hour exposure, occluded patch; 6 female animals; no mortalities; erythema at 72hrs: score of 1 in 6/6 animals for intact skin; PDIS = 1.21; CAT. IV; Acceptable. (Berliner 4-10-87)

SUPPLEMENTAL STUDIES

50583-003; 033448; Acute Intraperitoneal Toxicity; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/748, 10/4/82; Technical PP333 (paclobutrazol), 97.0% pure; 5 males/dose at 100, 128, 160, 200, 250, and 320 mg/kg, 5 females/dose at 64, 80, 100, 126, 128, and 160 mg/kg, intraperitoneal injection; mortalities - males: 0/5, 0/5, 0/5, 3/5, 5/5, 5/5, respectively; females: 0/5, 1/5, 4/5, 3/5, 4/5, 5/5, respectively; Signs of toxicity-subdued behavior, piloerection, urinary incontinence, respiratory difficulties, increased lachrymation, hypothermia, and coma; Body weight-most surviving animals increased by day 14; no necropsies; LD50 (male) between 160 and 250 mg/kg, LD50 (female) = 99 (79-117) mg/kg; Supplemental and not a required study. (Berliner 4/8/87, updated Klein 7/12/89)

50583-003; 033451; Repeated Dermal Irritation; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/741, 9/24/82; Technical PP333 (paclobutrazol), 97.0% pure; 250mg/kg (equiv. to approx. 2mg/cm²) as a 12.5% (w/v) suspension in propylene glycol; five alternate 24-hour exposures; occluded patch held in place with adhesive tape; 5M/5F; no mortalities; animals observed for a further 9 days; material caused slight erythema, desquamation and/or slight scabbing in some animals; supplemental. (Berliner 4-10-87)

50583-004 033462 "PP333: 6 Week Oral Dosing Study in Dogs" (ICI PLC Central Toxicology Laboratory, Alderley Park UK, Lab. Report No. CTL/P/767, 6/16/83) Paclobutrazol 91.9% pure; 0, 15, 75, or 225 mg/kg/day by oral capsule daily for six weeks to 1 beagle dog/sex/dose to determine suitable dose levels for a 6-month dog study; no mortalities; **no adverse effects noted**. NOEL = 15 mg/kg/day (increased liver weight, increased plasma alkaline phosphatase); **supplemental** (Klein, 8/15/89)

Paclobutrazol 4 g/l Formulation Acute Toxicity Categories

Acute Oral LD50	IV (4)
Acute Dermal LD50	III (3)
Acute Inhalation LC50	None Submitted
Eye Irritation	IV (4)
Dermal Irritation	IV (4)

Paclobutrazol 4 g/l Formulation Acute Toxicity Studies

Acute Oral LD50

50583-004; 033460; Acute Oral Toxicity; 811; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Study No. AR3487; 5/17/84; Paclobutrazol 4 g/l Formulation (0.39% paclobutrazol), diluted to approx. 50% in water for dosing; 5346 mg/kg at dosing volume of 11 ml diluted material/kg; 5 animals/sex; no mortalities; no signs of toxicity; normal weight gain; Necropsy- no

macroscopic abnormalities; LD50 (M/F) > 5346mg/kg; Toxicity Category IV; Acceptable. (Berliner, 4/20/87; Updated, Duncan, 5/17/89)

Acute Dermal LD50

50583-004; 033459; Acute Dermal Toxicity; 812; rat; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Study No. CR1843; 5/17/84; Paclobutrazol 4 g/l Formulation (0.39% paclobutrazol); 2 ml/kg (approx. 2.1 g/kg using density reported on Fed app.); 5 animals/sex; occluded patch, 24-h exposure period; no mortalities; normal weight gain; Clinical Observations- diarrhea, urinary incontinence, skin eruptions, staining of the coat; Necropsy- no macroscopic abnormalities; LD50 (M/F) > 2 ml/kg (reported); Toxicity Category III; Acceptable. (Berliner, 4/21/87; Updated, Duncan, 5/17/89)

Acute Inhalation LC50

None submitted.

Eye Irritation

50583-004; 033457; Primary Eye Irritation; 814; rabbit; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Study No. FB3075; 5/17/84; Paclobutrazol 4 g/l Formulation (0.39% paclobutrazol); 0.1 ml/eye; 9 females: 3 washed 20-30 sec after dosing, 6 unwashed; examined 1-2, 24, 48, 72 (term. 8), 96 h (term. 1); UNWASHED- conjunctivitis only (max. scores = 1/redn., 1/chem., 1/disch.), clear by 24 h; Toxicity Category IV; Acceptable. (Berliner, 4/23/87; Updated, Duncan, 5/17/89)

Dermal Irritation

50583-004; 033458; Primary Dermal Irritation; 815; rabbit; ICI PLC Central Toxicology Laboratory, Alderley Park UK, Study No. EB2500; 5/14/84; Paclobutrazol 4 g/l Formulation (0.39% paclobutrazol); 0.4 ml of undiluted or diluted (1:16 in water) test material per site; 6 female rabbits, one application of each solution per animal; 4-h exposure, occluded patch; examined 1, 20, 44, 68 h (term.); UNDILUTED- erythema of 1 in 1/6 animals at 1 h, clear at 20 h; DILUTED- erythema of 1 in 1/6 animals at 20 h, clear at 44 h; Toxicity Category IV; Acceptable. (Berliner, 4/23/87; Updated, Duncan, 5/17/89)

Paclobutrazol 20 g/l Formulation Acute Toxicity Categories

Acute Oral LD50	IV (4)
Acute Dermal LD50	III (3)
Acute Inhalation LC50	III (3)
Eye Irritation	I (1)
Dermal Irritation	IV (4)

Paclobutrazol 20 g/l Formulation Acute Toxicity Studies

Acute Oral LD50

50583-031; 74253; Acute Oral; 811; rat; ICI PLC Central Toxicology Laboratory, Cheshire, UK; Lab. Project No. CTL/P/1864; 6/11/87; Paclobutrazol 20 g/l (2.79% paclobutrazol), Formulation No. GFU484, dosed as a 50% w/v solution in polyethylene glycol (493 mg formulation/ml dosing solution); 5000 mg/kg; 5 animals/sex; No mortality; Clinical Observations- sedation; Necropsy- no abnormalities; LD50 > 5000 mg/kg (M/F); Toxicity Category IV; Acceptable. (Duncan, 6/30/89)

Acute Dermal LD50

50583-031; 74254; Acute Dermal; 812; rat; ICI PLC Central Toxicology Laboratory, Cheshire, UK; Lab. Project No. CTL/P/1838; 6/25/87; Paclobutrazol 20 g/l (2.79% paclobutrazol), Formulation No. GFU484, dosed neat; 2043 mg/kg; 5 animals/sex; occluded, 24-hour exposure; No mortality, no clinical abnormalities, no abnormalities noted at necropsy; LD50 > 2043 mg/kg (M/F); Toxicity Category III; Acceptable. (Duncan, 6/29/89)

Acute Inhalation LC50

50583-031; 74255; Acute Inhalation; 813; rat; ICI PLC Central Toxicology Laboratory, Cheshire, UK; Lab. Project No. CTL/P/1901; 9/15/87; Paclobutrazol 20 g/l (2.72% paclobutrazol in EtOH), Formulation No. GFU484, used neat; 0 (air), 4.1 mg/l (analytical); 5 animals/sex; 4-hour nose-only exposure; test atmosphere consisted of 0.111 mg paclobutrazol (particulate) and 20 mg EtOH (vapor) per liter; MMAD = 3.5 um, 66.1% of particles were < 6 um, particle samples were 87.9% paclobutrazol; No mortality; Clinical Observations- hunched posture, stains around snout, salivation, abnormal respiratory noises, piloerection, increased response to touch; Necropsy- no treatment-related abnormalities, no changes in lung or liver weight; LC50 > 4.1 mg/l (M/F); Toxicity Category III; Acceptable. (Duncan, 7/3/89)

Eye Irritation

50583-031; 74256; Primary Eye Irritation; 814; rabbit; Food & Drug Research Laboratories, Inc., Waverly, NY, Lab. Project No. CTL/P/1970; 10/16/87; Y00001/095/002, BN 018140 (Formulation GFU484, containing 20 g paclobutrazol/l in ethanol); 0.1 ml/eye; 6 animals unwashed; examined at 1, 24, 48, 72 h, and 4, 7, 10, 13, 16, 19, 21 d (termination); UNWASHED- corn. opacity (max. score = 4) persisting to Day 21 in one animal, and conjunctivitis (max. scores = 2/redn., 3/chem., 2/disch.) with blistering; all effects cleared in 5/6 animals by Day 13; Toxicity Category I; Acceptable. (Duncan, 7/3/89)

Dermal Irritation

50583-031; 74257; Primary Dermal Irritation; 815; rabbit; ICI PLC Central Toxicology Laboratory, Cheshire, UK; Lab. Project No. CTL/P/1829; 5/15/87; Paclobutrazol 20 g/l (2.79% paclobutrazol), Formulation No. GFU484, dosed neat; 0.5 ml/site; 1 site/animal, 6 animals; 4-h exposure, occluded sites; scored at 30-60 min, and 1, 2, 3 d (termination); erythema of 1 in 2/6 animals at 30-60 min and in 1/6 animals at 1 d; clear at 2 d; PDIS = 0.1; Toxicity Category IV; Acceptable. (Duncan, 7/5/89)

Paclobutrazol 250 g/l Formulation Acute Toxicity Categories

Acute Inhalation LC50

III (3)

Paclobutrazol 250 g/l Formulation Acute Toxicity Studies

Acute Inhalation LC50

50583-005; 033463, 033464; Acute Inhalation Toxicity; 813; rat; ICI PLC Central Toxicology Laboratory, Study No. HR0528; 1/30/85; Paclobutrazol 250 g/l Formulation (23.8% paclobutrazol), diluted to 10% w/w and 50% w/w in H2O for testing at low and high conc., respectively; 0 (air), 0.132, 0.337 (maximum attainable concentration) mg total particulates/l (gravimetric anal.), equivalent to 0, 0.099, 0.250 mg paclobutrazol/l (chemical anal.); MMAD = 0, 3.6, 4.5 um; 4 h nose-only exposure; 5 animals/sex/dose level; no mortality; clinical observations- absence of pinna reflex, reduced righting reflex, subdued behavior, abnormal respiratory noise, transient depression of

CNS activity; necropsy- no macroscopic abnormalities; organ weights- increased Lung:body; LC50 (M/F) > 0.250 mg paclobutrazol/l (reported), LC50 (M/F) > 1.1 mg formulation/l (calculated, based on test conditions); Toxicity Category III; Acceptable. (Berliner 4/14/87; Revised to add LC50 for formulation, Duncan 5/19/89)

SUBACUTE STUDIES

Repeated Dose Dermal Toxicity

50583-003; 033444; Repeated Dose Dermal Toxicity: 21-day Study; 822; rabbit; "The Effect Of Repeated Applications Of PP 333 To The Skin Of Rabbits For Twenty-One Days" (ICI PLC Central Toxicology Laboratory, 3/17/80) Paclobutrazol (PP333), 97.0% pure, was applied to intact (5M/5F) and abraded (5M/5F) skin of rabbits (covered) at 0 (1% aqueous methylcellulose), 10, 100, 1000 mg/kg/d for 6 hours/day, 5 days/week, 3 consecutive weeks; mortalities - males: 2/10, 0/10, 3/10, 0/10, respectively; females: 0/10, 0/10, 2/10, 0/10, respectively; the material caused slight to well-defined erythema, slight edema, persistent well-defined to moderate dermal irritation; Histopath.- varying degrees of hyperkeratosis, acanthosis and inflammatory changes of the superficial dermis present in the majority of animals at 1000 mg/kg/d; treated and control rabbits were similar for general health, bodyweight, food consumption, hematology, blood chemistry and organ weights; NOEL = 100mg/kg; Supplemental data only. (Berliner, 4-17-87, updated Klein 7/3/89)

SUBCHRONIC STUDIES

Subchronic Oral Toxicity

50583-003 033443 "Paclobutrazol (PP333): 90 Day Feeding Study In Rats" (ICI, Central Toxicology Laboratory, Alderley Park UK, 7/18/83) Paclobutrazol, CTL reference # Y00001/001/017, 92.4% pure, was fed to 20M/20F rats at 0, 50, 250, 1250 ppm; no adverse effects; NOEL = 250 ppm (females - decreased body weight gain and slight drop in food consumption, both sexes - an increase in liver weights and hepatic aminopyrine-N-demethylase activity, minor histopathologic liver effects, small changes in plasma cholesterol and alanine transaminase activity). Acceptable. (Berliner and Patterson 4/24/87, updated Klein 7/3/89)

METABOLISM STUDIES

Metabolism, Rat

50583-004; 033461; "Paclobutrazol: Excretion And Tissue Retention Of A Single Oral Dose (10mg/kg) In The Rat" ICI PLC Central Toxicology Laboratory, Cheshire UK, Report # CTL/P/870, 8/9/83; (Technical PP333); Dose level nominal 10mg/kg, 2MBq/kg, 3M/3F; 75-87% of the dose eliminated within 48 hours; Male 23-48% in the urine and 44-64% via the feces, Females 48-64% in the urine and 26-41% via the feces; retention of residues in the tissues was minimal; Unacceptable, this study will satisfy only one of the four necessary studies required for a complete metabolism study (see section IV B for further explanation). (Berliner and Patterson 4/24/87)

50583-023; 073300; "(¹⁴C)-Paclobutrazol: Excretion and Tissue Retention of a Single Oral Dose (5 mg/kg) in the Rat"; 851; Rats; Hazleton Laboratories Europe Ltd., North Yorkshire, UK, Lab. Report No.3456-72/267, 10/7/83; (¹⁴C)-Paclobutrazol (98% purity, specific activity = 5.87 MBq/mg); single oral via gavage (5 mg/kg); 4 rats/sex/dose; no observable toxic effects throughout

duration of study; 77% of the administered radioactivity was eliminated within the first 48 hrs; within 168 hrs post-dose 96.4% of the radioactivity was excreted by male rats (urine - 57.7%, feces - 37.4%, and cage washings - 1.3%); similarly, 97.3% of the administered dose was excreted by female rats (urine - 64.9%, feces - 28.4%, cage washing - 4.0%); low or undetectable tissue residues at 168 hrs post-dose; residual radioactivity detected in gastrointestinal tract and liver of most animals; **study not acceptable/ not upgradeable**; inadequate number of animals/sex/dose; this study will satisfy one of the four data requirements necessary for a complete metabolism study (Leung, 6/12/89).

50583-023; 073301; -"Paclobutrazol: Excretion And Tissue Retention Of A Single Oral Dose (10mg/kg) In The Rat"; ICI PLC Central Toxicology Laboratory, Cheshire, UK, Lab. Report No. CTL/P/870, 8/9/83; (¹⁴C)-paclobutrazol (99% purity, specific activity = 1.76 GBq/mg); Single oral via gavage (10mg/kg); 3 rats/sex/dose; 75-87% of the dose eliminated within 48 hours; Male 32-48% in the urine and 44-61% via the feces, Females 48-56% in the urine and 34-41% via the feces; retention of residues in the tissues was minimal; **study not acceptable/not upgradeable**; inadequate number of animals/sex/dose; this study will satisfy only one of the four data requirements necessary for a complete metabolism study; (Patterson, 4/24/87; updated Leung, 6/12/89).

50583-023; 073302; "(¹⁴C)-Paclobutrazol: Excretion and Tissue Retention of a Single Oral Dose (250 mg/kg) in the Rat"; 851; rats; Hazleton Laboratories Europe Ltd., North Yorkshire, UK, Lab. Report No. 3268-72/268, 2/16/84; (¹⁴C)-paclobutrazol (97.5% pure, specific activity = 5.87 MBq/mg); single oral via gavage (250 mg/kg); 4 rats/sex/dose; no toxic or pharmacologic effects which could have been attributed to administration of (¹⁴C)-paclobutrazol were observed; 98% of the administered radioactivity were recovered at 168 hours after dosing in excreta of male and female via urine (51-54%), feces (43-45%) and in the cage washing (1.2-1.7%); no significant difference between males and females in routes of elimination; overall elimination rate at this dose level, when compared to the 5 mg/kg dose level, was significantly slower in first 24 hours; tissue radioactive residues at 168 hrs post-dose were very low or undetectable; residual radioactivity was found in the gastrointestinal tract and liver; levels in all other analyzed tissues were below the limits of detection; overall levels of tissue radioactivity were similar to those obtained at the 5 mg/kg dose level; **study not acceptable/not upgradeable**; inadequate number of animals/sex/dose; this study will satisfy one of the four data requirements necessary for a complete metabolism study; (Leung, 6/13/89).

50582-023; 073303; "Paclobutrazol: Whole Body Autoradiography Study in the Rat Following a Single Oral Dose (250 mg/kg)"; 851; Rats; ICI PLC Central Toxicology Laboratory, Cheshire, UK, Lab. Report No. CTL/P/1035, 5/31/84; (¹⁴C)-paclobutrazol(98% purity, specific activity = 1.68 Mbq/mg); single oral (250 mg/kg); 1 rat/sex/dose; autoradiographs from male and female rats showed similar distribution of radioactivity; majority of the radiolabeling was found in the contents of the gastrointestinal tract; low levels of radioactivity were detected in liver, kidneys and peri-renal fat, but in no other tissues; therefore tissue disposition of paclobutrazol and its metabolites following a single 250 mg/kg oral dose is minimal; **supplemental** (Leung, 6/14/89)

50583-023; 073304; "(¹⁴C)-Paclobutrazol: Bioaccumulation of Repeated Oral Doses (5mg/kg/day) in the Rat"; 851; Rats (male); Hazleton Laboratories Europe Ltd., North Yorkshire, UK, Lab. Report No. 3743-72/269, 5/17/84; (¹⁴C)-paclobutrazol(96.9% purity, specific activity = 5.87 MBq/mg); repeated single daily oral dosing via gavage (5 mg/kg/day) for 49 days with interim sacrifices

for tissue sampling; concentrations of radioactivity in the liver and kidney appeared to plateau after the 28th dose, whereas a gradual accumulation of radioactivity in the blood was observed and its mean peak level was lower than those in the liver and kidney; radioactivity levels in liver and kidney declined biexponentially with terminal half-lives of 6.69 and 9.26 days, respectively; no detectable radioactive residues were present 28 days after the final dose; similar decreases were observed in blood levels after the final dose and its terminal half-life using day-42 levels was determined to be 3.16 days; no significant tissue retention of (^{14}C)-paclobutrazol and its metabolites on cessation of dosing; study not acceptable/not upgradeable; inadequate number of animals/dose; this study will satisfy one of the four data requirements necessary for a complete metabolism study (Leung, 6/15/89)

50583-023; 073305; "Paclobutrazol: The Effect of a Single Oral Dose (5 mg/kg or 250 mg/kg) on Liver Weight in the Rat"; 851; Rats; ICI PLC Central Toxicology Laboratories, Cheshire, UK, Lab. Report No. CTL/P/1065, 5/31/84; paclobutrazol (99% purity); single oral (0, 5, and 250 mg/kg); 5 rats/sex/dose; single oral dose of 250 mg paclobutrazol/kg produced a significant increase ($p < 0.01$) in liver weight relative to body weight; a less pronounced increase ($p < 0.05$) in liver weight was also observed in similarly dosed females; single oral dose of 5 mg/kg did not produce any significant changes in liver weight relative to body weight in both sexes; supplemental (Leung, 6/16/89).

50583-023; 073306; "Paclobutrazol: Biotransformation in the rat"; 851; Rats; ICI PLC Central Toxicology Laboratory, Cheshire, UK, Lab. Report No. CTL/P/1036, 5/31/84; (^{14}C)-paclobutrazol 97% radiochemical pure, specific activity = 1.68 GBq/mM; nonlabeled paclobutrazol 98% pure; paclobutrazol extensively metabolized by male and female rats following single oral dose of 5 or 250 mg/kg; at the higher dose about 5% of the dose was not absorbed and eliminated unchanged in the feces; biotransformation of the absorbed paclobutrazol is limited to the tertiary butyl moiety with no metabolism in either the triazole or halogenated phenyl rings; two main metabolites, paclobutrazol diol and acid were eliminated in the conjugated and unconjugated forms in the urine, bile and feces; all other metabolites were minor and each amounted to less than 5% of the dose; irrespective of the dose levels, male rats oxidized a greater proportion of paclobutrazol to carboxylic acid metabolite than female rats; although paclobutrazol is readily oxidized to the diol metabolite at both dose levels in the female, the second oxidation step to the acid metabolite is saturable in the females, as shown by the greater proportion of the conjugated diol metabolite excreted at the higher dose level; supplemental (Leung, 6/16/89).

Summary: No individual study (record #'s: 073300, 073301, 073302, 073303, 073304, 073305 and 073306) satisfies the necessary requirements for a complete animal metabolism study. Collectively, data from all seven studies provide enough information to fulfill the requirements for an acceptable animal metabolism study. Single intravenous dose of the labeled test substance is not required due to its poor solubility in water or physiological saline.

Paclobutrazol when given as a single oral dose (5, 10, or 250 mg/kg) is rapidly absorbed and rapidly eliminated (073300, 073301, 073302, 073303). A major portion (77-85%) of the dose is eliminated within 72 hours after administration. Tissue levels for all three doses at 168 hours post-dose were either very low or below the limits of detection. There were no significant differences between both sexes with regard to the routes or rates of excretion, or tissue retention of paclobutrazol and/or its metabolites.

Male and female rats showed similar distribution of ^{14}C -paclobutrazol as indicated by whole body autoradiography. Majority of the radioactivity was

associated with the contents of the gastrointestinal tract and liver. Following repeated single daily oral administration of ¹⁴C-paclobutrazol, concentrations of radioactivity appeared to plateau after the 28th dose, whereas a gradual accumulation of radioactivity in the blood was observed and its mean peak level was lower than those in the liver and kidney. With cessation of dosing, radioactivity levels in the liver and kidney decline biexponentially with terminal half-lives of 6.69 and 9.26 days, respectively. No detectable residues were present 28 days after the final dose.

Paclobutrazol is extensively metabolized by the male and female rats following single oral dose of 5 or 250 mg/kg. Biotransformation of the absorbed paclobutrazol is limited to the tertiary butyl moiety with no metabolism in either the triazole or halogenated phenyl rings. The two main metabolites, paclobutrazol diol and acid are eliminated in the conjugated and unconjugated forms in the urine, bile and feces. All other metabolites were minor and each amounted to less than 5% of the dose. Irrespective of the dose levels, male rats oxidized a greater fraction of the absorbed dose of paclobutrazol to the carboxylic acid metabolite than female rats. Although paclobutrazol is readily oxidized to the diol metabolite at both dose levels in the female, the second oxidation step to the acid metabolite is saturable in the females, as shown by the greater portion of the conjugated diol metabolite excreted at the higher dose level. (Leung 7/89)

SB950-MANDATED HEALTH EFFECTS STUDIES

Combined, Rat

** 030 073313; "Paclobutrazol: 104 Week Oral (Dietary Administration) Combined Toxicity and Carcinogenicity Study in the Rat with a 52 Week Interim Kill" (Hazleton Laboratories Europe Ltd., Harrogate England, Report # 5055-72/273, 10/17/86) Paclobutrazol, Batch # P29 (ICI reference #'s Y00001/001/032, 033, and 037), 92.4% pure, was administered in the feed to 60 Sprague Dawley-derived rats/sex/dose with 10/sex/dose for scheduled sacrifice at 52 weeks, at 0, 50, 250, and 1250 ppm for 104 weeks. **No adverse effects noted.** NOEL = 50 ppm (decreased body weight gain and decreased triglyceride values in females, hepatocellular fatty degeneration). **Acceptable.** (Klein and Gee, 6/9/89)

Chronic Toxicity, Rat

See under Combined Rat above.

Chronic Toxicity, Dog

004 033646; interim report for chronic toxicity dog study (# 073310) reviewed by Fred Martz, 4/20/87.

** 027; 073310; "Paclobutrazol: 1 year Oral Dosing Study in Dogs" (ICI PLC Central Toxicology laboratory, Alderley Park, Cheshire, UK, Lab. Report No. CTL/P/958, 5/29/84) Paclobutrazol 92.4% pure; 300, 75, 15 or 0 mg/kg/day by oral capsule daily for 1 year; 6 beagle dogs/sex/dose; no mortality at any dose levels throughout the study; males in 300 mg/kg/day group exhibited minor differences (6.94%) in total body weight as compared to control group at the end; no effects on food consumption and hematological indices; increases ($p < 0.01$) in plasma alkaline phosphatase activity at the 300 and 75 mg/kg/day dose level in males (580.0% and 73.4%, respectively) and females (620.5% and 119.3%, respectively); no changes in plasma levels of alanine transaminase or aspartate transaminase; elevated ($p < 0.01$) plasma triglycerides in males (73.8%) and females (80.1%) at the 300 mg/kg/day dose level with a reduction in albumin and calcium from 12 weeks onwards; liver weights were increased ($p < 0.01$) in males at all dose levels (11.1 - 41.6%) and in females at 300

mg/kg/day (31.2%); elevated hepatic aminopyrine N-demethylase were reported in males at all dose levels (15.9 - 138.9%) and in females at 300 mg/kg/day (98.4%); mild hepatocellular swelling in two males and three females at the 300 mg/kg/day dose level and two females at the 75 mg/kg/day dose level and was not considered to be of toxicologic significance at this time; NOAEL (M/F) \geq 300 mg/kg/day (no adverse effects in dogs were observed when this dose was administered daily for one year); NOEL (M/F) = 15 mg/kg/day (at this dose level, only minimal adaptive changes were observed in male dogs) study acceptable; (Leung, 7/7/89).

Oncogenicity, Rat

See under Combined Rat above.

Oncogenicity, Mouse

029 073312 "Paclobutrazol: 104 Week Oral (Dietary Administration) Combined Toxicity and Carcinogenicity Study in the Mouse with a 52 Week Interim Kill" (Hazleton Laboratories Europe Ltd., Harrogate England, Report # 5014-72/274, 9/86) Paclobutrazol, Batch #P29 (ICI reference #'s Y00001/001/032, 033 and 037), 92.4% pure, was administered in the feed to 63 mice/sex/dose with 12/sex/dose for scheduled sacrifice at 52 weeks, at 0, 0, 25, 125, and 750 ppm for 104 weeks. **No adverse effects noted.** NOEL = 125 ppm (decreased triglyceride levels (M, F), decreased cholesterol levels (M), increased liver weights (M, F), increased kidney weights (F)). NOAEL \geq 750 ppm; **unacceptable** (no dose justification and clinical chemistries and organ weights not adequate to determine if MTD was achieved); originally reviewed as upgradable (with the submission of data to justify dose levels and evidence that MTD was reached). (Klein and Gee, 6/22/89) Reviewed again with supplemental data (Record # 087665, 4 week oral dose range-finding study in the mouse). No status change (MTD was not reached). (Klein 6/5/90)

033 087665 "Paclobutrazol: 4 Week Oral (Dietary Administration) Dose Range-Finding Study in the Mouse" (Shaw, D.C., Hazleton Laboratories Europe Ltd., Harrogate, UK, Report # 3525-72/272, 5/84) Paclobutrazol, Batch # P29 (ICI reference #'s Y00001/001/032 and 033), 92.4% pure, was administered in the feed to 18 Cr1:CD-1(ICR)BR mice/sex/dose at 0, 50, 1000, 1500, and 2000 ppm for four weeks. **No adverse effects were noted.** The NOEL of 50 ppm was based on decreased serum cholesterol and triglyceride levels, increased serum alanine aminotransferase levels, and hepatic hypertrophy and microvacuolation in both males and females, and increased liver weights in males. The NOAEL of 1500 ppm was based on focal hepatocellular necrosis. This supplemental study was submitted as justification for the dose levels selected in Record # 073312. (Klein 6/4/90)

Summary: The supplemental study data (Record #087665) indicate that the highest dose (750 ppm) administered in the mouse oncogenicity study (Record #073312) may not represent the maximum tolerated dose for paclobutrazol. Collectively, data from the chronic toxicity study in dogs and the combined chronic/oncogenicity study in rats indicate that the liver has been identified as the target organ for paclobutrazol and have revealed no evidence of an oncogenic potential. Another mouse oncogenicity study using higher dose levels would probably not provide new significant information.

Reproduction, Rat

** 028 073311 "Paclobutrazol: Two Generation Reproduction Study in Rats Including Individual Animal Data", (ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, Study # RR0303, Report # CTL/P/1496, 2/27/87); paclobutrazol, 92.4% purity, batch P29, fed

continuously in diet for two generations at 0, 50, 250, and 1250 ppm; parental generations 15 males/dose, 30 females/dose, mated each male with 2 females; **No Adverse Effects**; Parental NOEL = 250 ppm (marginal reduction in body weight gain, hepatic centrilobular fatty change), Parental NOAEL \geq 1250 ppm, Reproductive NOEL \geq 1250 ppm; **Acceptable**. (DiBiasio and Patterson, 8/24/89)

Teratology, Rat

004 033649 033650 "Paclobutrazol: Teratogenicity Study in the Rat" (ICI Central Toxicology Laboratory, Cheshire UK, Report # CTL/P/842, 7/13/83) Paclobutrazol, 92.4% pure, was given by gavage to 24 rats/dose at 0 (corn oil), 40, 100, and 250 mg/kg/day on days 6-15 of gestation. Maternal NOEL = 40 mg/kg (decreased weight gain, increased urogenital staining). Developmental NOEL < 40 mg/kg (increased incidence of minor skeletal defects at all dose levels, cleft palate at 250 mg/kg/day may be related to treatment). **Possible adverse effect**, developmental NOEL < maternal NOEL. **Unacceptable** (developmental NOEL not established). Shimer and Parker 4/14/87.

**** 009 041209** "Paclobutrazol: Second Teratogenicity Study in the Rat" (ICI PLC Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/997, 6/1/84) Paclobutrazol, 92.4% pure, was given by gavage at 0 (corn oil), 2.5, 10, 40, or 100 mg/kg/day to 24 successfully mated female Wistar-derived rats/dose from days 7-16 inclusive of gestation; maternal toxicity NOEL \geq 100 mg/kg/day (no maternal toxicity; prior study [Record #'s 033649, 033650] demonstrated maternal toxicity at 250 mg/kg/day); developmental toxicity NOEL = 10 mg/kg/day (kidney and ureter defects; hydroureter at 100 mg/kg/day); **possible adverse effect**, developmental NOEL < maternal NOEL. **Acceptable**. Berliner and Parker 3/21/86; updated Klein and Patterson 8/15/89.

025 073308 Exact duplicate of 041209.

Teratology, Rabbit

**** 004 033647 033648** "Paclobutrazol: Teratogenicity Study in the Rabbit" (ICI Central Toxicology Laboratory, Cheshire UK, Report # CTL/P/861, 7/14/83) Paclobutrazol, 92.4% pure, was given by gavage at 0 (corn oil), 25, 75, and 125 mg/kg/day to 9, 12, 13, and 8 rabbits, respectively, for days 6-18 of gestation; Maternal NOEL = 75 mg/kg (decreased weight gain). Developmental NOEL \geq 125 mg/kg (maximum dose tolerated). **No adverse effects** (no fetotoxic effects, no fetal defects). **Acceptable**. Shimer and Parker 4/14/87.

****026 073309** "Paclobutrazol: Second Teratogenicity Study in the Rabbit Including Individual Animal Data", (ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK, ID # CTL/P/1460, October 22, 1986), Paclobutrazol (PP333), batch no. P29, CTL reference #'s Y00001/001/017 and Y00001/001/035, 92.4% purity; administered by oral gavage to 18 rabbits/dose at 0 (corn oil), 25, 75, or 125 mg/kg on days 7-19 of gestation (day 1 = day of insemination); **No adverse effects indicated**; Maternal NOEL = 75 mg/kg (marginal effect on body weight gain); Maternal NOAEL \geq 125 mg/kg; Developmental NOEL \geq 125 mg/kg. **Acceptable** (DiBiasio and Gee, 8/21/89)

Gene Mutation

**** 006 41734** "PP333 - An Evaluation in the Salmonella/Microsome Mutagenicity Assay" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Alderley Park UK, Report # CTL/P/722, 9/14/82) Paclobutrazol, Code Name = PP333, CTL reference # Y00001/001/011, 92.4% pure, was tested with Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100, with and without Aroclor-stimulated rat liver S9 fraction, at 0 (DMSO) and over a dose range of 1.6 to 5000 ug/plate, 3 plates/dose, confirmatory assays for all strains with

a third trial for TA98; **no adverse effects noted** (no increase in number of revertant colonies); **acceptable**. Davis 4/7/87, updated Klein and Patterson 7/5/89.

** 004 033652 "PP333 - Assessment of Mutagenic Potential in the Mouse Lymphoma Mutation Assay" (Inveresk Research International, IRI Project # 730415, 3/83) Paclobutrazol, Code Name = PP333 (Y00001/001/011), 92.4% pure, was tested with L5178Y TK⁺ mouse lymphoma cells for 3 hours at 0 (methanol) and over a dose range of 1.0 to 100 ug/ml in the first assay and 60 to 140 ug/ml in the second assay, with and without Aroclor-stimulated rat liver S9 fraction, 3 plates/dose; **no adverse effects noted** (no increase in number of colonies); **acceptable**. Davis 4/8/87, updated Klein and Patterson 7/5/89.

Chromosome Effects

** 004 033651 "An Evaluation of Paclobutrazol in the Mouse Micronucleus Test" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Report # CTL/P/848, 8/4/83) Paclobutrazol, CTL reference # Y00001/001/030, 92.4% pure, was given in a single intraperitoneal injection to 5 C57Bl/6j mice/sex/sacrifice time/dose at 0 (corn oil), 87.5 or 140 mg/kg; at 24, 48, and 72 hours animals were sacrificed, bone marrow slides prepared, and 500 polychromatic erythrocytes examined/sex/sacrifice time/dose. **Possible adverse effect**, highly significant elevation of the frequency of micronuclei at 140 mg/kg at 24 hours. **Acceptable**. Davis 4/8/87, updated Klein and Patterson 7/6/89.

** 009 041210 "Paclobutrazol: Dominant Lethal Study in the Mouse" (Imperial Chemical Industries PLC, Central Toxicology Laboratory, Report # CTL/P/922, 12/29/83) Paclobutrazol, CTL reference # Y0001/001/020, Batch P29, 92.4% pure, was given by gavage to 15 male CD-1 mice/dose at 0 (corn oil), 25, 100, and 300 mg/kg/day for 5 consecutive days; each male was mated to 2 females/week for 8 weeks; males dosed with 300 mg/kg/day exhibited piloerection, urinary incontinence, and tremors. **No adverse effects** (no dominant lethal effects, no effect on fertility). **Acceptable**. Remsen 3/5/86, updated Klein and Patterson 7/7/89.

** 009 041211 "Paclobutrazol: A Cytogenetic Study in the Rat" (Imperial Chemical Industries PLC, Central Toxicology Laboratory, Report # CTL/P/891, 5/2/84) Paclobutrazol, CTL reference # Y00001/001/001, Batch P29, 92.4% pure, was given by gavage to 8 Alderley Park rats/sex/dose/sacrifice time at 30, 150, and 300 mg/kg and to 12 rats/sex in negative (corn oil) and positive controls; animals were sacrificed at 24 hr except animals given 300 mg/kg were sacrificed at 12, 24, and 48 hr, chromosome preparations made from bone marrow. **No adverse effect** (statistically significant increase in chromosomal abnormalities at 300 mg/kg, 12 hr, considered not biologically significant when compared with control data). **Acceptable**. Remsen 3/5/86, updated Klein and Patterson 7/7/89.

** 036; 88828; "Paclobutrazol: An Evaluation in the In Vitro Cytogenetic Assay in Human Lymphocytes"; ICI Central Toxicology Laboratory, Cheshire, UK; 8/24/90; paclobutrazol (lot# Bx P18, 98.8% (w/w)); 2 donors (1 male, 1 female); cells were exposed in two cytotoxicity tests to either 0 (DMSO), 1.6, 8, 40, 200, or 1000 ug/ml or 0 (DMSO), 50, 100, 250, 500, 750, or 1000 ug/ml of the test compound \pm S9 fraction. Chromosomal aberrations scored in cells exposed to 50, 250, or 500 ug/ml of test compound; human lymphocytes derived from two donors; too cytotoxic \geq 500 ug/ml (\pm S9) (based on mitotic index); no dose dependent increase in chromosomal aberrations, only in the 500 ug/ml cultures was a significant increase reported. Study previously unacceptable, but upgradeable (the study needed 1) documentation of test compound's

stability in the vehicle and 2) justification for using only single time points for treatment and harvesting) (Moore, 9/21/90); Requested information submitted (fax, 2/6/91); Test article is not considered to be clastogenic in this assay; Study acceptable (Revised, Moore, 3/27/91).

** 037; 96620; "Paclobutrazol: An Evaluation in the Mouse Micronucleus Test" (ICI Central Toxicology Laboratory, Cheshire, UK, Report No. CTL/P/3216, 2/21/91); paclobutrazol technical (Batch # P29 D2517/62, 92% purity); single oral; 0 (corn oil), 233, or 373 mg/kg to 5 mice/sex/dose/sampling time; additional 5 mice/sex were dosed at 373 mg/kg to replace any animals dosed at that level that were found dead or killed in extremis; bone marrow samples taken at 24, 48, and 72 hours after dosing; 1000 PCE/animal scored for incidence of micronuclei; positive control functional; **no adverse effects**; clinical signs include urinary incontinence, hunched posture, tiptoe gait, eye discharge and piloerection; 1 male and 3 males at low and high doses, respectively, were killed in extremis, 2 females at the high dose killed in extremis; paclobutrazol did not induce any significant increases in the incidence of micronucleated polychromatic erythrocytes; **acceptable**; (Leung, 5/1/91).

Summary: Five acceptable studies have been submitted in this category. The dominant lethal study was negative, but this assay lacks sensitivity. In the in vitro cytogenetic assay in human lymphocytes, the test article was not considered to be clastogenic. The chromosome aberration study and micronucleus study reports conclude that there is no mutagenicity, but in each there were significantly elevated values at the high dose and early sample time. The most recent chromosomal aberration study (CDFA record # 96620, 2/21/91) submitted did not indicate any significant increases in the incidence of micronucleated polychromatic erythrocytes. Individually, these results might be dismissed as not biologically significant (the CDFA review of the chromosome aberration study on 3/5/86 did so), but taken together they support a possible weak clastogenicity. (B. Davis, 4/8/87; updated, Leung, 5/1/91)

DNA Damage

** 016 053470 "Paclobutrazol: Assessment for the Induction of Unscheduled DNA Synthesis in Rat Hepatocytes In Vivo" (Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Report # CTL/P/1608, 10/21/86) Paclobutrazol, CTL reference # Y00001/001/017, 92.4% pure, given by oral gavage to male Alpk:AP rats at 0 (corn oil), 40, 200 or 400 mg/kg; animals sacrificed at 4 and 12 hours after test article administration, 2 animals/dose/sacrifice time in Trial 1, 3 animals/dose/sacrifice time in Trial 2; rat hepatocytes into culture with ³H-thymidine for 4 hours, autoradiography for analysis of UDS. **No adverse effect** (no induction of unscheduled DNA synthesis under conditions of the test). **Acceptable**. Gee 4/3/87, updated Klein and Patterson 7/8/89.

024 073307 Exact duplicate of 053470.

Neurotoxicity

Not required at this time.

CONCLUSIONS: Do data support registration, if applicable? For formulated product, do data support registration of product as labelled?

Toxicology data for Bonzi Ornamental Growth Regulator and the active ingredient, paclobutrazol, were reviewed under CFR 40, section 158.340 for Section 3 registration for a major new use (greenhouse, non-food).

Although the individual acute dermal toxicity studies using the paclubutrazol, technical, were not acceptable, there were sufficient data for a Toxicity Category II determination. All other acute oral and dermal toxicity studies and skin and eye irritation studies on paclobutrazol technical, paclobutrazol 4 g/l formulation, and 20 g/l formulation were acceptable. The hazards indicated in the data submitted have been identified on the label.

The acute inhalation toxicity hazard indicated by the data was determined to be Toxicity Category III. Although the limit test level of 5 mg/l was not achieved (Record # 074255), the actual concentration approached the limit value. Since no deaths and no severe adverse effects were observed, the proposed precautionary statements on the label are acceptable.

Although the individual metabolism studies are unacceptable, collectively, the data provide adequate information to fulfill guideline requirements.

The subchronic, chronic, combined chronic/oncogenicity, reproduction, and teratology studies are acceptable. Data from the chronic toxicity study in dogs and the combined chronic/oncogenicity study in rats indicate that the liver has been identified as the target organ for paclobutrazol and have revealed no evidence of an oncogenic potential.

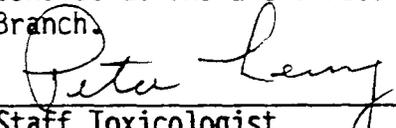
The studies submitted to fulfill the gene mutation, structural chromosomal aberration, and other genotoxic effects categories are acceptable. The results indicate that paclobutrazol may be a weak clastogen.

RECOMMENDATIONS: What type of registration action is being requested? In case of ongoing registration, register or do not register? What other specific studies or data are requested?

Submitted as a Section 3 registration action for greenhouse use on container-grown poinsettias, geraniums, and chrysanthemums and on bedding plants.

Chronic and SB950 Required Studies - The 4 week oral dose range-finding study in the mouse (Record #087665), submitted as justification for the dose levels selected for the mouse oncogenicity study (Record #073312), indicated that the highest dose administered in the mouse oncogenicity study was probably not at the maximum tolerated dose. Collectively, data from the chronic toxicity study in dogs and the combined chronic/oncogenicity study in rats indicate that the liver has been identified as the target organ for paclobutrazol and have revealed no evidence of an oncogenic potential. For these reasons, the Medical Toxicology Branch will not require another mouse oncogenicity study at this time.

The Worker, Health and Safety Branch is requested to complete an exposure assessment on the greenhouse use of this product before health assessment considerations and a recommendation can be made by the Medical Toxicology Branch.



Staff Toxicologist

5/1/91
Date



Senior Toxicologist

5/9/91
Date

Senior Toxicologist

Date

APPENDIX B

Occupational Exposure Assessment

Human Exposure Assessment for Paclobutrazol

by

James R. Sanborn, Staff Toxicologist

HS 1606

October 23, 1990
Revised April 21, 1992

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch
1220 N Street, Sacramento CA 95814

ABSTRACT

The plant growth regulator, paclobutrazol, is proposed for a Section 3 registration in California to increase flowering and/or fruiting of plants grown in greenhouses. Metabolism and pharmacokinetic information indicate that it is extensively transformed either into a diol that is excreted unchanged or conjugated with glucuronic acid or into a carboxylic acid derivative. All three of these metabolites are readily eliminated. Using surrogate data it is suggested that the skin is the primary route of exposure for mixer/loader/applicators or greenhouse workers with Absorbed Daily Dosages of 67.8 ug/kg/day and 9.1 ug/kg/day, respectively. This human exposure characterization was prepared as an Appendix B for the department's risk assessment document for paclobutrazol. The necessity for this risk assessment stemmed from the observation of hepatotoxicity in a combined study in rats which provided a NOEL of 1.5 mg/kg/day.

APPENDIX B

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
 DEPARTMENT OF PESTICIDE REGULATION
 WORKER HEALTH AND SAFETY BRANCH

HUMAN EXPOSURE ASSESSMENT

PACLOBUTRAZOL

October 23, 1990
 Revised April 21, 1992

INTRODUCTION

The plant growth regulator, paclobutrazol [(2RS,3RS-1-(4-chlorophenyl)-4,4-dimethyl-2-(1-H-triazol-1-ylpentanol)] (CAS # 76762-62-0, formula $C_{15}H_{20}ClN_3O$) is a crystalline solid. It is applied to either roots or foliage to produce compact plants that have increased flowering and fruiting. Some physical properties of paclobutrazol are listed below:

Melting point($^{\circ}C$)	165
Vapor pressure($25^{\circ}C$, mm Hg)	0.0000008
Density(g/ml)	1.22
Water solubility($25^{\circ}C$, mg/l)	20
K_{ow}^a	5600

a/ Estimate based on water solubility

EPA STATUS

This plant growth regulator (PGR) is a candidate for a Section 3 registration in California. Paclobutrazol has a federal label (EPA Reg. No. 10182-92) for greenhouse use on container-grown poinsettias, geraniums and fresias.

USAGE

There are no use figures for this PGR in the state of California as it is undergoing registration. This chemical may be applied either as a spray (6-63 ppm), drench (0.13-0.5 mg/pot) or bulb dip (6-300 ppm).

FORMULATIONS

The formulation to be sold in California contains 0.4% by weight of the active ingredient in water.

LABEL PRECAUTIONS

The signal word on the label is **CAUTION** with the following additional language:

HARMFUL IF ABSORBED THROUGH SKIN. AVOID CONTACT WITH THE SKIN OR CLOTHING. WEAR PROTECTIVE CLOTHING, LONG SLEEVED SHIRT AND RUBBER GLOVES. REMOVE CONTAMINATED CLOTHING AND WASH BEFORE REUSE. WASH THOROUGHLY WITH SOAP AND WATER AFTER HANDLING.

WORKER ILLNESS

Since this is a new active ingredient undergoing registration, it is not unexpected that there is an absence of reported illnesses in California from exposure to paclobutrazol (Edmiston, 1990).

PLANT RESIDUES

There are no registrant-submitted data on the dissipation of foliar residues of paclobutrazol.

DERMAL TOXICITY

The acute dermal median lethal toxicity (LD₅₀) of paclobutrazol for rats is >1000 mg/kg (Barber and Parkinson, 1982). Formulated paclobutrazol (2.79%) is not an irritant or skin sensitizer to the skin of rabbits (Parkinson, 1982).

ANIMAL METABOLISM

An investigation of the metabolic transformations of paclobutrazol (Jones et al., 1984) involved the oral treatment of male and female rats with either 5 or 250 mg/kg of triazole ¹⁴C-labeled paclobutrazol (specific activity 1.68 GBq/mole, radiochemical purity >97%). The treated animals (four/dose) were held for either 3 days (5 mg/kg dose) or 4 days (250 mg/dose) during which time the urine and feces were collected daily. The urine samples were pooled for the entire 72-hr period for eventual metabolite characterization. Lyophilized feces and urine were extracted with ether or methanol. Further treatments of the extracts with beta-glucuronidase or sulfatase followed by hot hydrochloric acid were carried out to transform the conjugates into entities that were more easily characterized by mass spectrometry and/or nmr spectroscopy. Four additional male and female animals dosed with 250 mg/kg, surgery under anesthesia was performed to insert a biliary canula for the collection of metabolites eliminated by this route.

Urinary Metabolites

The major urinary metabolite (dose independent) excreted by male rats was identified as paclobutrazol acid. This degradation product constituted 75-78% of the urinary radioactivity and 39-44% of the administered dose. The carboxylic acid is formed by

the oxidation of one of the t-butyl methyl groups. The intermediate diol metabolite which is further oxidized to the carboxylic acid is either excreted unconjugated (2% of the administered dose), conjugated as a glucuronide (1-3% of administered dose), or as an acid labile uncharacterized conjugate (3-5% of administered dose).

For females, the urinary elimination of paclobutrazol acid was dose dependent with 32% and 14% of the administered dose excreted respectively, for the 5 and 250 mg/kg dosed animals. The glucuronide conjugated diol metabolite observed in male rats urine was in female urine in amounts ranging from 6-14% of the administered dose. The unidentified conjugated form of this metabolite ranged from 17-25% of the administered dose. The small amount of the unconjugated diol metabolite excreted in the urine averaged about 5% with all other metabolites observed to be less than 2% of the administered dose.

These metabolism data for male and female rats are summarized below in Table 1:

Table 1. Urinary metabolites in male and female rats treated with paclobutrazol

<u>Metabolite</u>	<u>Percent of administered dose</u>	
	<u>Male</u>	<u>Female</u>
Paclobutra- zol acid	39-44	14-32
Diol		
Unconjugated	2	5
glucuronide	1-3	-
Uncharact. conjugate	3-5	17-25

Sanborn WH&S, 1992 after Jones, 1984

Fecal Metabolites

The amount of unchanged paclobutrazol isolated from the fecal methanol extracts was dose and sex independent. For animals dosed with 250 mg/kg, 5% of the administered dose was found to be unchanged paclobutrazol. Other metabolites found were as a percentage of the fecal extract paclobutrazol acid (12-31), free diol (6-15), and conjugated diols (35-65). Animals dosed with 5 mg/kg had a similar metabolite pattern to the animals treated with the higher dose as paclobutrazol acid and unconjugated diol represented 60% and 16%, respectively, of the fecal extract.

Biliary Excretion

Approximately 50-52% of the administered dose was eliminated by this route as a 3:1 mixture of the glucuronide conjugate or uncharacterized conjugate of the diol in females. The percentage of the dose eliminated by this route was similar for males but the ratio of the diol conjugates was not characterized.

Balance and Tissue Residues

To determine the elimination and tissue retention of paclobutrazol, rats were dosed orally with either 5 or 10 mg/kg and followed for four days (Jones et al., 1983). Since the data generated for either dose is basically the same, the ensuing discussion will focus on the 10 mg/kg dose. Three rats each (male and female) were treated orally with ¹⁴C-triazole labeled paclobutrazol (specific activity 1.06 MBq/mg in polyethylene glycol 600; radiochemical purity >99%). Urine and feces were collected at 24-hr intervals for the duration of the experiment. Carbon dioxide was collected for 48 hours after dosing. For male rats 32-48% of the radioactivity was excreted in the urine and 44-61% was excreted in the feces for an average of 87% by these two routes in the first 48 hours. For females, 48-56% of the dose was excreted in the urine and 34-56% was eliminated in the feces with the range for these two routes averaging 75-83% eliminated in the first 48 hours. Analysis of the carbon dioxide traps yielded data indicating that the triazole ring was not extensively metabolized during the experiment as only 0.03% of the administered dose was collected. Tissue residues (liver, kidney, testes or ovaries, adipose tissue, whole blood, and plasma) contained less than 0.1% of the administered dose. The highest tissue residues were in the liver of both sexes and ranged from 1-2%.

Bioavailability after an oral dose.

The bioavailability of paclobutrazol in rats dosed orally with 250 mg/kg in polyethylene glycol 600 is 95% and ~85% respectively, for male and female rats (Jones et al., 1984).

DERMAL ABSORPTION

The dermal absorption of paclobutrazol was evaluated in male rats (five animals/dose) except for the formulation concentrate where only three animals were deemed acceptable by the registrant at end of the 24 hr exposure period. The test solutions were dilutions of the aqueous formulation [25%(12.5 mg/animal)], and four dilutions yielding the amounts per animal in mg/kg of 1/10 (1.25), 1/100, (0.125), 1/451, (0.025) and 1/1000 (0.013). These test solutions were contained ¹⁴C-paclobutrazol that was 97% radiochemically pure prior to the preparation of the formulation dilutions. An area of 10 cm² was shaved, treated and then covered with an aluminum ring and nylon cloth to prevent physical abrasion during the absorption period. Additionally, the rats had

Queen Anne collars to further restrict their head movement and restrict the abrasion of the treated area. The time of exposure was either 10 or 24 hrs which was followed with a detergent wash of the treated area. The excreta along with the carcass were analyzed for the amount of radioactivity. The study was performed under GLP guidelines as required by FIFRA. The average recoveries for the five doses were 96.6%. The following table has been constructed for the dermal absorption of paclobutazol in rats:

Table 2: Dermal absorption of ¹⁴C-triazole-labeled paclobutrazol in male rats at five doses and two time periods.

Dose (mg/cm ²)	Time (hrs):	Percent Absorbed ^{a/}		Percent in Skin After Wash ^{b/}	
		<u>10</u>	<u>24</u>	<u>10</u>	<u>24</u>
1.25		3.8	5.2	2.6	2.4
0.12		4.9	5.1	1.3	1.2
0.013		11.8	12.5	1.0	1.5
0.003		19.5	24.8	2.6	2.7
0.001		18.2	27.8	3.2	3.0

Sanborn WH&S, 1992

a/ This calculation includes the radioactive equivalents remaining in the skin after washing and the amount in excreta and carcass and is based on the total amount recovered.

b/ Calculated on the basis of recovered radioactivity.

This appears to be a well conducted study in terms of the number of doses, proper vehicle controls and mass balance recovery. However, studies of this type normally are extended for a longer period of time (96-120 hrs) to determine to what extent the radioactivity left in the skin after washing is either excreted or remains in the carcass. For the purpose of exposure assessment, a value of 27.8% for a dermal dose of 0.001 mg/cm² will be used for the dermal penetration value as this dose level corresponds most closely to that experienced by workers harvesting, trimming or pruning plants.

WORKER EXPOSURE

Worker exposure to paclobutrazol involve mixer/loaders/applicators and greenhouse workers who water, handle, harvest or trim plants treated with this plant growth regulator. The maximum rate for a spray application is 0.10 lb/100 gal. Higher rates for bulb-dipping are suggested to be 2.4 lbs/100 gal. The exposure for bulb dipping is likely to be

less since the pesticide is not in the form of a mist which typically results in increased dermal exposure. Since the registrant has not submitted data for exposure to paclobutrazol, surrogate data for exposure during application of fluvalinate and for dislodgeable foliar residues (DFR) will be used for these calculations. Justification for use of fluvalinate as a surrogate for paclobutrazol stems from the similarity in vapor pressure values and use rates.

Mixer/Loader/Applicator

Surrogate data from greenhouse application of fluvalinate will be used for paclobutrazol (Stamper et al., 1989). The maximum application rate for fluvalinate (0.100 lb/100 gal; Rech, 1988) is the same as for paclobutrazol.

These exposures are summarized in Table 3 below:

Table 3 Mixer/loader/applicator exposure for Paclobutrazol dermal exposure using surrogate data from application of fluvalinate in greenhouses

<u>Dermal</u> <u>(mg/person/day)</u>	<u>ADD^{a/}</u> <u>(ug/kg/day)</u>	<u>AADD^{b/}</u> <u>(ug/kg/day)</u>	<u>LADD^{c/}</u> <u>(ug/kg/day)</u>
17.1	67.8	6.5	3.7

a/ ADD (Average Daily Dosage): Dermal Absorption-27.8%; 70-kg person

b/ AADD (Average Annual Daily Dosage): Sprays/year-35; assuming every 10 days.

c/ LADD: Lifetime Average Daily Dosage: 40 years exposure, 70- year life. LADD = AADD (40 yr exposure/70 yr life)

Sanborn WH&S, 1992

Air exposures have not been reported as they represent much less than .1% of the dermal exposure (Stamper, et al., 1989). The estimate for lifetime exposure is probably excessive as most chemicals do not remain in commerce for 40 years.

Further, the annual exposure is likely to be extremely conservative given the rotation of plants through greenhouses with not all plants requiring treatment with this PGR because of lack of efficacy or because of the absence of label for the product. Additionally, the adjustment of exposure data using lower body weight values is not justified in light of information from a survey in California indicating this task does not conventionally employ women (Mines and Martin, 1986). Finally, another reason for not adjusting exposure data to female body weight stems from the surrogate exposure data of Stamper et al., 1989 which typically requires the use of geometric statistics for calculations of mean values. Also for reasons iterated previously about default body weight and surface area, our

exposure estimates of exposure are highly conservative. The use of our standard default male body weight and surface area comes from EPA's guidance document (Subdivision U). Both body weight and surface area defaults are inherently conservative, tending to overestimate dosage. That is because the default male body weight is taken from demographic data at the 25th percentile. The male default surface area, on the other hand is taken from the 75th percentile."

The ratio of body surface area to body weight for the "EPA default individual" referred to in the previous paragraph (21100 cm² is 302 cm²/kg This ratio exceeds the surface to weight ratio for almost any group of individuals, male or female. A more realistic estimate of body surface area to weight comes from the 50th percentile at 20090 cm² per 76 kg or 264 cm²/kg. Thus, we currently overestimate dosage by approximately 14% for the average "man".

Greenhouse workers other than mixer/loaders/applicators

Since the decay data for dislodgeable foliar residues (DFR) for paclobutrazol is not available, residues for the surrogate, fluvalinate, will be utilized. Application of fluvalinate on carnations and Gerba daisies provided DFR values that averaged 0.057 ug/cm². A default transfer factor (TF) of 5000 cm²/hr was utilized (Zweig et al., 1988) which also is in the range found by Brouwer et al., 1989 of 2800-10000 cm²/hr for greenhouse reentry workers exposed to zineb, thiram, thiophanate-methyl or chlorothalonil on carnations.

Table 4: Exposure of greenhouse workers handling plants treated with paclobutrazol using fluvalinate surrogate data.

Dermal Exposure ^{a/} ug/person/day	ADD ^{b/} ug/kg/day	AADD ^{c/} ug/kg/day	LADD ^{d/} ug/kg/day
2.3	9.1	6.0	3.4

a/ 8-hr work day; TF = 5000 cm²/hr; DFR 0.057 ug/cm²

b/ ADD: Average Daily Dosage: 70-kg person; 27.8% dermal absorption; no gloves worn, 99.7% residues on hands Grosso et al., 1989

c/ AADD: Average Annual Daily Dosage: 240 days exposure /year/365 days/year.

d/ LADD: Lifetime Average Daily Dosage: 40 years exposure/ 70- year life.

Sanborn WH&S, 1992

The exposure values for greenhouse workers are likely an overestimate for several reasons. There has been no factoring in of the decay of the residues over time and this would occur via environmental degradation or plant growth dilution. Secondly, it is unlikely that given the rotation of plants through

greenhouses that all plants will be treated with this PGR either because all plants do not respond to this PGR or because some plants are not labeled for treatment with this chemical. Another overestimate stems from the use of the conservative 40-year lifetime exposure. Since most chemicals do not have a 40-year use in commerce, the assumption of a 40 year exposure potential is highly conservative.

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