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

003457

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

To: Robert J. Taylor
Product Manager 25
Registration Division (TS-767)

From: Roger Gardner
Toxicologist Roger Gardner 12/15/83
Toxicology Branch
Hazard Evaluation Division (TS-769)

Subject: Paclobutrazol (PP333) Request for Data Waiver (Correspondence #35) and Data Review (EPA Acc. No. 248688). Reg. No. 10182-TT. Tox. Chem. No. 628C

Actions Requested

1. Data review of the following studies:

Technical material and 50% powder

Acute oral LD_{50}
Acute dermal LD_{50}

Primary eye irritation
Primary skin irritation
Skin sensitization

50% formulation

Acute inhalation LC_{50}

Ornamental and turf formulation (granular)

Acute oral LD_{50}
Acute Dermal LD_{50}
Primary eye irritation
Skin irritation

Technical grade

Mutagenicity (Ames test)

2. Waiver of a 21-day dermal toxicity study.

Recommendations

1. The above mentioned acute studies are adequate to support registration of the granular formulation proposed for use on greenhouse ornamentals and ornamental turf uses (See Section III. A., for data summary). However, an exposure analysis for the greenhouse use must be submitted to demonstrate that exposure to applicators will not be repeated (several consecutive days).

2. The request for waiver of the 21-day dermal study on the basis of results from acute dermal and irritation studies is not sufficiently supported. As mentioned above, additional information on the nature of exposure to applicators is needed---specifically to determine whether applicators are repeatedly exposed during application. Based on these considerations the request for waiver should be denied.

3. It should be noted that additional data requirements may be fulfilled by studies recently submitted (Reg. No. 10182-IE, Acc. Nos. 251746 and 251747). Reports in that submission include subchronic studies in dogs and rats, teratogenicity studies in rats and rabbits, a 21-day dermal toxicity study, and a mutagenicity study with a discussion of the test battery. Therefore, a final conclusion about the actions discussed herein will be made after review of the new data.

I. Background

Paclobutrazol is a tree-growth regulator for use on greenhouse ornamentals, lawn, and turf. Its chemical name is [(2 RS,3 RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazole-1yl)pentan-3-ol].

Section II of this review provides comments on points which the Registrant requested the Toxicology Branch to consider. Section III contains a summary and reviews of the studies submitted.

II. Correspondence

A. Summary of Submissions

A letter from ICI Americas, Inc. to the Registration Division (dated December 13, 1982) contained comments to be considered, at the Registrant's request, by the Toxicology Branch. The letter also contained a summary of a pre-registration conference to determine the data which would be required to support registration of PP333. The conference was held on November 30, 1982. The conference summary attached to the letter noted that the uses for which registrations are sought were ornamental lawn and turf grasses (granular formulation) and greenhouse ornamentals. Data required for these uses were listed as acute oral and dermal studies, primary skin and eye irritation studies, a 21-day dermal study, teratology study (in one species for conditional registration and 2 for full registration), mutagenicity studies, and a 2-generation reproduction study.

Three comments were made as footnotes to the list of data requirements. These comments were:

1. If acute tests are available on one formulation of PP333, it is not necessary to conduct additional acute tests on a second formulation provided the second formulation has a lower concentration of the active ingredient and provided that the inert components are similar for both formulations.

2. (The 21-day dermal) test would be conducted with the technical grade of the active ingredient. ICI proposes that the end-use formulation would be tested only if a component of the formulation is likely to increase dermal absorption or potentiate toxic and pharmacologic effects.

3. It is the Agency's position that a reproduction study is required if the active ingredient remains at the site of application for longer than one week. It is ICI's position that this study should not be required since human exposure from these use patterns will be very low. Please consider the following:

-All three use patterns are limited to a single application of the product;

-Liquid ornamental formulations are applied at high use dilutions;

-Granular formulations are watered into turf and lawns; and

-Teratology and mutagenicity studies which are required should provide an adequate evaluation of the compound's potential to cause reproductive effects.

A second correspondence from ICI Americas, Inc. to the Registration Division (dated April 13, 1983) contained a formal request for a data waiver along with information supporting that request. A second similar request from O. M. Scott and Sons Company was also mentioned (see below). ICI concluded:

> ...the use of PP333 for greenhouse ornamentals, lawn and turf grasses will not provide a repeated exposure to significant levels of active ingredient. Further, the results of acute and subacute dermal toxicity tests on technical grade PP333 have provided no indication of systemic toxicity. ICI therefore requests that the Agency waive the requirement to conduct a repeat dose 21-day dermal study with end-use formulations to support registrations for the above use patterns.

In supporting the conclusions, the Registrant noted that for the greenhouse use only one application is made per plant, and the use dilution is 2 ppm for the soil drench application and 44 ppm for the foliar application. These two points were described as an indication that applicator exposure is insignificant for the ornamental lawn and turf use. However, there was no mention of how frequently an applicator would be using the formulation in a greenhouse (repeated applicator exposure). There was also no exposure analysis for the greenhouse applicator.

ICI stated that a granular formulation with an application rate of 1.0 pound active ingredient per acre would be used on the average homeowner's lawn (17% of an acre). The Registrant estimated that on the basis of these data maximum potential exposure would be 0.17 pound. A study by the O. M. Scott & Sons Company was cited as the basis for reducing the exposure

estimate to 0.053 pounds, and ICI noted that the granules would be washed down to the base of the grass plants, into the thatch layer and into the soil. These factors were described by the Registrant as likely to reduce the potential exposure further.

In addition, the toxicological data reviewed in Section III below was summarized. A 21-day dermal study with technical grade PP333, which is to be submitted at a later date, was also summarized.

Draft labels were also provided with the second submission. The formulation to be used on container-grown chrysanthemums and poinsettias contains 0.0264% PP333. Two other formulations described in a separate letter (dated April 1, 1983) from O. M. Scott & Sons Co. to Registration Division indicated that the percentage active ingredient in the two granular formulations for ornamental lawn and turf use were less than 1% (0.4 and 0.66%). Acute oral and dermal toxicity studies as well as eye and skin irritation studies were included in Scott's submission (see Section III. F., below) along with technical summaries of the toxicity and chemistry of three inert ingredients.

The letter from Scott stated that submission of the above mentioned information would serve to demonstrate the following:

1. Technical PP-333 is not particularly dermatotoxic.

2. Scott's formulations contain PP-333 at very low rates.

3. The "inert" ingredients in the Scott formulations will not potentiate a dermatotoxic effect.

B. Discussion

1. Data waiver

Section III below describes acute toxicity studies with the technical grade, a 50% formulation, and a formulation containing less than 1% PP333. Studies with the technical grade and the 50% formulation indicate that PP333 has a moderate potential to cause dermal irritation (Toxicity Category III, see Section III. A., below). The 50% formulation has somewhat less potential to cause dermal effects (Toxicity Category IV), and the formulations containing less than 1% active ingredient caused no skin reactions in an irritation

study (see Section III. G., below). Although the acute dermal LD_{50} studies used 1000 mg/kg as the highest dose, the results of a similar study using the formulation containing less than 1% PP333 showed that dermal toxicity is not enhanced by the "inert" ingredients (an LD_{50} of 8 g/kg).

The concentrations of PP333 in three formulations, according to the confidential statements submitted, ranged from 0.026% to 0.66%. The evidence provided by acute dermal, skin irritation, and skin sensitization studies suggests that the formulations are unlikely to cause toxicity by the dermal route. The moderate dermal toxicity of the technical grade material and the low concentrations of the active ingredient in formulations to be used on turf and ornamentals indirectly indicate that the request for data waiver could be toxicologically supported. However, without information to indicate that exposures to greenhouse applicators are not repeated, a 21-day dermal toxicity study is needed on the formulations used.

2. Reproduction

ICI solicited comments on its position regarding the use of mutagenicity and teratogenicity studies to substitute for a two-generation reproduction study.

The following discussion paraphrases the preamble (Sections IV. E., pages 53193-194; V. E., pages 53195-196; and §158.105 (e)(4), page 53206 of the Agency's published Pesticide Regulations: Proposed Data Requirements. Federal Register, Vol. 47. No. 247. November 24, 1982).

Two objectives of mutagenicity testing are sensitive screening of chemicals for genetic toxicity and establishment of the relevance of results to mammals. When genetic toxicity is observed, testing should also establish a basis for assessment of heritable or other related health risks. These objectives are met by using a battery of tests that evaluate a chemical with respect to its potential for causing gene mutations, chromosome structure aberrations, and other related effects which are mentioned below.

Tests which are useful in determining a chemical's potential for causing gene mutations could include microbial assays with bacteria or eucaryotic microorganisms (fungi), submammalian assays such as the sex-linked recessive lethal test in Drosophila (fruit fly), and mammalian tests with cell cultures or in vivo (specific locus test).

Evaluation of a chemical's potential to damage chromosome structure could be done with eucaryotic microorganisms (mitotic segregation tests), submammalian tests (chromosome tests in Drosophila), in vitro mammalian cell tests (sister chromatid exchange and cytogenetic assays), and in vivo assays with

mammals (micronucleus, sister chromati. exchange, cytogenetics, dominant lethal, and heritable translocation tests).

Other genotoxic effects could be evaluated in bacteria (DNA damage and repair, differential toxicity), eucaryotic microorganisms (mitotic recombination/gene conversion, mitotic segregation, numerical chromosomal aberrations), and mammalian cells in culture or whole animal (unscheduled DNA synthesis, alkaline DNA elution, sister chromatid exchange, mitotic interference, micronucleus formation, DNA-synthesis inhibition, DNA alkylation, and mammalian cell transformation in vitro).

The selection of assays for a mutagenicity battery should consider the nature of the test chemical, and a justification for test selection should be provided. A point to consider in the selection is that some tests such as the sister chromatid exchange or cytogenetics assays are useful in evaluating more than one of the three categories of genetic toxicity.

The mutagenicity assay discussed in Section III. D., below indicates that only one microbial assay for evaluating the potential of PP333 to cause gene mutations has been reviewed. Since no mammalian gene mutation studies are available, and since teratogenicity studies only evaluate the in utero phase of reproduction and development, the available studies on PP333 cannot be considered as substitutes for a reproduction study.

ICI notes in its April 13, 1983 correspondence:

> The Agency agreed at the March 23 meeting that the two-generation reproduction study could be submitted as a condition of registration at a time to be specified in the conditional registration notice.

The circumstances described above support that conclusion.

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III. Data Review

A. Summary of Data Reviewed.

1. Technical grade and 50% formulation

The results of acute toxicity studies on technical PP333 are summarized as follows:

Route of Administration	Species	Sex	LD_{50} or LC_{50}	Toxicity Category
Oral	Rat	Male	1.954 g/kg	III
		Female	1.336 g/kg	III
	Mouse	Male	490 mg/kg	II
		Female	1,219 mg/kg	III
	Guinea pig	Male	542 mg/kg	III
		Female	400-640 mg/kg	III
	Rabbits	Male	835 mg/kg	III
		Female	937 mg/kg	
Intraperitoneal	Rat	Male	160-250 mg/kg	-
		Female	99 mg/kg	
Dermal	Rat	Both	>1000 mg/kg	II
	Rabbit	Both	>1000 mg/kg	II

The acute toxicity results for the powder formulation containing 50% PP333 are summarized as follows:

Route of Administration	Species	Sex	LD_{50} or LC_{50}	Toxicity Category
Oral	Rat	Both	>5000 mg/kg	IV
Inhalation	Rat	Male	>766 mg/m^3	II
		Female	359-766 mg/m^3	
Dermal	Rabbit	Both	>1000 mg/kg	II

Signs of acute toxicity were observed to begin one to three hours after dosing or exposure. Deaths occurred within 2 to 4 days after treatment. Treated animals exhibited subdued behavior, unsteady gait, loss of righting reflex, piloerection, coma, hypothermia, respiratory stress, and urinary incontinence. Surviving animals appeared normal 6 to 9 days after treatment.

The technical material causes mild skin irritation that persists in rabbits for 72 hours (Toxicity Category III). It also causes reversible corneal opacities with irritation that persist in treated eyes of rabbits for 72 hours (Toxicity Category II). PP333 is not a skin sensitizer in guinea pigs.

The 50% formulation is in Toxicity Category IV for skin irritation and Toxicity Category II for eye irritation. The technical grade material did not induce mutations in Salmonella strains.

2. Ornamental and turf formulation

The acute oral and dermal LD_{50}'s for the formulation containing less than 1% active ingredient are greater than 8 g/kg and greater than 20 g/kg, respectively. The formulation also caused no eye or skin irritation. These results place the formulation into Toxicity Category IV for acute oral and dermal toxicity as well as for eye and skin irritation.

B. Acute Oral and Dermal Studies on the Technical Grade Material

1. Citation: Barber, J. E. and G. R. Parkinson. 1982. PP333: Acute oral, dermal and intraperitoneal toxicity. (Unpublished report No. CTL/P/748 prepared by Imperial Chemical Industries, PLC, Central Toxicology Laboratory, Cheshire, UK; submitted by ICI America under 1082-TT. Acc. No. 248688).

2. Materials and Methods

Test substance: PP333 [(2RS,3RS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl) pentan-3-ol], 97.0 percent pure.

Test species: Alderly Park SPF male and female albino rats and mice and Dunkin Hartley albino guinea pigs were used. The strain of rabbits used was New Zealand white.

Experimental Procedures: Acute oral toxicity studies.

Groups of 5 or 10 male and 5 or 10 female animals were used per dose level. At the beginning of the experiment the rats were 5-7 weeks old, and the males weighed 140-230 g and the females weighed 115-180 g. A maximum of 5 rats were housed per cage. The mice were 5-7 weeks old, and the males weighed 25-45 g and the females weighed 20-40 g. A maximum 5 mice were housed per cage.

Guinea pigs were 4-7 weeks old, and the males weighed 190-365 g and the females weighed 245-330 g. These animals were housed individually. The rabbits were 11-17 weeks old and the males weighed 1.95-3.30 kg and the females weighed 1.85-3.20 kg. All animals were fed and allowed tap water ad libitum. They were fasted for a period of 16-20 hours, then they were given by oral gavage a suspension of PP333 in aqueous 0.5 percent LISSATAN AC. A standard volume of 10 ml/kg was given to each animal. Animals were observed once daily for signs of systemic toxicity for up to 14 days. Body weights were determined on days -1, 1, 2, 7, and 14 of the study. The acute oral LD_{50} values and 95 percent confidence limits were calculated from the mortality data. Surviving animals were killed at the end of the study.

Acute dermal toxicity studies: The rats and rabbits used in this study are described above.

The test material was suspended in propylene glycol and applied at one dose level of 1000 mg/kg. The test material was applied to the intact skin of the dorsolumbar region of 5 male and 5 female rats, the intact skin of 2 male and 2 female rabbits, and the abraded skin of 2 male and 2 female rabbits. In addition, groups of 1 male and 1 female rabbits with intact and abraded skin served as controls, whereas no control rats were used. The test material was kept in contact with the skin for 24 hours by means of an occlusive dressing, which was then discarded, and the skin washed free of PP333. The animals were observed for signs of systemic toxicity once daily for 14 days, and weighed at various intervals during the same period.

Acute intraperitoneal dosing: The male and female rats used in this study were the same type as that described above.

Groups of 5 male and/or 5 female rats were injected intraperitonealy with PP333 in aqueous 0.5 percent LISSATAN AC at various dose levels. A standard volume of 10 ml/kg was injected into each rat, with differences in dose levels being achieved by altering the concentration in the dosed suspension. The rats were observed for signs of systemic toxicity once daily, and weighed at various intervals during the 14-day observation period.

3. Reported Results

Acute oral toxicity:

According to the author, all rats given the 400 and all female rats given 500 or 800 mg/kg doses survived. The remaining doses, including the 5000 mg/kg group (highest dose

tested) contained survivors. All deaths were reported to occur within 4 days after dosing.

Signs of toxicity in the rats were noted within an hour after treatment and included subdued behavior, unsteady gait, loss of righting reflex, piloerection, coma, hypothermia, respiratory stress, and urinary incontinence. Surviving animals were described as normal by 9 days following dosing, and the authors noted that all males showed no toxic signs in the 400 mg/kg group. Three females in that group also showed no toxic signs. Body weights decreased during the first 7 days of the observation period after dosing and mean body weight gain during the two-week observation period for treated rats ranged from 66 (3200 mg/kg group) to 110 g (500 mg/kg dose group) for males, and from 30 (in the group given 3200 mg/kg) to 67 g (in the 500 mg/kg dose group) for treated females. The LD_{50} values are tabulated below.

In the mouse studies no males given the 250 mg/kg dose died. All males given 800 mg/kg died while those groups receiving the 320, 400, 500, or 640 mg/kg doses contained survivors. The groups of females given one of the six doses each contained survivors also. The authors reported that all deaths occurred within 3 days after treatment. The signs of toxicity noted were the same as those reported for treated rats, and they began to appear an hour after dosing according to the report. Six days after treatment survivors were described as normal in appearance. Body weight results were similar to those reported for treated rats in that there was an initial weight loss. For male mice the group mean body weight gains ranged from 0 (400 and 640 mg/kg groups) to 7 g (500 mg/kg group) during the 14-day observation periods.

Group mean weight gains for female mice ranged from -3 (640 mg/kg group) to 8 g (for the 500 and 800 mg/kg groups). The LD_{50} calculations are summarized below.

All 5 of the male guinea pigs given a 320 mg/kg dose survived, while the remaining groups contained from two (in the 500 mg/kg group) to 4 (in the 400 mg/kg group) survivors. All of the male guinea pigs given 800 mg/kg died. No female animals died after dosing with 320 or 400 mg/kg, and all those receiving 640 mg/kg died. All of the deaths were reported to occur within the first two days after dosing. The authors noted that signs of toxicity appeared within 3 hours following treatment and none of the males given 320 mg/kg were reported to show signs of intoxication. The signs noted most frequently were subdued behavior and unsteady gait. Survivors appeared normal within 3 days following dosing, according to the authors. Body weight results showed patterns similar to those described above for rats and mice. Group mean body weight gains for

the male guinea pigs during the 14-day observation period ranged from 45 (in the 640 mg/kg group) to 98 g (in the 400 mg/kg group). For females these changes ranged from 49 (in the 400 mg/kg group) to 65 g (in the 320 mg/kg group).

The authors reported that the 5 male and female rabbits given a 250 mg/kg dose survived, and all 5 males and females given 2300 mg/kg died. All other groups contained survivors. The authors noted that signs of toxicity appeared within an hour after treatment, and the most frequently observed signs were subdued behavior and unsteady gait. The other signs reported are similar to those observed in rats, mice, and guinea pigs. Recovery was noted in survivors within 12 days after treatment. Group mean body weight data were similar to that reported in the studies of rats, mice, and guinea pigs. The LD_{50} calculations are summarized below.

Acute dermal toxicity studies:

None of the treated rats or rabbits died during the course of the study. Consequently, the LD_{50} values were assumed to be in excess of 1000 mg/kg for both species. None of the animals showed any signs of systemic toxicity during the study and all animals gained weight.

Acute intraperitoneal toxicity study:

All male rats injected with the 100, 128, or 160 mg/kg doses survived while all females given the 64 mg/kg dose survived. Three of 5 males that received the 200 mg/kg dose and all male rats given 250 or 320 mg/kg died. All female rats given 138 or 160 mg/kg died while the remaining groups (80, 100, or 126 mg/kg dose groups) contained two or more survivors. Deaths among male rats were noted within 24 hours after dosing, and those among female rats occurred during the two days after treatment. The authors stated that an LD_{50} could not be calculated for the male rats, but they estimated that the 160 and 250 mg/kg doses were likely 95% confidence limits. The estimated LD_{50} in female rats is 99 (79-117) mg/kg.

The authors noted that signs of toxicity occurred within an hour after dosing and included effects similar to those reported above for rats given oral doses of PP333. They further stated that survivors appeared to be normal by the sixth day of the observation period. No compound-related effect on body weight was noted in the treated rats.

4. Discussion and Conclusions

The acute oral LD_{50} values and 95 percent confidence limits (where possible) were calculated to be as follows:

Species and Sex	LD_{50} Values	Toxicity Category
Rat, male	1.954 (1.147-4.985) g/kg	III
female	1.336 (0.837-1.969) g/kg	
Mouse, male	490 (394-642) mg/kg	II
female	1,219 mg/kg	
Guinea Pig, male	542 (432-717) mg/kg	III
female	>400 - <640 mg/kg	
Rabbits, male	835 mg/kg	III
female	937 mg/kg	

Treated animals were reported to exhibit signs of toxicity 1 to 3 hours after dosing. These signs included subdued behavior, unsteady gait, and piloerection. However, most of the surviving animals appeared normal 3-12 days after dosing, and they exhibited increased body weights at the end of the 14-day experiment.

No gross or histological examinations were done on the test animals and the report did not include an explanation for this omission.

Although the authors reported slopes for some of the experiments, the lack of a clear dose-response for mortality in groups given doses between those causing no mortality and those causing 100% mortality was variable. Slopes and their 95% confidence limits were reported as follows:

Species	Sex	Slope	95% Confidence Limits
Rat	Male	0.60	0.19 to 1.01
	Female	0.85	0.41 to 1.28
Mouse	Male	2.90	1.13 to 4.67
	Female	0.66	0.87 to 2.20

Species	Sex	Slope	95% Confidence Limits
Guinea pig	Male	3.23	1.01 to 5.44
	Female		
Rabbits	Male	1.20	-6.05 to 6.46
	Female	1.89	0.46 to 3.31

The extensive confidence limits on both the LD_{50} and dose-reponse slopes determined by the probit method as well as the lack of necropsy data indicate that the oral LD_{50} studies cannot be considered separately. All the LD_{50}'s summarized above suggest that Toxicity Category III is appropriate for oral toxicity of PP333.

The results from the intraperitoneal LD_{50} study in rats had the same variability as was found in the oral studies. The LD_{50} could not be determined from treated male rats, but it was estimated to be between 160 and 250 mg/kg. The acute i.p. LD_{50} in females was 99 mg/kg with 95% confidence limits from 79 to 117 mg/kg, and the slope of the dose-reponse curve was calculated to be 3.69 with 95% confidence limits from 1.44 to 5.93.

Although the acute dermal results indicate an LD_{50} greater than 1000 mg/kg in rats and rabbits, there were no higher doses tested. On that basis PP333 can be classified into Toxicity Category II for acute dermal toxicity.

5. Core Classification: Minimum, when all of the acute studies are considered together.

C. Skin and Eye Irritation and Skin Sensitization - Technical Material

1. Citation: Parkinson, G. R. September 24, 1982. PP333: Skin irritation, eye irritation, and skin sensitization. Unpublished report No. CTL/P/741 prepared by Imperial Chemical Industries, PLC. Central Toxicology Laboratory. Alderley Park, Macclesfield, Cheshire, UK. Submitted by ICI Americas. EPA Acc. No. 248688.

2. Materials and Methods.

Test Material: P333 [(2RS,3KS)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-ol, 97.0 percent pure (this sample was used in the skin and eye irritation studies) or 92.4% pure (this sample was used in skin sensitization studies).

Test Species: Albino Alderley Park specific pathogen free male and female rats were used. They were 5 to 7 weeks old at the start of the study. Female albino New Zealand strain rabbits of approximately 11 to 14 weeks of age were also used. The male guinea pigs used in sensitization studies were of the Dunkin Hartley strain, and they were between 4 and 7 weeks of age at the start of the tests.

Experimental Procedures: Skin irritation in rats. The hair was clipped from the dorsolumbar region of five male and five female rats. A suspension of PP333 in polyethylene glycol (12.5% w/v) was applied to the clipped skin at a dose of 250 mg/kg. The treated skin was covered with an occlusive dressing for 24 hours. At the end of that time the dressing was removed, and the residue was washed from the skin. The treatment site was blotted dry and scored for irritation one to two hours later. Twenty-four hours later a second application of 250 mg PP333/kg body weight was made, and the skin was again occluded and observed in the same manner. A series of 5 applications during alternate 24 hour periods was conducted, and the rats were observed for 9 more days after the last treatment. At the end of the observation the animals were sacrificed.

One day before treatment the hair was clipped from both flanks of 6 female rabbits. The clipped skin on one flank of each animal was abraded just before the test substance was applied. The test material was applied to the intact and abraded skin of each rabbit as a paste in olive oil at a dosage rate of 500 mg/kg. Each application site was covered with a polyethylene patch held in place by adhesive tape. The trunks of the animals were then wrapped with a cloth bandage. These dressings were removed 24 hours after application of the test material. The treatment sites were washed with warm water and gently blotted dry. Test sites were observed one to two hours after washing, and the Draize method was used to score the skin reactions. Application sites were also assessed 72 hours after treatment.

Eye Irritation Study: Approximately 100 mg of the powdered test substance was placed in the cup formed by pulling the lower lid away from the eyeball of test rabbits. The lids of the treated eye were gently held together for one to two seconds and then released. The other eye of each rabbit was left untreated. Three rabbits had their treated eyes irrigated with lukewarm water 20 to 30 seconds after treatment. Treated eyes in the six remaining rabbits were not irrigated. Eye reactions were scored 1 to 2 hours and 1, 2, 3, 4, and 7 days after treatment by the Draize method.

Skin sensitization in guinea pigs: The authors described preliminary studies in which groups of two guinea pigs were used to test up to 2 concentrations of PP333. These preliminary tests were used to determine the highest concentrations below 5% which could be tolerated locally or generally after intradermal injection. The concentration selected for topical application was that which did not cause excessive inflammation. PP333 was suspended in corn oil for intradermal injection and dissolved in dimethylformamide for topical applications.

Concentrations selected on the basis of results from these studies were used as induction doses, while results from animals previously injected with Freund's complete adjuvant were used in similar studies to determine challenge doses. The Freund's adjuvant was administered 14 days prior to the preliminary experiments with PP333.

In the main study the hair was clipped from the scapular region of each test animal (20 treated and 8 control animals). Three injections were made on each side of the midline. The first contained Freund's complete adjuvant and corn oil (1:1); the second contained 1% PP333 (w/v) in a mixture of dimethylformamide, corn oil, and Freund's complete adjuvant. One week after each animal received these intradermal injections, the test substance was applied topically to the clipped area of skin. A 75% (w/v) mixture of the test material in dimethylformamide as put on filter paper in 0.2 to 0.3 ml amounts. The filter paper was then applied to the injection sites and held in place with surgical tape. An occlusive dressing was placed around each animal and left for 48 hours. Control group animals were treated similarly except that the three injections consisted of a mixture of Freund's adjuvant and corn oil (two sites) and corn oil alone (one injection site). The topical application was made in the same manner except that corn oil was used by itself.

Two weeks after the topical applications, the hair of each guinea pig was clipped from two flanks. Three challenge concentrations of 50, 25 and 10% (w/v) of the test substance in dimethylformamide were applied on separate sites of the clipped skin. The challenge concentrations were topically applied in the same manner as those in the topical applications described in the previous paragraph, but the occlusive dressings were removed 24 hours after application. The treatment sites were observed at 24 and 48 hours after removal of the dressings. The investigators quantified the reactions according to the following scale:

0 - no reaction
1 - scattered mild redness
2 - moderate and diffuse redness
3 - intense redness and swelling

The overall sensitization response was then classified on a 5 point scale (1-5) based on the percentage of animals responding as follows:

% Responding	Grade	Description
>0-8	1	Weak
9-28	2	Mild

29-64		
65-80	3	
81-100	4	Moderate
	5	Strong
		Extreme

3. Reported Results

Skin irritation in rats: After 5 consecutive applications of the test substance, 3 of 5 males showed erythema. Two of 5 female rats were reported to have desquamation and scabbing. The authors stated that these effects were not persistent and classified PP333 as a slight irritant to skin of rats. No further details were reported.

Skin irritation in rabbits: After application of 500 mg/kg to intact or abraded skin the investigators noted erythema at all test sites. The erythema persisted for 72 hours at these sites, and mean Draize scores were 1.3 and 1.5 at 24 hours for intact and abraded skin, respectively. Mean scores of 1.0 were reported for both skin types at 72 hours. No individual animal scores were reported.

Eye irritation: The author noted slight corneal opacity in 5 of 6 unwashed eyes. All of those eyes were found to have moderate redness of the conjuctiva with some chemosis and discharges. The investigators also stated that no iritis was observed. All treated eyes appeared normal after the seven day observation period. Mean scores reached a maximum of 17 (110 is maximum possible score) one day after treatment. No individual animal scores were reported.

The three irrigated eyes were described as having slight redness of the conjuctiva, some chemosis and discharge. No corneal opactiy or iritis was reported. Mean scores for the washed eyes ranged from 5 (110 maximum possible score) one to 2 hours after treatment to a mean score of one 2 days after treatment. Treated eyes appeared normal on the third day following treatment.

Skin sensitization: The author noted that one of the test animals died and the occlusive dressings slipped on 3 other animals. These animals were not examined for skin reactions. Four of the 16 treated and 2 of 7 untreated animals responded to the 50% (w/v) concentration challenge, and one guinea pig from each group was reported to respond to the 25% concentration. No animals exhibited a response at the site challenged with the 10% concentration according to the author.

4. Discussion and Conclusion

There are adequate data to support the conclusions stated in the report. The results of the studies indicate that PP333 (Paclobutrazol) causes mild primary skin irritation which persists in rabbits for 72 hours (Toxicity Category III). The test substance also causes reversible corneal opacity in the eyes of treated rabbits with irritation that persisted for 72 hours (Toxicity Category II). The studies in guinea pigs indicate that paclobutrazol is not a skin sensitizer under the test conditions.

5. Core Classification

Minimum

D. Mutagenicity - Technical Material

1. Citation: Callander, R. D. September 9, 1982. PP333. An evaluation in the Salmonella/microsome mutagenicity assay. Unpublished report prepared by Imperial Chemical Industries PLC. Central Toxicology Laboratory. Alderley Park, Macclesfield, Cheshire, UK. Submitted by ICI, Americas. EPA Acc. No. 248688.

2. Materials and Methods

Test substance: PP333 or [2RS,3RS)-1-(4-chlorophenyl)-4, 4-dimethyl-2-(1H-1,2,4-triazol-1-yl)pentan-3-ol], was an off-white colored powder of 92.4 percent w/w purity from batch ref. P29, and was intended for use as a plant growth regulator.

Test species: Five tester strains of Salmonella were used for the assay, TA1535, TA1537, TA1538, TA98, and TA100.

Experimental procedure: The test substance was dissolved in dimethylsulfoxide (DMSO) and incorporated into culture media at concentrations of 0, 1.6, 8.0, 40, 200, 1,000, and 5,000 ug/plate (experiments 1 and 2) and 100, 200, 500, 1,000, 2,500, and 5,000 ug/plate (experiment 3).

Positive controls included 9-amino acridine (9-AA; 80, 20 and 5 mg/plate without activation), 2-aminoanthracene (2-AA; 5, 2, 1 and 0.5 mg/plate with activation (S9), Daunorubicin (DRB; 2, 1 and 0.5 ug/plate without activation), 4-nitro-O-phenylene diamine (4NP; 5, 2, 1, 0.5 ug/plate without activation), and N-methyl-N-nitro-N-nitrosoguanidine (MNNG; 5, 2, 1 and 0.5 mg/plate without activation).

A plate incorporation test was conducted according to the method of Ames et al., 1975. The test was conducted in

triplicate in two separate assays. Strain TA98 was repeated in triplicate at the concentrations stated above. All three experiments were conducted in the presence and absence of liver S9-mix prepared from Aroclor 1254 induced Sprague Dawley rats.

A positive response was defined as a two-fold or greater increase in the mean number of revertant colonies per plate over the control value for at least one dose level or the observation of a statistically significant dose-related increase in the number of revertants using a one-tailed Student's t-test.

3. Reported Results:

The test compound produced no results that were two-fold greater than the control in the presence or absence of metabolic activation. The authors report a dose related response for strain TA1537 (Experiment 2, with S9) and increased revertants in strain TA98 (with and without S9); however, neither result was two-fold above the control result. Cytotoxicity and precipitation occurred at the highest dose tested (5,000 ug/plate).

4. Discussion and Conclusions:

The test compound produced negative results for mutagenicity, while cytotoxicity resulted at the highest dose tested (5000 ug/plate).

Adequate data were produced for determining that the test compound was not mutagenic in any of the tester strains in the presence or absence of metabolic activation. The positive control compounds, however, produced an increase in the number of revertants, demonstrating that the assay was capable of producing a positive response.

E. Acute Oral, Dermal, Primary Eye and Skin Irritation, and Skin Sensitization Studies of a Formulation

1. Citation: Keeffe, I. and G. R. Parkinson. June, 1982. PP333 Formulation JF6047A (GFU029): Acute oral toxicity, acute dermal toxicity, skin irritation, eye irritation, and skin sensitization. Unpublished report no. CTL/P/742 prepared by Imperial Chemical Industries PLC. Central Toxicology Laboratory. Alderley Park, Macclesfield, Chesire, UK. Submitted by ICI Americas. EPA Acc. No. 248688.

2. Materials and Methods

Test substance: PP333 formulation JF6047A containing 50% active ingredient (w/v). No other ingredients were specified.

Test species: Alderley Park strain specific pathogen free rats, New Zealand white albino rabbits, and Dunkin Hartley strain guinea pigs were used.

Experimental procedures: Acute oral toxicity. The authors stated that dose selection for the main study was based on a preliminary range finding experiment. The range finding study was not reported in detail. In the main study a group of 5 male and 5 female rats was fasted for 16 to 20 hours prior to administration of a single 5000 mg/kg dose of the formulation. The formulation was administered by gavage as a 50% (w/v) suspension in distilled water. The animals were observed for 15 days after treatment, and they were weighed the day before and on the day of treatment. They were also weighed 3, 8, and 15 days after dosing. At the end of the observation period survivors were sacrificed and subjected to gross necropsy.

Acute dermal toxicity: Two groups of rabbits (5 per sex in the treatment group and 2 per sex in the control group) had the hair clipped from the dorsolumbar region. Prior to application of the test substance, control and treatment group animals also had the clipped areas of skin abraded. A 1000 mg/kg dose was applied to the prepared skin as a 50% (w/v) suspension in distilled water. The sites were then covered with occlusive dressing and the rabbits were restrained to prevent them from attempting to remove the dressings. After 24 hours the dressings were removed, and the application sites were gently cleaned with warm water and blotted dry. The rabbits were observed for 15 days for signs of toxicity. They were weighed on days 1, 3, 7, and 15 of the experiment and sacrificed on day 15. At sacrifice the rabbits were grossly necropsied. Skin samples were taken from test sites on control and treated animals and prepared for histological examination.

Skin irritation: One day before treatment the hair was clipped from both flanks of 6 female rabbits. The clipped skin on one flank of each animal was abraded just before the test substance was applied. The test material was applied to the intact and abraded skin of each rabbit as a paste in physiological saline at a dosage rate of 500 mg/kg. Each application site was covered with a polyethylene patch held in place by adhesive tape. The trunks of the animals were then wrapped with a cloth bandage. These dressings were

removed 24 hours after application of the test material. The treatment sites were washed with warm water and gently blotted dry. Test sites were observed one to two hours after washing, and the Draize method was used to score the skin reactions. Application sites were also assessed 72 hours after treatment as well as 4, 5, 6, and 7 days after the application of the test substance.

Eye irritation study: Approximately 100 mg of the powdered test substance was placed in the cup formed by pulling the lower lid away from the eyeball of test rabbits.

The lids of the treated eye were gently held together for one to two seconds and then released. The other eye of each rabbit was left untreated. Three rabbits had their treated eye irrigated with lukewarm water 20 to 30 seconds after treatment. Treated eyes in the six remaining rabbits were not irrigated. Eye reactions were scored 1 to 2 hours and 1, 2, 3, 4, and 7 days after treatment by the Draize method.

Skin sensitization in guinea pigs: The authors described preliminary studies in which groups of two guinea pigs were used to test up to 2 concentrations of PP333. These preliminary tests were used to determine the highest concentrations below 5% which could be tolerated locally or generally after intradermal injection application was that which did not cause excessive inflammation. PP333 was suspended in corn oil for intradermal injection and dissolved in dimethylformamide for topical applications. Concentrations selected on the basis of results from these studies were used as induction doses, while results from animals previously injected with Freund's complete adjuvant were used in similar studies to determine challenge doses. The Freund's adjuvant was administered 14 days prior to these preliminary experiments with the formulation.

In the main study the hair was clipped from the scapular region of each test animal (20 treated and 8 control animals). Three injections were made on each side of the midline. The first contained Freund's complete adjuvant and distilled water (1:1); the second contained 0.5% formulation (w/v) in distilled water; and the third contained a 0.5% suspension of the formulation (w/v) in distilled water, and Freund's complete adjuvant. One week after each animal received these intradermal injections, the test substance was applied topically to the clipped area of skin. A 75% (w/v) mixture of the test material in distilled water was put on filter paper in 0.2 to 0.3 ml amounts. the filter paper was then applied to the injection sites and held in place with surgical tape. An occlusive dressing was placed around each animal and left for 48 hours.

Control group animals were treated similarly except that the three injections consisted of a mixture of Freund's adjuvant and distilled water (two sites) and distilled water alone (one injection site). The topical application was made in the same manner as described above.

Two weeks after the topical application, the hair of each guinea pig was clipped from its flanks. A challenge concentration of 75% (w/v) of the test substance in distilled water was applied on clipped skin. The challenge concentration was topically applied in the same manner as those in the topical applications described in the previous paragraph, but the occlusive dressings were removed 24 hours after application. The treatment sites were observed at 24 and 48 hours after removal of the dressings. The investigators quantified the reactions according to the following scale:

0 - no reaction
1 - scattered mild redness
2 - moderate and diffuse redness
3 - intense redness and swelling

The overall sensitization response was then classified on a 5 point scale (1-5) based on the percentage of animals responding as follows:

% Responding	Grade	Description
>0-8	1	Weak
9-28	2	Mild
29-64	3	Moderate
65-80	4	Strong
81-100	5	Extreme

3. Reported Results

Acute oral toxicity: One male and one female rat died on days 3 and 2 of the study, respectively. The authors noted that signs of toxicity appeared in the survivors on the second day after treatment. They stated that decreased activity, piloerection, chromodacryorrhea, staining around the snout, upward curvature of the spine, and pinched-in sides were observed. Some of these signs persisted until the end of the 14-day observation period. The only reported observation from gross necropsy was the occurrence of yellow or light areas on the livers of 3 of the males and one of the females. The acute oral LD_{50} was estimated by the authors to be greater than 5000 mg/kg.

Acute dermal toxicity. The authors stated that one female died on the ninth day of the experiment. No toxic

signs were observed, and the only observations noted at gross necropsy were dark red patches on the lungs of all control group rabbits and in 4 each of the treatment group males and females. The authors stated that histological observation of treated skin showed a sparse distribution of neutrophils in the stratum spongiosum without other signs of irritation.

Skin irritaton: Well defined erythema and moderate edema were observed by the investigators shortly after application of the test substance to intact skin. Abraded skin treated with the formulation showed no erythema to well defined erythema and slight to severe edema. The authors noted that the test substance stained the treated skin but they stated that the staining did not interfere with scoring of treated sites. Slight erythema was observed on the 6th day after application while edema persisted for 72 hours. The investigators also reported slight thickening of the skin (3 rabbits) and desquamation (1 rabbit). The total score recorded at 72 hours was 94 and the primary irritation index was 1.96 (94/48).

Eye irritation: The authors noted that all six rabbits whose treated eyes were unirrigated had diffuse opacities involving one-fourth to the entire cornea. Slight iritis and conjunctivitis with redness, chemosis, and discharge were also noted. Corneal opacities persisted in some rabbits for up to 4 days with a maximum mean score of 25 (out of a maximum possible score of 80) on the first day after treatment, Iris effects were noted for up to 4 days after treatment with a maximum mean score of 5.8 (out of 10 possible) on the day of treatment. Conjunctival effects (redness) persisted for up to 9 days in one rabbit. The maximum mean score of 12 was noted on the day of treatment. The investigators stated that one rabbit died of pneumonia during the observation period after dosing. Five rabbits were reported to have an irregular corneal surface on Day 2 after treatment and two of those had that effect on the third day following treatment as well.

The three rabbits with irrigated eyes were reported to have diffuse opacities covering up to three quarters of the cornea and slight conjuctivitis one to two hours after treatment. Two of the rabbits were also found to have slight iritis. All of the rabbits' eyes were described as normal 7 days after treatment. Reported mean scores showed that corneal opacities persisted for up to 3 days and iritis was observed up to two days after treatment. Conjunctivitis was noted up to 4 days after treatment.

Skin sensitization. None of the guinea pigs in the control or test group were reported to exhibit signs of sensitization when challenged with the test substance.

4. Discussion and Conclusions

The reported data adequately support classification of the 50% formulation into Toxicity Category IV for oral toxicity (LD_{50} greater than 5000 mg/kg) and Toxicity Category II for dermal toxicity (LD_{50} greater than 1000 mg/kg). It should be noted that the classification for dermal toxicity could be changed if a study conducted at higher doses were submitted. The skin irritation study indicates that the formulation is in Toxicity Category IV, and the eye irritation results reported indicate a classification of Toxicity Category II since corneal opacities persisted for up to 9 days in unwashed eyes. No skin sensitization was observed in a maximization test in guinea pigs.

5. Core Classification: Minimum

F. Acute Inhalation Study of a Formulation

1. Citation: Hodge, M.C.E., I.P. Bennett and A. M. Curry. October 4, 1982. PP333 Formulation JF6047A (GFU029): Four hour acute inhalation toxicity study in the rat. Unpublished report No. CTL/P/759 prepared by Imperial Chemical Industries, PLC, Central Toxicology Laboratory. Alderly Park, Macclesfield, Cheshire, UK. Submitted by ICI Americas. EPA Acc. No. 248688.

2. Materials and Methods

Test substance: A 50% (w/w) formulation of PP333 [(2RS,3RS)-1-(4-chlorophenyl-4,4-dimethyl-2-(IH-1,2,4-triazol-1-yl)pentan-3-ol).

Test species: Alderly Park Wistar derived male and female rats.

Experimental procedures: A Wright dust feed generator was used to produce test atmospheres in a two liter chamber. Animals were exposed nose-only for four hours, and airflow through the exposure chamber was 15 to 20 liters per minute. The report stated that test substance concentrations were measured regularly (4 to 6 times) during the exposure period using 25 mm open-faced filters for sample collection. Particle sizes were determined by a centripeter and/or a cascade impactor. Temperature and humidity was also measured at intervals during exposure.

Groups of 5 male and 5 female rats were exposed to air concentrations ranging from the maximum attainable (see Reported Results below) to approximately one-tenth of the maximum. Another group was exposed to air containig no test substance.

Animals were observed for occurrence of toxic signs and mortality at least once daily for the 14 days following the exposure. They were also weighed on the day before the experiment began and on days 1, 2, 3, 4, 5, and 15. Three of the 6 test groups were weighed on days 7 and 9, while the remaining three groups were weighed on day 8 of the observation period. On the day prior to the beginning of the study and the day of sacrifice (15th day of the study) all animals were examined clinically. The checklist reported by the authors included condition of eyes, skin, and coat, motor activity, righting reflex, pain sensitivity, corneal reflex, pinna reflex, hearing, respiration, salivation and feces.

After sacrifice the lungs and liver were removed and weighed. The head, larynx, trachea, lungs, liver, heart, spleen, kidneys, gonads, and any grossly abnormal tissues were preserved for future reference according to the report.

3. Reported Results

Mean air concentrations (mg/m^3) in the 4 treated groups were reported as follows:

Group No.*	Mean Concentration	Standard Deviation
2	101.4	73.3
3	765.7	24.9
5	243.1	17.0
6	369.3	21.1

* Groups 1 and 4 were controls

The authors described the test atmospheres as highly respirable. They reported that 90% of the particles in air samples were less than 12.5 um mass median aerodynamic diameter. The lower concentrations were reported to have smaller particle sizes because of difficulties encountered in generating the test atmospheres at the lower concentrations.

Clinical signs reported during the exposure period included red nasal discharges in animals from the control and test groups, and nasal irritation in the group exposed to air containing 359 mg/m^3. No other signs were noted in the remaining groups during the 4 hour exposure. All 5 female rats exposed to the highest test concentration (766 mg/m^3) died or were sacrificed in extremis within two days following exposure. None of the male rats exposed to 766 mg/m^3 died,

but exhibited signs of reduced activity after exposure. Signs of upper respiratory tract irritation were reported and these included wheezing and slight nasal discharge ("snuffles"). These signs persisted in the treated groups for a few days after exposure.

The authors noted that body weights of treated rats were decreased after exposure, but weight gains during the observation period were comparable in treated and untreated groups. The mean body weights of male rats exposed to the 766 mg/m^3 concentration were approximately 5% less than those of the control males on days 3, 4, and 7 of the observation period. Those were the only statistically significant differences with respect to mean body weight in surviving test animals.

Organ weight results were reported to show statistically significant decreases for the liver (absolute and relative to body weight) in the males. These data were reported for male rats as follows:

Dose mg/m^3	Mean Liver Weight (g)	Liver/Body Weight (%)
0	15.0 (1.20)	5.093 (0.355)
101	14.73 (1.01)	4.187 (0.773)
766	12.43 (1.35)	4.429 (0.501)
0	14.89 (1.87)	4.83 (0.33)
243	17.42 (2.53)	5.593 (0.614)
369	14.25 (1.49)	4.776 (0.310)

* Standard deviation in parentheses.

No other statistically significant differences regarding organ weights in rats sacrificed at the end of the study.

The only gross abnormalities noted by the authors were found in 3 female rats from the 766 mg/m^3 group. These animals had dark red lungs (2/3), dark thymus (1/3), hydrothorax and hemorrhage around the heart (2/3), pale liver (2/3), and pale kidneys (1/3). Two of the 5 females from the same group were not examined because of autolysis according to the authors.

The authors stated that the LC_{50} for male rats is greater than 766 mg/m^3, while that for female rats is between 369 and 766 mg/m^3.

4. Discussion and Conclusions

The reported results adequately support the conclusions of the authors that the LC_{50} for the 50% powder formulation in female rats is between 369 and 766 mg/m^3. For male rats the acute inhalation LC_{50} is reported to be greater than 766 mg/m^3. Based on these results the 50% powder formulation can be classified into Toxicity Category II for acute inhalation.

5. Core Classification: Minimum

G. Acute Toxicity Studies with a Formulation Containing Less Than 1% PP333

1. Citation: WARF Institute. October 19, 1977. Acute oral LD_{50}, primary skin irritation, primary eye irritation acute dermal LD_{50}. Unpublished Report No. 6064414. No EPA Accession Number is given.

2. Materials and Methods

Test material: Granular formulation containing 0.40% PP333.

Test species: Seven week old male Sprague Dawley rats and 14 week old male New Zealand white rabbits were used in these studies.

Experimental procedures: Acute oral toxicity. The test material was fed to rats in feed crocks because the test material when mixed or diluted in a vehicle could not pass through a gavaging needle. A mixture of 25% of the formulation with 75% feed was used. The dosage tested was 20 g formulation per kg body weight. The animals were observed for signs of toxicity or mortality hourly for the first 5 hours after dosing, and twice daily for 14 more days. At the end of the observation period surviving rats were sacrificed and necropsies were performed. Gross tissue pathology was noted.

Acute dermal toxicity: Four rabbits had the skin of their trunks clipped free of hair before application of 8 g formulation/kg body weight. The application sites were then occluded with a rubber sleeve for a 24 hour period. At the end of that time the sleeves were removed, but the report does not indicate whether the application sites were cleaned. The rabbits were observed at the same frequency as the animals in the oral toxicity study described above. Body weights were also recorded one and two weeks after dosing.

Primary skin irritation: The back and flanks of six rabbits were clipped free of hair. One area of clipped skin was abraded. The formulation was applied to that site and a

second site which was intact. A 0.5 g amount of the formulation was applied to the two types of skin on each rabbit. Each treated site was covered with a gauze patch and taped. The rabbits were then restrained for 24 hours. At the end of that time, they were examined for the appearance of edema and erythema/escher at the treated sites. The treatment sites were scored at 24 and 72 hours after treatment. A primary irritation index was determined from the average of the reaction scores.

Primary eye irritation: One-tenth gram of the test formulation was instilled into one eye in each of 6 rabbits. The eyes of each rabbit were examined 24, 48, and 72 hours after instillation of the formulation for reactions in the iris, conjunctiva, and cornea. These reactions were scored and averaged to obtain an eye irritation index.

3. Reported Results

None of the 10 rats given 20 g of the formulation died, and no signs of toxicity or gross pathological findings were observed.

None of the 4 rabbits dermally exposed to 8 g/kg showed signs of toxicity or mortality.

There were also no skin or eye irritation reactions noted in appropriately treated rabbits.

4. Discussion and Conclusions

The data presented are adequate to support classification to acute oral toxicity (LD_{50} >20 g/kg), acute dermal toxicity LD_{50} >8 g/kg), or primary skin and eye irritation (no reactions were noted).

5. Core Classification: Minimum.

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