UTAH STATE UNIVERSITY · LOGAN, UTAH 84322
COLLEGE OF AGRICULTURE

DEPARTMENT OF
ANIMAL, DAIRY AND
VETERINARY SCIENCES

801/750-1600

MEMORANDUM

003281

TO: Tom Roetzel

FROM: J.C. Street

DATE: August 17, 1981

SUBJECT: Scientific validations of Bromacil records

Enclosed are the evaluations, together with original documents, on Bromacil as contracted for by your office through Dr. Stephenson. Approximately three records are outstanding, requiring corrections; they will be forwarded in a few days. The Sulfur job is also in the mail under separate cover.

J.C. Street

B

B Some studies used

1 of 119

(B)

DATA EVALUATION REPORT

(1) CHEMICAL; Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Emulsifiable concentrate

(3) CITATION: Cavalli, R.D.; Hallesy, D.W.(1969) Acute Respiratory Toxicity of Triox Liquid Vegetation Killer: SOCO 96/II:135. (Unpublished study received Dec 1, 1969 under unknown admin. no.; submitted by Chevron Chemical Co., Richmond, Calif.; DCL:107589-E)

(4) REVIEWED BY: David B. Drown
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Date 7/15/81

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(6) TEST TYPE: Acute inhalation toxicity study. Guideline 40CFR 163.81-3

(7) CONCLUSIONS:

1) This study involved a 1-hour acute inhalation exposure of male and female rats to Bromacil (TRIOX Liquid Vegetation Killer). Two groups of rats were exposed to concentrations of 6.8 mg/l and 16.3 mg/l. No morbidity or mortality was observed in the rats during exposure or the subsequent 14-day observation period. Although not reported it is implied from the data that the LC50 for TRIOX is in excess of 16.3 mg/l of air.

2) With some exceptions, the format of the study reported here follows the Proposed Guidelines 40CFR 163.81-3. Variations from the Guidelines are listed below:

a) Concurrent untreated control groups were not utilized.

b) Details of the exposure chamber and makeup air system were not given.

c) Nominal chamber concentrations were given. However, actual chamber concentrations were not measured.

d) Exposure temperature was included in the data but humidity data are not included.

e) Particle sizing of the aerosol was not carried out.

f) Observation information during exposure and the subsequent 14-day observation period is lacking. Also no animal weight data is included.

3) The results of this study, as reported, suggest a low order of acute toxicity with respect to relatively high airborne concentrations of liquid TRIOX.

(8) MATERIAL AND METHODS:

A) TRIOX Liquid Vegetations Killer (Chevron Chemical Company) was used in the study. In addition to the product name, the label carried a code SX210. Formulation consisted of an emulsifiable concentrate.

B) The aminals were male and female rats of a Sprague-Dawley derived strain. Age and size information was not included. The rats were housed in individual cages in an air-conditioned room. They were allowed free access to food and water except during exposure.

C) The animals were whole-body-exposed for a period of one hour. Two concentration groups were utilized. One group was exposed to 6-8 mg/l TRIOX and the other was exposed to 16.3 mg/l. The amount of TRIOX used during exposure and air flow were used to determine concentrations.

D) The animals were sacrificed at 14 days and the following organs or tissues were examined: lung, heart, thymus, liver, kidney, spleen, gastro-intestinal tract, adrenal glands, pancreas, bladder, gonads, body fat, skeletal muscle, skin and eyes.

(9) REPORTED RESULTS:

There was no mortality or morbidity in either group of exposed rats. Animals scarificed at 14 days showed all tissues examined to be normal. It was reported that a chamber operator inhaled a slight amount of the 6.8 mg/l aerosol. This resulted in severe acute upper respiratory tract irritation and bronchoconstriction, lasting several minutes.

(10) DISCUSSIONS:

Although the details of this study do not exactly comply with the Proposed Guidelines, it appears that the effects of acute respiratory exposure of rats to concentrations of TRIOX Liquid Vegetation Killer in the order of 6.8 mg/l and 16.3 mg/l are negligible. It can be concluded from these data that the LC50 value for TRIOX is greater that 16.3 mg/liter of air.

(11) TECHNICAL REVIEW TIME:

2.5 hours

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File No. 00013272

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Technical chemical

(3) CITATION: Colburn, C.W.; Frank, K.M. (1969) Skin Absorption LD_{50}: Haskell Laboratory Report No. 276-69. (Unpublished study received Oct 2, 1969 under 352-87; submitted by E.I. du Pont de Nemours & Co., Wilmington Del.; CDL:002921-C).

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(6) TEST TYPE: Acute dermal toxicity study. Guideline 40 CFR 163.81-2

(7) CONCLUSIONS:

1) The procedures reported in this study are similar but do not exactly coincide with Proposed Guidelines 40 CFR 163.81-2. Some procedural discrepancies are listed below:

   a) Only male rabbits of unspecified age and weight were used.

   b) An appropriate number of test animals was not used for the initial dosing levels to satisfy the 2g/kg, no further testing criterion.

   c) A control group was not included in the study.

   d) The percent body area tested was not specified.

   e) Histopathology of the treated skin was not included.

2) There were no deaths in any of the exposed groups.

3) The LD_{50} of the test material was reported to be in excess of 5g/kg. This material probably represents a low order of acute dermal toxicity.

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(8) MATERIAL AND METHODS:

A) The test material consisted of TRIOX Liquid Vegetation Killer (Chevron Chemical Company). A clear amber non-viscous liquid. The label was coded SX 210.

B) Test species was the New Zealand White Strain rabbit. All specimens were male. Age and body weights were not included in the report. The rabbits were individually caged and kept in an airconditioned room at 22C (± 1C).

C) The rabbits were prepared by clipping the fur from the trunk area. The skin of 5 of the animals was abraded on the back, flank and abdomen with a hypodermic needle. The animals were then wrapped in a plastic dam and undiluted TRIOX was introduced under the dam according to the following schedule:

Dose g/kg	Abraded skin	Intact skin
1	1 rabbit	1 rabbit
2	1 rabbit	1 rabbit
5	3 rabbits	3 rabbits

The animals were restrained for 24-hours and then the dam was removed and the skin wiped dry. A 14-day observation period followed.

D) Subsequent to the 14-day observation period the animals were terminated. The following organs or tissues were examined for gross abnormalities: lung, heart, thymus, liver, kidney, spleen, gastro-intestinal tract, adrenal glands, pancreas, bladder, gonads, body fat, skeletal muscle and skin.

(9) REPORTED RESULTS:

There were no deaths in any of the dosage groups. The skin of the trunk in all groups showed severe irritation, eschar and shedding. New fur bearing skin was evident by 14 days. Ther was some scarring at the edges of the burn. Necropsies at 14 days showed no gross changes except for one rabbit at 5g/kg (intact skin) which showed inflamed renal medullae, and greatly enlarged liver. It was reported doubtful that this condition could be treatment related.

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(10) DISCUSSIONS:

Although the details of the study do not exactly comply with the Proposed Guidelines, it appears that test animals did survive a rather large dose (5g/kg) of TRIOX applied to the skin. The acute dermal LD_{50} of TRIOX is stated to be in excess of 5g/kg. This statement is probably acceptable.

(11) TECHNICAL REVIEW TIME:

2.6 Hours

File No. 00013271

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DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil ; Hyvar XL Herbicide)

(2) FORMULATION: Soluble concentrate

(3) CITATION: Tayfun, F.O. (1969) One-Hour Inhalation Toxicity: Haskell Laboratory Report No. 265-69. (Unpublished study received Oct 2, 1969 under 352-87; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:002921-B)

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(6) TEST TYPE: Acute inhalation toxicity study. Guideline 40 CFR 163.81-3

(7) CONCLUSIONS:

1) The study outlined in this report has been been crudely conducted and does not relate to the Proposed Guidelines 40 CFR 163.81-3.

2) The LC_{50} for du Pont Hyvar XL Herbicide has been reported as greater than 5mg/liter. However, it is difficult from the reported data to determine exactly how that value was arrived at.

3) An indirect method of measuring concentration of the test material was employed. Little information as to how that was accomplished is included in the report. Apparently, gas chromatographic analysis of [redacted] (components of the Hyvar XL formulation) were related to total concentration of the material.

4) Neither untreated or vehicle controls were utilized.

5) The methods of aerosol generation were rather crude and are not well described.

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

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6) Necropsy did not follow the 14-day observation period.

7) Temperature and humidity measurements were not made.

8) Makeup air source, flow rates and other exposure chamber details were not given.

9) Particle sizing techniques were not included.

10) The above comments are but a few criticisms of the report with respect to the Proposed Guidelines.

11) Young adult male and female ChR-CD rats were used in head only exposure.

12) The report stated that no toxic signs were observed during exposure. Except for hypersensitivity to touchand loss of facial hair the third recovery day, no toxic signs were observed during the recovery period.

13) The data available suggest a low order of acute toxicity with respect to exposures to Hyvar XL Herbicide in excess of 5mg/l.

(8) MATERIAL AND METHODS:

A) Formulation of the test substance, du Pont Hyvar XL Herbicide (Bromacil), consisted of a soluble concentrate apparently containing [redacted] (not clearly stated in the report).

B) Male and female, two-month old, 210 to 260 gram ChR-CD rats were used in the studies. Caging specifications were not given.

C) The animals were exposed, head only, for a period of one hour per group of six in a 16-liter bell jar. The animals were subsequently held for a 14-day observation period.

D) Gross external condition or mortality seemed to be the parameters considered during exposure and the 14-day observation period.

(9) REPORTED RESULTS:

No mortality was observed in the test animals during exposure to Hyvar XL Herbicide in concentrations up to 12mg/l or during the subsequent 14-day exposure period. It was noted that on the third day following exposure, some hypersensitivity to touch and loss of facial hair in some animals was observed.

(10) DISCUSSIONS:

The format of this study, since it was conducted prior to the issuance of the Proposed Guidelines, differs markedly from 40 CFR 163.81-3. There is little documentation of procedures and no pathology report. The initial exposure lasted for 1 hour and the 14-day observation period was adhered to. However, there is considerable information lacking on the actual concentration of test material as well as its formulation. Also, no untreated control group was utilized. In light of the deficiencies of this study, it is difficult to accept the results as they stand.

(11) TECHNICAL REVIEW TIME:

3 Hours

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DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Active ingredient

(3) CITATION: Raltech Scientific Services, Incorporated (1979) Eye Irritation. (Unpublished study received Oct. 25, 1979 under 34704-52; submitted by Platte Chemical Co., Fremont, Neb.; CDL:241218-C).

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Date _____

(6) TEST TYPE: Primary eye irritation study. Guideline 40 CFR 163.81-4.

(7) CONCLUSIONS:

1) The test procedures described here were conducted in accord with Proposed Guidelines 40 CFR 163.81-4.

2) Nine young adult, male and female New Zealand White Strain rabbits were used in the study.

3) The rabbits in both the test groups (washed and unwashed) received 0.1 ml Bromacil liquid in one eye while the other eye served as a control.

4) The rabbits were mildly affected by the test material. Sodium fluorescein treatment of the test animal eyes at 24 and 72 hours and 7 days showed no corneal injury. Conjunctival irritation was evident up to 72 hours in both groups. However, all irritation was absent by day four.

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5) Irritation scores at 24, 48 and 72 hours as well as 4 and 7 days were very low. No major problems or corrosive actions were observed. The results suggest a relatively low eye irritation potential associated with Bromacil.

(8) MATERIAL AND METHODS:

A) The test substance consisted of Bromacil liquid (formulation equivalent to the active ingredient).

B) Male and female young adult rabbits (approximately 14 weeks of age) of the New Zealand White Strain were used in the testing. Initial weights ranged from 2377 to 2857 grams. The animals were housed in screen bottom cages in air conditioned quarters and were provided continuous access to commercial laboratory feed and water.

C) The animals were held for a minimum conditioning period of 7 days prior to dosing. The eyes were examined at least 24 hours prior to administration of the test compound using fluorescein dye procedures. Only those animals with no sign of corneal injury were utilized.

The animals were divided into 2 groups, group I consisted of 6 rabbits and group II consisted of 3 rabbits. The rabbits in both groups received 0.1 ml of test material according to the method outlined in the Proposed Guidelines.

D) Parameters to be examined included ocular lesions in the treated eyes of both groups as well as the scoring and grading of irritation.

(9) REPORTED RESULTS:

No occular lesions were observed in either the unwashed or the washed group. Primary eye irritation scores for the two groups were reported as follows:

Primary Eye Irritation Score	Group I (Unwashed)	Group II (Washed)
24 hours	1.3	2.0
48 hours	0.0	0.0
72 hours	1.7	0.7
4 days	0.0	0.0
7 days	0.0	0.0

(10) DISCUSSION:

The procedures followed in this study were in compliance with Proposed Guidelines 40 CFR 163.81-4. Primary irritation scores at all stages of the study were low and indicate negligible effects as a result of the application of Bromacil to test animal eyes.

(11) TECHNICAL REVIEW TIME:

3 hours

[redacted]

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil; Hyvar XL).

(2) FORMULATION: Soluble concentrate

(3) CITATION: Schmayer, L.A. (1969) Oral LD 50 - Test: Haskell Laboratory Report No. 253-69. (Unpublished study received Oct. 2, 1969 under 352-87; submitted by E. I. duPont deNemours & Co., Wilmington, Del.; CDL:002921-A).

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(6) TEST TYPE: Acute oral toxicity study. Proposed Guideline 40 CFR 163.81-1.

(7) CONCLUSIONS:

1) The procedures reported in this study are similar but do not exactly coincide with Proposed Guidelines 40 CFR 163.81-1. Some procedural discrepancies are listed below:

   a) Details are lacking on time of death and on the schedule of observations following dosing.

   b) Animal weights were not recorded at weekly intervals following dosing.

   c) Animals terminated at the end of the 14-day observation period, were not subjected to gross micropsy.

2) Male and female ChR-CD young adult rats were used in the study.

3) The LD50 for Hyvar XL was determined as 1414 mg/kg for both male and female rats. The material appears to be moderately toxic.

4) Signs of toxicity included pallor, heavy breathing, decreased muscle tone, and watery eyes.

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INERT INGREDIENT INFORMATION IS NOT INCLUDED

(8) MATERIAL AND METHODS

A) The test substance consisted of an aqueous solution based on the product as received for testing (soluble concentrate) from E. I. duPont deNemours and Company. The composition of the formulated product was given as follows:

[redacted]	
Technical Bromacil (Lot 58)	32.3%

B) Tests were performed on young adult male and female ChR-CD rats. The range of average body weights per test group were 236 to 248 g for males and 188 to 193 g for females. Individual weights were not given. Housing specifications were not given.

C) The animals (5 per group) received single doses administered by intragastric intubation after an overnight fast. Dose amounts were as follows:

mg/kg Dose	Sex
4000	Male
2000	Male
1000	Male
2000	Female
1000	Female
500	Female

D) Toxicological clinical signs during the 14 days subsequent to dosing and death were the parameters examined during the study.

E) The oral LD50 value was calculated from C. S. Weil's moving average tables.

(9) REPORTED RESULTS:

Mortality results were reported as follows:

	Dose mg/kg	Mortality Ratio
Males:	4000	5/5
	2000	5/5
	1000	0/5
Females:	2000	5/5
	1000	0/5
	500	0/5

Clinical signs included pallor, heavy breathing and decreased muscle tone in males and pallor, discomfort, decreased muscle tone and watery eyes at the highest level in females. The LD50 for both fasted males and females was reported as 1414 mg/kg.

(10) DISCUSSION:

The conduct of this study is basically similar to the Proposed Guidelines 40 CFR 163.81-1, acute oral toxicity study. Minor differences in study format are listed in the Conclusion Section of this review. From the data available, it is reasonable to accept the conclusion of this report, which states that Hyvar XL is slightly toxic when administered orally to fasted male and female rats, its LD50 being 1414 mg/kg for each sex. One must be careful, however, when evaluating these results with respect to the chemical Bromacil. Information has not been included or considered here which relates to the individual components of the formulation products.

(11) TECHNICAL REVIEW TIME:

2.8 Hours

(6)

File No. 00022080

Page No. 1 of 3

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DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Active ingredient

(3) CITATION: Biesemeier, J.A.; Argevine, D.M. (1979) Inhalation -- EPA. (Unpublished study received Oct 25, 1979 Under 34704-52; prepared by Raltech Scientific Services, Inc., submitted by Platte Chemical Co., Fremont, Nebr.; CDL:241218-D)

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Date _____

(6) TEST TYPE: Acute inhalation toxicity study. Guideline 40 CFR 163.81-3

(7) CONCLUSIONS:

1) This study entailed an initial screening of the acute toxicity of Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil). Ten young male and (10) female adult Sprague-Dawley rats were exposed to an average concentration of 57.6 mg Bromacil/liter of air. A concurrent sham control group of the same makeup was also utilized in the study. No mortality was observed during the subsequent 14-day observation period. Pathology reports on the terminated animals showed no gross differences between the control and exposed groups. The only difference reported between the treated and control rats was an increase in the lesions of moderate degree in the treated rats. The reporting pathologist stated that in his opinion, the differences were real but probably were not very significant.

2) With few exceptions, the format of the study reported here follows very closely the Proposed Guidelines 40 CFR 163.81-3. Variations from the Guidelines are listed below:
   a) Reported initial test duration of 1 hour may not have been entirely adequate since the measured concentration within the chamber during the 1-hour exposure varied considerably

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(36.0 mg/l to 102.0 mg/l). However, the average measured concentration was reported as 57.6 mg/l and the nominal concentration was 60 mg/l. Both were considerably in excess of the LC_{50} cutoff point for initial screening of 5 mg/l.

b) Humidity measurements were not made during exposure. Temperature was adequate, however, instrumentation details were not included.

c) Details of aerosol generation are completely lacking.

d) Particle sizing was carried out only once during the 1-hour exposure. The particle sizing procedure was not state of the art, however, is acceptable.

e) Chamber makeup air was not described.

3) The results of this study suggest a low order of acute toxicity with respect to exposure to relatively high airborne concentrations of Bromacil.

(8) MATERIAL AND METHODS:

A) The test substance consists of Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil) as a solid. The particle sizing analysis reported a range of 0.5 micro meters to 15 micro meters with a mean diameter of 6.0 micro meters. Eighty percent of the particles were less than 10 micro meters in size. Source or purity of the material (active ingredient) was not given.

B) Test animals were young (8 weeks of age) male and female adult Sprague-Dawley rats. The animals weighed between 210 and 345 grams at the start of the study. The test animals were housed in individual wire mesh cages both during exposure and the 14-day observation period. The animals were fed and watered ad libitum throughout the study except during whole body exposure.

C) The animals were whole body-exposed for a 1-hour period to an average concentration of 57.6 mg/l Bromacil in a 765-liter stainless steel exposure chamber. The animals were subsequently held for a 14-day period prior to termination for necropsy.

D) Parameters of effect included primarily the pathological evaluation of lung tissue. Liver, kidney and, to a lesser degree, sex organs.

E) Pathological findings were not treated statistically.

(9) REPORTED RESULTS:

Principle pathologic findings included microscopic lesions of the lungs consisting of foci of mononuclear leukocytes and lymphocytes. These lesions occurred throughout the lung

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and were usually perivascular or near the terminal bronchioles, but most often were located at the perifery of the lungs. These lesions were observed in the lungs of both control and treated rats. They were classified as mild focal (usually a single focus) or multifocal. Moderate or severe lesions were always multifocal. The pathologic findings were reported as follows:

	Control	Test
Lung:		
No significant lesions	6	4
Mild focal and multifocal lesions	8	9
Moderate focal lesions	3	6
Moderate/severe lesions	1	1
Congestion	2	-

The liver and kidney showed no significant lesions. Hydrometra was observed in two control and two treated rats. Atrophy of both testes was observed in one rat of the treated group. In the opinion of the pathologist, the observed results were probably not very significant.

(10) DISCUSSION:

It appears from these data that the effects of acute respiratory exposure of rats to 57.6 mg Bromacil per liter of air are negligible. The LC_{50} for Bromacil is indeed in excess of 57.6 mg/l with respect to the test animals. It can be concluded that the results of this study are acceptable under 40 CFR 163.81-3.

(11) TECHNICAL REVIEW TIME:

3.5 Hours

File No. 000 35376

Page No. 1 of 2

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DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (and others)

2. FORMULATION: Active ingredient, technical grade

3. CITATION: Andersen K. J.; Leighty, E. G.; Takahashi, M. T.; (1967?) Evaluation of herbicides for possible mutagenic properties. (Unpublished study received Jun 30, 1977 under 976-36; prepared by Battelle Memorial Institute, Columbus Laboratories, submitted by Velsicol Chemical Corp., Chicago, Ill.; CDL:232392-A) CDL:232392-A)

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5. APPROVED BY:

6. TEST TYPE: Gene mutations in bacteria (163.84-2)
Gene mutations in phage (not in guidelines)

7. CONCLUSIONS:

1. This report is useless in determining the mutagenicity of bromacil.

2. This report does not satisfy the guidelines for mutagenicity testing.

3. No evidence legible in this report suggests the mutagenicity of bromacil.

8. MATERIALS AND METHODS:

1. Materials and methods are referenced but not detailed, nor are protocols given.

2. The Salmonella test of Ames is used, but no tabular data is presented.

3. Metabolic activation is not employed.

4. Several phage mutation experiments are reported done by referenced methods.

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Supplementary data ~~base~~ refer to Fitzhugh report

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9. RESULTS:

1. Results of the Ames test are presented only in pictoral form. These, fortunately or unfortunately, did not reproduce on the "best document available."

2. The frequency of induction of T4 rII mutants was 0.11% based on 3495 plaques. This was precisely the control frequency.

3. The frequency of reversion of bacteriophage AP 72 to T4 is reported to be 0.09 per 10^6 after treatment with bromacil. This was much lower than the control frequency, 0.93 per 10^5.

4. The reversion of bacteriophage M17 to T4 after bromacil treatment is reported to be 0.10 per 10^6. The control frequency was 0.09 per 10^6.

10. DISCUSSION:

1. Any information from the Ames test is lost from this review document.

2. Procedures are so poorly documented that evaluation is impossible.

3. The authors claim that no evidence of mutagenicity was found. This is true of the data still legible.

11. TECHNICAL REVIEW TIME: 1 hour.

File No. 05016869

003281

DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (and others)

2. FORMULATION: Isocil (N.B. 7.1 below)

3. CITATION: Epstein, S. S.; Arnold, E.; Andrea, J.; Bass, W.; Bishop, Y. (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicology and Applied Pharmacology 23(2):288-325.

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6. TEST TYPE: Dominant lethal effects in rodents. (163.84-3)

7. CONCLUSIONS:

1. If the nomenclature is consistent, Epstein et al. did not test Bromacil = 5-bromo-3-sec-butyl-6-methyluracil but Isocil = 5-bromo-3-isopropyl-6-methyluracil.

2. The study does satisfy the guidelines for assaying dominant lethals in rodents. Epstein is the author of the protocol referenced in the guidelines.

3. The conclusion that Isocil is if at all only weakly mutagenic appears to be justified.

8. MATERIALS AND METHODS:

1. Male mice of the ICR/Ha Swiss strain 8 - 10 weeks old were exposed to Isocil in tricaprylin or distilled water by ip injection or gavage. "Concentrations were adjusted so that approximately LD5 and LD25 doses, as determined by preliminary acute toxicity tests, were administered."

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2. Each male was caged with 3 consecutive harems of 3 virgin females for 1 week each.

3. Thirteen days after the midweek of their presumptive mating, the females were autopsied for live implants, early fetal deaths, and late fetal deaths.

4. An experiment was terminated if a pregnancy rate less than 30% or a mean of less than 8 implants per pregnancy was encountered in the concurrent control.

5. Mutagenicity was determined by comparing the data to a set of criteria developed in a large control study.

   Standard criteria.

   a. One or more weekly means exceeding 1.00 early fetal deaths per pregnancy, with at least 55% of the pregnant females having early deaths.

   b. One or more weekly means of less than 8 total implants per pregnancy.

   c. One or more weekly mean pregnancy rates of less than 30%.

6. To minimize false negatives, the data were also compared to a less rigid set of criteria.

   Less rigid criteria.

   a. One or more weeks with a mean of 0.90 or more early deaths per pregnancy.

   b. One or more weeks with 55% or more of the pregnant females having early deaths.

   c. One or more weeks with a mean of less than 9 total implants per pregnancy.

7. Agents mutagenic by the less rigid but not by the standard criteria were reexamined by subjecting the data to an analysis of variance.

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9. RESULTS:

1. Pertinent data from table 3.

Agent	Route and frequency of administration	Doses (mg/kg)	No. of males (No. of deaths)	Parameters selected in screen (mating week) % Pregnancy	Early deaths per pregnancy	% pregnant females with early deaths
"Bromacil" (?)	po x 5*	15	10(2)		1.00(5) 1.07(7)	57(7)
	ip	150	7			
	po x 5	750	9(1)	19(1)		
		1000	10	29(2)	0.90(3)	56(6)

* gavage on 5 consecutive days.

2. The above data are included in a list of agents that exceeded control limits but with differences found to be non-significant in an analysis of variance. "Bromacil" is tagged as meeting only the less stringent screening criteria.

10. DISCUSSION:

1. Table 1. a classification of the compounds tested, clearly states the synonomy of "Bromacil" with the herbicide "Isocil" obtained from E. I. duPont de Nemours and Co. The Merck Index (8th ed.) does not list "Bromacil" and designates "Isocil" as the isopropyl, not the butyl compound.

2. The conclusion that the compound does not induce a significant frequency of lethal mutations appears to be well founded.

11. TECHNICAL REVIEW TIME: 3.25 hours

File No. 05014405

Page No. 1 of 2 003281

DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (and others)

2. FORMULATION: Commercial preparation Hybar X

3. CITATION: Siebert, D.; Lemperle, E. (1974) Genetic effects of herbicides: induction of mitotic gene conversion in "Saccharomyces" cervisiae. Mutation Research 22;111-120.

4. REVIEWED BY: James T. Bowman
Professor of Biology
Utah State University
Department of Biology
Logan, Utah 84322
801-750-2492

Signature James T. Bowman

Date 7/25/81

5. APPROVED BY:

6. TEST TYPE: Mitotic gene conversion in yeast. (163.84-4)

7. CONCLUSIONS:

1. The data presented support but do not prove the contention that Bromacil is non-recombiongenic in mitotic yeasts.

2. A single dose level was employed and the data were not reported in such a manner that a stistical test of significance can be made.

8. METHODS AND MATERIALS:

1. Cells of the diploid strain of Saccharomyces cerevisiae

D4 MA 20: , gal2, ade2-2, trp5-12 - - leu
Md 20:a. + , ade2-1, trp5-27 - - +

were harvested from cultures in late lagarithmic phase and tested for frequency of spontaneous convertants. Cultures with a high frequency were eliminated. Cells from cultures with a normal background frequency of convertants were washed twice with distilled water. Sediments of about 5 x 10^7 cells were suspended in 2 ml of 1000 ppm Hyvar X in citrate-HCl buffer (pH 4.5). By ellipsis the buffer concentration is presumed to be 0.1M.

Lore Mennemann

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2. The treatment mixtures were shaken in a water bath for 16 hours.

3. Aliquots were plated on selective medium for the determination of frequency of convertants and on complete medium to determine survival. Colonies were counted 6 days later.

4. All experiments were performed 3 times and "representative" results reported.

9. RESULTS:

Pertinent data from Tables II and III.

Trade name	Convertants/10^6 survivors ade2	trp5	Survival (%)
Hyvar X	8.1(7.0)*	11.7(12.4)	46
Reglone**	23.2(3.8)	30.6(6.8)	

* Untreated control values in parentheses.
** Included for comparison.

10. DISCUSSION:

1. Metabolic activation was not employed.

2. Control values varied from 2.8 to 11.1 convertants/10^6 at the ade2 locus and from 1.9 to 19.2 at the trp5 locus. This and the "representative" nature of the data reported frustrate any effort to reach a defensible conclusion.

11. TECHNICAL REVIEW TIME: 2.0 hours

File No. 05020709

Page No. 1 of 3

003281

DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (and others)

2. FORMULATION: Not specified. Presumably active ingredient.

3. CITATION: Griffiths, A. J. F. (1979) Neurospora prototroph selection system for studying aneuploid production. Environmental Health Perspectives 31:75-80.

4. REVIEWED BY: James T. Bowman
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Signature James T. Bowman

Date 7/25/81

5. APPROVED BY:

Man accepted

6. TEST TYPE: Aneuploidy in fungi. (Not in guidelines.)

7. CONCLUSIONS:

1. The frequency of aneuploid exceptions following treatment with Bromacil, 7.6×10^{-5}, slightly exceeded that in untreated controls, 5.5×10^{-5}.

2. Raw data are not provided from which a statistical evaluation of the difference can be extracted. The author does not include Bromacil in the list of ". . . those ten agents whose PWT frequencies were consistently well above control values. Significance levels of 5% were used."

3. The data suggest but do not establish that treatment with Bromacil does not significantly increase the frequency of meiotic nondisjunction in Neurospora under the conditions employed.

Need Supplementation

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8. MATERIALS AND METHODS:

1. Standard Neurospora techniques appear to have been used. The compositions of the media are not detailed.

2. The auxotrophic mutants arg-1, ad-3A, ad-3B, and nic-2 at four closely linked sites in linkage group I facilitated the detection of prototrophic pseudo-wild type disomics for chromosome 1. Mutants at several other loci served to select against chance heterokaryon formation by the fusion of germ tubes of adjacent ascospores. Mutants at still other loci were gratuitously present but were not selected in these experiments.

3. Cultures of the protoperithecial parent (+ ad-3A + nic-2) were inoculated with conidia of the genotype arg-1 + ad-3B +. After "usually" 6 hours, the plates were exposed to Bromacil. "A wide range of doses was utilized in five or six crosses; the highest dose compatible with adequate fertility was eventually analyzed."

4. After 22 days, ascospores were collected and plated on selective and non-selective media. About 10^5 spores were plated on selective medium to determine prototroph frequency. A "diluted suspension" was plated on non-selective medium to assay total viable spores.

5. After two days, prototrophic colonies were examined to determine their origin from single ascospores. Two to three days later, colonies were counted and recorded.

6. Statistical analyses are not provided. An analysis of variance is stated to be in preparation.

9. REPORTED RESULTS:

Relevant data from Table 1.

Agent	Mean PWT x 10^5	No. of tests
Control	5.5	123
Bromacil	7.6	6
m-Aminophenol*	36.5	3

* for comparison as positive control.

10. DISCUSSION:

1. In general, the genetic methods employed in the study appear to be both reasonable and effective in measuring induced aneuploidy in Neurospora.

2. Documentation of toxicity, dose levels, and raw data is inadequate to nonexistent.

11. TECHNICAL REVIEW TIME: 1.5 hours

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DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl 6-methyluracil)

2. FORMULATION: An aqueous solution of bromacil (grade not specified)

3. CITATION: McCahen, J.W.; Hoffmann, C.E. (1965) Absence of Mutagenic Effects of 3- and 6-Alkyl-5-bromouracil Herbicides on a Bacteriophage. (Unpublished study received Nov 1, 1965 under unknown admin. no.: submitted by E. I. du Pont de Nemours & Co., Wilimington, Del.; CDL:107587-A).

4. REVIEWED BY: Charles F. Luke
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801-750-1600

5. APPROVED BY:

Not acceptable

6. TOPIC:

The study has information pertinent to discipline 45, topic 20 (Mutagenicity). This study relates to the proposed guidelines data requirement 40 CFR 163.84-1b2i.

7. CONCLUSION:

A. The test consisted of measuring the reversion of a coliphage T_4 mutant, incapable of infecting E. Coli K, back to the wild-type capable of infecting E. Coli K.

B. Bromacil and other substituted bromouracils were found to be not mutagenic, but 5-bromouracil was mutagenic.

C. The test system was not adequate to meet the guidelines in that: (1) it lacked a mammalian metabolizing system, and (2) only one concentration of the test chemicals (20 µg/ml) was used.

8. METHODS AND MATERIALS:

A. The test system consisted of a wild-type coliphage T$_2$r$^+$, which is capable of forming plaques in both E. Coli (Escherichia coli) B and E.coli K, and a mutant (AP 72) of this phage, which is not capable of forming plaques in E. Coli K unless it is reverted by a mutagen back to the wild type where it is capable of plaque formation in both strains of E. Coli.

B. E. Coli B, grown in mineral salts medium, was infected with AP72 at 37° C. The infected cells were then placed in mineral salts solution containing various suppliments including 5-fluorodeoxy-uridine used to block thymine synthesis. Bromacil, 5-bromouracil, 5-bromo-6-methyluracil, 5-bromo-3-isopropyluracil, or 5-bromo-3-isopropyl-6-methyluracil in 10^{-3} M NaOH was added to the solution to a final concentration of 20 ug/ml. This mixture was incubated for 60 min at 37° C. Chloroform was added and cultures were shaken for 20 min. The phage preparations were then assayed with E. Coli B and E. Coli K on tryptone agar plates.

C. The reversion rate induced by the test compounds was then compared to the spontaneous reversion rate with thymine.

9. REPORTED RESULTS:

A. Bromacil and the other substituted bromouracils showed no mutagenic activity, but 5-bromouracil, a positive control, did.

B. In another experiment, cells were supplemented with a small amount of thymine hypothesizing that this might prime the incorporation of bromacil into DNA resulting in phage reversion. Again, bromacil failed to increase the back-mutation rate, whereas, 5-bromouracil did increase the mutation rate.

C. Also tested was the hypothesis that bromacil may increase or decrease mutagenic activity of 5-bromouracil. This hypothesis was also found to be negative.

10. DISCUSSIONS:

A. This study does not meet current guidelines because of the following:

1. No mammalian metabolizing system
2. Only one dose concentration of test chemicals was used
3. The grade of bromacil used in this study was not specified

11. REVIEW TIME: 3 hours

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DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl 6-methyluracil)

2. FORMULATION: Active Ingredient of a Commercial Grade of Hyvar X

3. CITATION: Wuu, K.D.; Grant, W.F. (1967). Chromosomal aberrations induced in somatic cells of Vicia faba by pesticides. Nucleus (Calcutta) 10(1):37-46.

4. REVIEWED BY: Charles F. Luke
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5. APPROVED BY:

Not acceptable

6. TOPIC:

This study has information pertinent to discipline 20 topic 2000 (Mutagenicity). This study relates to the Proposed Guidelines data requirement 40 CFR 163.84-1b2ii.

7. CONCLUSION:

A. The test method met the criteria found in the Proposed Guideline, except no mammalian metabolic activating system was used.

B. Vicia faba plants were incubated in 200, 400, or 600 ppm bromacil for 3, 6, or 12 hrs. The root tip cells from these plants were then stained and scored for chromosomal aberrations.

C. Bromacil increased the percentage of cells having chromosomal aberration; however, this finding should be viewed with reservations in that all 15 pesticides tested (many are not known to be mutagenic) were found to be mutagenic in this test system.

Supplementary

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8. MATERIALS AND METHODS:

A. Test chemical was commercial grade Hyvar X, whose active ingredient is bromacil. The herbicide was diluted on a weight basis of active ingredient with distilled water and assayed at the following concentrations: 200, 400, and 600 ppm.

B. Along with Hyvar X, 14 other pesticides were tested.

C. After washing all soil from the roots, Vicia faba plants (15 cm tall) were placed in a beaker containing the herbicide for 3, 6, and 12 hrs, then thoroughly washed. The root tips were stained and examined microscopically for chromosomal aberrations.

C. The effect of each treatment was compared with controls using the $\bar{X}$ test.

9. REPORTED RESULTS:

A. Hyvar X caused a higher percent of chromosomal aberrations; however, this was not dose related.

Effect of concentrations of Hyvar X on the production of chromosomal aberrations in root tip cells of Vicia faba

Concentration ppm	Mean percentage of cells with chromosomal aberrations[a]
200	10.71
400	26.58[b]
600	12.05[b]

[a] Mean for 3 incubation time periods (3, 6, and 12 hr) for each concentration

[b] Significantly different from controls ($p < 0.05$)

B. Mean percentage of cells with chromosomal aberrations decreased with increasing incubation times.

Effect of incubating Vicia faba for various lenghts of time in Hyvar X solution upon the number of root tip cells having chromosomal aberration

Incubation time (hr)	Mean percentage of cells with chromosomal aberration
3	25.43[a]
6	13.60[a]
12	9.30

[a]Significantly different from controls ($p < 0.05$)

C. Hyvar X increased the number of cells which had chromosomal breakage occurring in the satellite region of the chromosome.

10. DISCUSSIONS:

A. The finding that Hyvar X increased the percentage of chromosomal aberrations should be viewed with much reservations because of the following:

1. All pesticides tested (most not known to be mutagenic) caused a higher percentage of chromosomal aberration than did the controls.

2. The effect was not dose related

11. TECHNICAL REVIEW TIME: 3.0 hrs

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J., Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-933: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-107 prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232182-A)

4. REVIEWED BY: Janette R. Cushman
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5. APPROVED BY:

Acceptable

6. TOPIC:

a. The study has information pertinent to toxicology, acute dermal toxicity.

b. This study relates to the Proposed Guidelines data requirement, 163.81-2. Acute dermal toxicity study.

7. CONCLUSION:

The study does not meet the requirements of the Proposed Guidelines with regard ~~to number of animals~~, calculation of LD_{50} values separately for animals with intact and abraded skin, concurrent untreated control group, body weights at death, and histology of treated skin.

The LD_{50} for animals of both sexes with abraded or intact skin combined was 542.3 mg/kg with a standard deviation of $\pm$ 84.29 mg/kg. According to the accompanying Study Audit Report, all animals receiving 266.7, 1350, and 2000 mg/kg and two animals receiving 400 mg/kg received slightly lower doses than expected due to an error in dose calculations.

Supplementary

Tox III

~~Core Minimum~~

Hypoactivity, salivation, mydriasis, rapid respiration, convulsions, muscular weakness, and prostration were noted in animals at 600 mg/kg and above. Mydriasis alone was seen in the 400 mg/kg group. Skin reactions consisted of well-defined erythema, moderate edema, and second degree burns at 24 hours, and escharosis and fissuring at 7 and 14 days. Slight to moderate decreases in body weights were noted in five survivors. Gross pathology findings as corrected in the Audit Report included hemorrhaged or red lungs, vasodilation of mesenteric capillaries, and mottled kidneys for treated animals. Toxicity Category III.

8. MATERIAL AND METHODS:

A. Test substance - BX-933 from the Nalco Chemical Company, a clear tan liquid, undiluted.

B. Species - young adult, albino, New Zealand, male and female rabbits housed individually in wire-bottomed cages, fed a standard laboratory diet and water ad libitum.

C. Dosing schedule - rabbits were shaved on backs 24 hours prior to the dermal applications. Shaved area was approximately 30 percent of the total body area. Skin of half the rabbits was abraded (method not described). The test material was applied to the skin, and the test site covered by wrapping the trunk with plastic sheeting. Each rabbit was fitted with a collar.

One male and one female rabbit with either intact or abraded skin received the following dose levels: 266.7, 400, 600, 900, 1,350, and 2,000 mg/kg. After 24 hours, the sheeting and residual material were removed.

D. Parameters - Test sites were examined at 24 hours. Observations for mortality, local skin reactions, and behavioral abnormalities were continued for 14 days (at unspecified intervals). Initial, 7 and 14-day body weights were recorded. A necropsy examination was conducted on all animals.

E. Statistics - LD_{50} and standard deviation.

9. REPORTED RESULTS:

The following animals died during the study: the male with intact skin receiving 400 mg/kg, the male and female with intact skin receiving 600 mg/kg, and all animals receiving 900, 1,350, or 2,000 mg/kg.

The LD_{50} for all animals (with abraded or intact skin)was 542.3 mg/kg with a standard deviation of ± 84.29 mg/kg. According to the accompanying Study Audit Report, all animals receiving 266,7, 1,350, and 2,000 mg/kg and two animals receiving 400 mg/kg received slightly lower doses than expected due to an error in dose calculations. Hypoactivity, salivation, mydriasis, rapid respiration, convulsions, muscular weakness, and prostration were noted in animals at 600 mg/kg and above. Mydriasis alone was seen in the 400 mg/kg group.

Skin reactions consisted of red, well-defined erythema, moderate edema, and second degree burns at 24 hours, and escharosis and fissuring at 7 and 14 days. Slight to moderate decreases in body weights were noted in five of the nine animals that survived at 14 days. Gross pathology findings as corrected in the Audit Report included gastroenteritis, enlarged gallbladder, and clear fluid in peritoneal cavity for survivors, and hemorrhaged or red lungs, vasodilation of mesenteric capillaries, and mottled kidneys for treated animals.

10. DISCUSSION:

The LD_{50} for all rabbits tested is correct as reported. It would not be meaningful to calculate four separate LD_{50}s for males and females with intact or abraded skin based on one animal per group. The study also does not meet the Proposed Guidelines requirements for an untreated control group, body weight measurements at death, and histology of treated skin. In addition, errors in dose calculations were noted in the Study Audit Report.

This study provides a very rough overall LD_{50} for rabbits of both sexes with intact and abraded skin, and does not provide enough information for LD_{50} calculations by sex and skin treatment as required by the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 1.8 hours

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Emulsifiable Concentrate

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-939: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-105; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232176)

4. REVIEWED BY: Janette R. Cushman
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801-750-1600

5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary eye irrication.

b. This study relates to the Proposed Guidelines data requirement 163.81-4, Primary eye irritation study.

7. CONCLUSION:

The test establishes the extremely irritating properties of the test chemical to the eyes of New Zealand white rabbits. The maximum mean irritation score was 52.8 points out of a possible score of 110 observed at 72 hours.

However, the study does not meet the requirements of the Proposed Guidelines as follows: the flushing of the eyes of three rabbits following compound administration was not performed, eye examinations were conducted at three days rather than four days and not at 10 days

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even though injury persisted, and rabbits' eyes were not examined with fluorescein dye prior to the study.

The eye irritation involved the cornea, iris, and conjunctiva. The cornea had scattered or diffuse opacity to opalescent areas over one-half to more than three-quarters of the area. Some opacity continued in all animals through 14 days. The iris was congested with swelling or circumcorneal injection and still responsive to light. The conjunctiva was characterized by vessels redder than normal to diffuse crimson red, obvious swelling to swelling with lids half-closed to completely shut through 72 hours and discharge around the eye. By Day 14, the iris appeared normal in all animals and the conjunctiva appeared normal in two-thirds of the animals.

Toxicity Category I.

8. MATERIALS AND METHODS:

A. Test substance - BX-939 from the Nalco Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young New Zealand white rabbits, sex and housing not specified.

C. Dosing schedule - The test material, 0.1 ml, was instilled into the conjunctival sac of the right eye of each rabbit. The eyes of all rabbits were not washed.

D. Parameters - The cornea, iris, and conjunctiva were examined and graded for irritation and injury according to the system of Draize at 1, 24, 48, and 72 hours, and 7 and 14 days.

E. Statistics - No statistics were performed.

9. REPORTED RESULTS:

The average scores for the six rabbits are presented below:

	1hr	24hr	48hr	72hr	7 d	14 d
Cornea	20.0	20.0	30.0	35.8	27.5	11.7
Iris	5.0	5.0	5.0	5.0	4.2	0.0
Conjunctiva	15.0	14.0	14.7	12.0	5.3	1.0
Total	40.0	39.0	49.7	52.8	37.0	12.7

The irritation peaked at 72 hours, with diffuse to translucent areas over more than three-quarters of the cornea. The iris had above normal folds with swelling, circumcorneal injection and still reacted to light through seven days. The conjunctiva was red and swollen with notable discharge in all animals through 48 hours and in three animals at 72

003281

hours. At 14 days, some opacity of the cornea persisted in all animals but the iris appeared normal in all animals and only limited redness of the cornea with or without discharge existed in two animals.

10. DISCUSSION:

Although the requirements of the Proposed Guidelines are not met in their entirety this study is adequate to establish the severe eye irritancy potential of the test compound The study was audited by a consultant for the Nalco Chemical Company and no discrepancies were found between the report and the raw data. The test does not need to be repeated, unless the effects of immediate washing of the eye must be known for human exposures.

11. TECHNICAL REVIEW TIME: 1.0 h

00328

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION: Emulsifiable Concentrate

3. CITATION: Cavalli, R.D.; Hallesy, D.W. (1969) Acute oral toxicity of Triox Liquid Vegetation Killer: SOCO 94/II:134. (Unpublished study received December 1, 1969 under unknown admin. no.; submitted by Chevron Chemical Co., Richmond, California; CDL:107589-C)

4. REVIEWED BY: Janette R. Cushman
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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinant to toxicology, acute oral toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-1, acute oral toxicity study.

7. CONCLUSION:

With a few deviations from the proposed requirements, this study is an adequate investigation of the acute oral toxicity of the test substance. The test was performed in four groups of Sprague-Dawley-derived rats, five males and five females per group. The LD_{50} for males was 3.32 g/kg with a 95% confidence interval of 2.56 to 4.28 g/kg and for females was 3.58 g/kg with a 95% confidence interval of 2.94 to 4.47 g/kg. Signs of toxicity included depression, weakness, and tremors. Death occurred within 48 hours. No gross abnormalities were noted upon necropsy of the survivors. Toxicity Category III. The exceptions to the proposed requirements include no data on body weights, frequency of

Tox III

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observation unspecified, apparently no autopsy of animals that died, no age of animals specified.

8. MATERIAL AND METHODS:

A. Test substance - TRIOX Liquid Vegetation Killer, a liquid, from the Chevron Chemical Company.

B. Species - Sprague-Dawley-derived rats of unspecified size, 5 males and 5 females per group. Housed individually in an air-conditioned room at 70° F. Laboratory rat diet and water provided ad libitum; rats were fasted for 24 hours prior to dosing.

C. Dosing schedule - A single dose of undiluted test liquid by gavage, at 1.66, 2.50, 3.75, and 5.63 g/kg.

D. Parameters - Observations were made for 14 days. Survivors were sacrificed and the following organs examined grossly: lungs, heart, thymus, liver, kidney, spleen, gastro-intestinal tract, adrenal glands, pancreas, bladder, gonads, body fat, skeletal muscle, and skin.

E. Statistics - The LD_{50} and 95% confidence interval was calculated according to the method of Weil (Biometrics 8:249-263, 1952).

9. REPORTED RESULTS:

Dose (g/kg)	Mortality	
	Male	Female
1.66	0/5	0/5
2.50	1/5	0/5
3.75	3/5	3/5
5.63	5/5	5/5
LD_{50} (g/kg)	3.32	3.58
95% confidence interval	2.56 - 4.28	2.94 - 4.47

Signs of toxicity consisted of depression, weakness, and tremors. Death occurred within 48 hrs after dosing. Survivors necropsied at 14 days showed no gross abnormalities.

10. DISCUSSION:

This study is an adequate investigation of the acute oral toxicity of bromacil, although information on the body weights and age of the animals, and necropsy of the animals that died are lacking.

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[redacted]

The check of the calculated LD_{50} values and their confidence intervals yielded one figure that did not agree with the reported value: the upper limit of the confidence interval for females is 4.38 rather than 4.47. All other values were in agreement.

11. TECHNICAL REVIEW TIME: 1.5 hr

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyluracil)

2. FORMULATION: Technical Material

3. CITATION: E.I. du Pont de Nemours and Company (1966) Analysis of Urine from Bromacil Production Workers. (Unpublished study received Nov 22, 1966 under 352-87; CDL:002921-D)

4. REVIEWED BY:
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William M. Draper
7/13/81

5. APPROVED BY:

6. TEST TYPE:

Special study of bromacil residues in urine of workers involved in manufacture and formulation of bromacil.

7. CONCLUSIONS:

1. Humans exposed occupationally to bromacil eliminated a conjugate of 5-bromo-3-sec-butyl-6-hydroxymethyluracil and smaller amounts of unmetabolized bromacil in the urine.

2. 5-Bromouracil was not detectable in the urine of occupationally exposed workers.

3. Workers involved in formulating/packaging were exposed to greater amounts of bromacil than workers involved in manufacturing.

8. MATERIAL AND METHODS:

1. Urine samples from workers at two locations in a bromacil production plant were taken: workers involved in manufacturing versus workers involved in packaging and formulating. Urines were combined to form two composite samples, one from each group.

Acceptable

Supplementary

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2. Samples were analyzed for bromacil and metabolites before and after enzymatic hydrolysis of glucuronide and/or sulfonate conjugates.

3. Metabolites were detected by thin-layer chromatography and structures confirmed by mass spectrometry.

4. Bromacil, 5-bromo-3-sec-butyl-6-hydroxymethyluracil (6-HMU), and 5-bromouracil were analyzed with a quantitative gas chromatography procedure.

9. REPORTED RESULTS:

1. Residues found were:

Worker Job Function	Bromacil (mg/L)		6-HMU (mg/L)	
	Before Hydrolysis	After Hydrolysis	Before Hydrolysis	After Hydrolysis
Formulator/Packager	0.1	0.12	< 0.08	6.3
Manufacturing	< 0.1	< 0.1	< 0.08	0.49

2. 5-Bromouracil was not detected in any sample; the detection limit was 0.2 mg/L.

10. DISCUSSION:

Considerable experimental detail was not described in this research summary. The process by which the metabolites of bromacil were detected in the complex urine matrix is not described; a control group was not mentioned. For this reason it is difficult to ruleout the presence of unique metabolites. Bromacil metabolism in the human and the rat are similar in that conjugates of 6-HMU are major urinary metabolites. The composite sampling approach used in this study does not provide an estimate of the variability in urinary residues among the workers.

11. TECHNICAL REVIEW TIME: 1.4 hr

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Active ingredient

3. CITATION: Raltech Scientific Services, Incorporated (1979) Oral Defined LD_{50}. (Unpublished study received Oct 25, 1979 under 34704-52; submitted by Platte Chemical Co., Fremont, Nebr.; CDL:241218-A)

4. REVIEWED BY: Janette R. Cushman
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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute oral toxicity.

b. This study relates t the Proposed Guidelines data requirement, 163.81-1.

7. CONCLUSION:

This study adequately determines the oral LD_{50} of the test material in male and female Sprague-Dawley rats. The requirements of the Proposed Guidelines are met with the exception of the requirements of a 95 percent confidence interval of 20 percent or less for the males and of determination body weights for animals that died before the end of the study. A range-finding study is mentioned in the methods section of the report but no data or results are presented.

The LD_{50} for male rats was 5.126 g/kg with a 95 percent confidence interval of 3.042 to 7.210 g/kg and for female rats was 3.989 g/kg with a 95 percent confidence interval of 3.281 to 4.899 g/kg. Rats died within three days of dosing.

III

Minimum

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Males at the 5.126 g/kg dosage level that died had dark lungs and/or bloody urine or blood in the area of the penis. Males that received 8.137 g/kg had dark lungs or no unusual signs. Necropsy observations in females at the 3.229 and 5.126 g/kg levels that died included dark lungs or bloody urine in the bladder or bloody vaginal discharge. Females that received 8.137 g/kg had no abnormal lesions. Animals that were sacrificed at 14 days had white pinpoint foci on the lungs or no visible lesions.

Gross pharmacotoxic observations included piloerection, hypothermia to touch, hypoactivity, decreased limb tone, ataxia, bradypnea, bradycardia, bloody nasal discharge, jerking, lacrimation, righting reflex absent, grasping reflex absent, pinna reflex absent, placement reflex absent, and gasping.

Toxicity Category: males - IV
females - III

8. MATERIAL AND METHODS:

A. Test substance - Bromacil liquid from an unspecified source; diluted in distilled water.

B. Species - Eight male and eight female Sprague-Dawley rats per group, 200 to 272 grams. Conditioned at least 7 days prior to test. Food and water was available ad libitum except food was withheld overnight prior to compound administration. Rats were individually housed.

C. Dosing schedule - A single oral dose was administered by intubation to each animal. The dose volume was 10 ml/kg of body weight. Dose levels were 1.281, 2.034, 3.229, 5.126 and 8.137 mg/kg. A range-finding study with four dose levels is mentioned but not reported.

D. Parameters - Observations were made at 1, 2.5, and 4.0 hours following dosing and daily thereafter for 14 days for pharmacotoxic signs and twice daily for mortality.

Body weights were measured prior to dosing and at 7 and 14 days. Animals that died were apparently not weighed before necropsy.

Animals that died or were sacrificed at 14 days were necropsied.

E. Statistics - The LD_{50} and 95 percent confidence interval were calculated for males and females.

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9. REPORTED RESULTS:

The mortality and body weight data are presented below:

Sex	Dosage Level (g/kg)	Mean Body Weights (g) 0 d	7 d	14 d	Mortality No. Dead/No. Dosed
Male	1.281	236	287	305	0/8
	2.034	227	263	333	0/8
	3.229	234	267	302	0/8
	5.126	219	239	258	4/8
	8.137	228	-	-	8/8
Female	1.281	210	221	224	0/8
	2.034	205	216	258	0/8
	3.229	203	213	241	2/3
	5.126	205	211	156	7/8
	8.137	208	-	-	8/8

LD_{50} and 95 percent confidence interval:

Male - 5.126 g/kg; 3.042 to 7.210 g/kg
Female - 3.989 g/kg; 3.281 to 4.899 g/kg

Rats that did not survive the test period died within three days of dosing.

Males at the 5.126 g/kg dose level that died had dark lungs (3 of 4 rats) and/or bloody urine or blood in the area of the penis (4 of 4). Males that received 8.137 g/kg had dark lungs (3 of 8) or no visible lesions. In the females at the 3.229 and 5.126 g/kg level that died, dark lungs (in 1 of 2 and 6 of 7 rats) and bloody urine in the bladder or bloody vaginal discharge (in 1 of 2 and 2 of 7 rats) were seen. The highest dose group had no lesions. Animals that were sacrificed at 14 days had white pinpoint foci on the lungs or no visible lesions.

Gross pharmacotoxic observations were limited to the first two days after dosing. The lowest dose group displayed hypoactivity through four hours post-dose. Observations in the 2.034 g/kg group consisted of piloerection, hypothermic to touch, hypoactivity, decreased limb tone, ataxia, bradypnea, and bradycardia. At the 3.229 g/kg dose level, the males showed bloody nasal discharge and the female showed bloody nasal discharge, and absent grasping, righting and pinna reflexes in addition to the signs noted above. Animals at the two highest dose levels also showed these signs plus lacrimation, prostration, ataxia, gasping, and jerking.

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10. DISCUSSION:

Although the study does not conform to all of the requirements of the Proposed Guidelines, it does provide an adequate estimation of the oral toxicity of the test material. The confidence interval for the male rats is wider than desirable but this problem probably does not warrent repeating the test.

11. TECHNICAL REVIEW TIME: 1.9 h

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DATA EVALUATION RECORD

1. CHEMICAL Bromacil and salts

2. FORMULATION: Not Identified

3. CITATION: Palazzolo, R.J. (1964) Report to the Nalco Chemical Company: Acute toxicity studies on Nalkil Weed Killer 400 Liquid. (Unpublished study received May 20, 1965 under 1706-38; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:050395-A).

4. REVIEWED BY: Janette R. Cushman
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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary skin irritation.

b. This study relates to the Proposed Guidelines data requirement, 163.81-5, Primary skin irritation study.

7. CONCLUSION:

This report states that the test material was moderately irritating, with a primary irritation score of 4.0 for both intact and abraded skin sites at 24 hours and 6.0 at 72 hours. Thus, the overall mean primary irritation score was 5.0 out of a possible score of 8.0. The scores for edema and erythema were not given separately.

The study does not meet the requirements of the Proposed Guidelines as follows:

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1. One page with the description of most of the methods is missing from the report. The number of sex, age, and housing of rabbits, the selection criteria for rabbits, and the dosing schedule and procedure are not stated.

2. Four animals were tested rather than six.

3. Observation was not continued beyond 72 hours.

4. Combined scores for edema and erythema were reported.

Toxicity Category III.

8. MATERIAL AND METHODS:

A. Test substance - Nalkil Weed Killer 400 Liquid from the Nalco Chemical Company.

B. Species - Four albino rabbits; age, strain, sex, and housing arrangements unspecified.

C. Dosing schedule - The description of the dosing procedure is missing from the report. At the end of the 24-hour exposure period, the patches, wrapping and residual compound were removed.

D. Parameters - The skin sites were scored for erythema and edema according to the Draize system at 24 and 72 hours post-application.

E. Statistics - No statistical tests were performed.

9. REPORTED RESULTS:

The mean irritation scores are presented below:

	Combined Score (Erythema and Edema)
Abraded Skin - 24 hours	4.0
72 hours	6.0
Intact Skin - 24 hours	4.0
72 hours	6.0

The individual scores for erythema and edema were not reported.

10. DISCUSSION:

This report does not meet the requirements of the Proposed Guidelines in part due to the missing page which appears to have described most of the dosing procedures. An audit of the original data record may clarify the dosing procedure used as well as yield the individual scores for edema and erythema. Without an audit, it cannot be known

for certain how much test material was used to dose the animals (although one could assume that this study followed IBT's standard procedures) or the relative importance of edema and erythema to the overall irritation. If this information cannot be obtained from an audit, the study should be repeated in accordance with the Proposed Guidelines requirements.

11. TECHNICAL REVIEW TIME: 0.9 h

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION: Not Identified

3. CITATION: Palazzolo, R.J. (1964) Report to the Nalco Chemical Company: Acute toxicity studies on Nalkil Weed Killer 400 Liquid. (Unpublished study received May 20, 1965 under 1706-38; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:050395-A)

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute oral toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-1, Acute oral toxicity study.

7. CONCLUSION:

The test does not meet the requirements of the Proposed Guidelines for acute oral toxicity regarding number of animals tested (two male and two female rats were tested per dose level), frequency of observation, body weight measurements, testing of groups with mortality between 10 and 90 percent, and reporting of 95 percent confidence interval, dose-response cure, and observations for individual animals.

The LD_{50} was reported as 5.6 g/kg with a standard deviation of ± 0.3 g/kg. No rats died when dosed with 3.0 or 4.6 g/kg of test material while all four rats per group died when dosed with 6.8 or 10.2 g/kg. The rats that survived showed hypoactivity, ruffled fur, and mild dyspnea from 18 to 36 hours after dosing. Generalized inactivity, muscular weakness, anorexia, and mild sedation were noted in the rats in the 6.8 and 10.2 g/kg dose groups until they died at 18 to 72 hours after dosing. Mild gastro-enteritis was observed at necropsy.

Toxicity Category IV.

5. MATERIAL AND METHODS:

A. Test substance - Nalkil Weed Killer 400 Liquid from the Nalco Chemical Company, used undiluted.

B. Species - Young Sprague-Dawley male and female rats, approximately 110 grams, housed two of each sex per group, individually, and permitted Wayne Lab-Blox plus water ad libitum. Food was withheld 16 hours prior to dosing.

C. Dosing schedule - The rats were orally intubated with a single dose of test material.

D. Parameters - The rats were observed for 14 days following dosing. Rats which died were necropsied.

E. Statistics - The LD_{50} and its confidence interval were calculated.

6. REPORTED RESULTS:

The mortality data are presented below:

Dose (g/kg)	No. Dead/No. Tested
3.0	0/4
4.6	0/4
6.8	4/4
10.2	4/4

The LD_{50} was calculated to be 5.6 g/kg with a standard deviation of ± 0.3 g/kg.

Animals that survived were noted to have the following signs from 18 to 36 hours after dosing: hypoactivity, ruffled fur and mild dyspnea. Animals that died exhibited generalized inactivity, muscular weakness, anorexia, and mild sedation until death at 18 to 72 hours after dosing. Mild acute gastroenteritis was seen at necropsy.

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10. DISCUSSION:

This study does not meet the requirements of the Proposed Guidelines with regard to a number of procedures as given above in the conclusion. The reported LD_{50} is a crude estimation. However, due to the low toxicity of the compound, it may not be worth the cost to repeat the study. Probably a trial test using 5 animals per sex should be conducted to ascertain if the LD_{50} is indeed above 5 g/kg.

11. TECHNICAL REVIEW TIME: 1.0 h

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Not Identified

3. CITATION: Palazzolo, R.J. (1964) Report to the Nalco Chemical Company: Acute toxicity studies on Nalkil Weed Killer 400 Liquid. (Unpublished study received May 20, 1965 under 1706-38; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:050395-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute dermal toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-2, Acute dermal toxicity study.

7. CONCLUSION:

The study reports the LD_{50} of the test substance for male and female New Zealand rabbits combined at 10.2 g/kg with a standard deviation of 1.2 g/kg. The signs of toxicity consisted of anorexia, muscular weakness, and lethargy.

The study does not meet the requirements of the Proposed Guidelines as follows:

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1. No animals with abraded skin were tested.

2. Only two animals of each sex were tested.

3. Data for each sex are not reported separately.

4. No concurrent untreated control group was tested.

5. Body weights are not reported.

6. Histologic examination of treated skin was not performed.

7. The 95 percent confidence interval and dose response curve and slope were not reported.

Based on these deviations from the requirements, it is concluded that this study of the acute dermal toxicity of the test material is inadequate.

Toxicity Category III.

8. METHOD AND MATERIALS:

A. Test substance - Nalkil Weed Killer 400 Liquid from the Nalco Chemical Company.

B. Species - Two male and two female New Zealand strain rabbits per group, average body weight 2.5 kg. Animals were observed for seven days prior to the study, housed individually in stainless steel cages and fed Wayne Rabbit Ration and water ad libitum.

C. Dosing schedule - The rabbits received applications of the test material on the dorsal skin which had been clipped 24 hours previous and which consisted of approximately 10 percent of the body surface area. The exposure site was covered by wrapping the trunk of the animal with plastic sheeting. The test material remained in contact with the skin for 24 hours, after which it was removed. The report does not state that any remaining test substance was removed by wiping the skin.

D. Parameters - Observations for mortality, local reactions, and behavioral abnormalities were made at unstated intervals for 14 days. Animals that died during the study were necropsied.

E. Statistics - The LD_{50} and its standard deviation were calculated.

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9. REPORTED RESULTS:

The mortality data are presented below:

Dose (g/kg)	No. Dead/No. Tested
4.6	0/4
6.8	0/4
10.2	2/4
15.4	4/4

The LD_{50} is reported as 10.2 g/kg $\pm$ 1.2 g/kg.

No unusual gross pharmacotoxic signs were noted for the two lower dose groups. The animals in the two higher dose groups exhibited anorexia, muscular weakness, and lethargy starting 18 hours after dosing and persisting up to 72 hours or until death. Death occurred from 48 to 72 hours after dosing.

No significant gross pathologic alterations were observed during the necropsy of the animals that died.

10. DISCUSSION:

This study is not an adequate investigation of the dermal toxicity of the test substance for the reasons stated above in the conclusion. The study should be repeated using the information in this report to establish dose levels. Due to the high LD_{50} reported here, a trial test may be sufficient to establish that the LD_{50} for abraded skin is higher than 2 g/kg.

11. TECHNICAL REVIEW TIME: 0.9 h

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Not Identified

3. CITATION: Palazzolo, R.J. (1964) Report to the Nalco Chemical Company: Acute toxicity studies on Nalkil Weed Killer 400 Liquid. (Unpublished study received May 20, 1965 under 1706-38; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brock, Ill.; CDL:050395-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information, pertinent to toxicology, acute inhalation toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-3, Acute inhalation toxicity study.

7. CONCLUSION:

This study does not meet the requirements of the Proposed Guidelines for acute inhalation toxicity studies but seems adequate to establish the relatively low toxicity of the test material. The study does not meet the requirements for a concurrent untreated control group, monitoring of temperature, humidity, oxygen, particle sizing analysis and frequency of analysis, body weights of animals, and histopathology of specified tissues.

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Five male and five female Sprague-Dawley rats were exposed to an aerosol of the test material of particle sizes 0.5 to 3.0 microns at an average concentration of 13.5 mg/l for four hours. No deaths occurred during the 14 day observation period. During the exposure period, the animals exhibited generalized inactivity, moderate nasal discharge, and moderate dyspnea. Hyperemia in the lungs was noted at necropsy.

8. MATERIAL AND METHODS:

A. Test substance - Nalkil Weed Killer 400 Liquid from the Nalco Chemical Company. An aerosol was generated with an OHIO Nebulizer which delivered a mist with particle sizes of 0.5 to 3.0 microns. The average concentration of the mist was 13.5 mg/L.

B. Species - Five male and five female Sprague-Dawley rats with an average body weight of 250 g were observed for five days prior to test. The rats were housed individually and fed Wayne Lab-Blox and water ad libitum.

C. Dosing schedule - The inhalation experiment was conducted in a 38-liter glass inhalation chamber and lasted four hours.

D. Parameters - The animals were observed for pharmacotoxic signs during exposure and for 14 days thereafter at unspecified intervals. At the end of the 14-day period, the animals were sacrificed and necropsied. Tissues examined during necropsy were not specified.

E. Statistics - No statistics were performed.

9. REPORTED RESULTS:

None of the animals died during the 14-day observation period. During the exposure, animals exhibited generalized inactivity, moderate nasal discharge, and moderate dyspnea. All animals appeared normal approximately one hour following removal from the exposure chamber. Necropsy of the animals at the end of the observation period revealed only mild to moderate hyperemia in the lungs.

10. DISCUSSION:

This study does not meet several requirements of the Proposed Guidelines, as indicated in the conclusion. However, it does provide evidence that the LC_{50} is greater than 5 mg/L during a four hour exposure based on testing with five animals per sex. The operation measurements are summarized very briefly in the report and the brevity of their description provides the most reason to question the adequacy of the study. The

particle sizes reported meet the Guidelines requirement but only the average chamber concentration without the individual measurements or range is provided. Additional data on the chamber operation may be available from an audit of the original data records or from a sub-chronic study if one was conducted by the same laboratory. The test should be repeated using the data contained in this report to establish dose levels in order to determine the LC_{50} for the test material.

11. TECHNICAL REVIEW TIME: 1.0 h

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Not Identified

3. CITATION: Palazzolo, R.J. (1964) Report to the Nalco Chemical Company: Acute toxicity studies on Nalkil Weed Killer 400 Liquid. (Unpublished study received May 20, 1965 under 1706-38; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:050395-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary eye irritation.

b. This study relates to the Proposed Guidelines data requirement 163.81-4, primary eye irritation study.

7. CONCLUSION:

This study does not meet the requirements of the Proposed Guidelines with regard to number of rabbits tested, washing of eyes in three rabbits, screening of eyes with fluorescein prior to dosing, and observation for at least 13 days. The study does establish that the test material is mildly irritating to the eyes of rabbits of unspecified sex.

The average irritation score was the highest at one hour after dosing, 11.3 points out of a possible 110 points. No damage to the cornea was

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seen in any animal. The iris had folds above normal, with congestion, swelling, and/or circumcorneal injection, and still reacted to light. The scores for the conjunctiva were reported as a total without specifying individual scores for redness, chemosis, and discharge.

By 7 days, the irritation had been reversed completely in four of the five rabbits tested but persisted at nearly the original level in the remaining raboit. The average irritation score was 1.8 out of 110.

Toxicity Category III.

3. MATERIAL AND METHODS:

A. Test substance - Nalkil Weed Killer 400 Liquid from the Nalco Chemical Company, used undiluted.

B. Species - Five, young adult New Zealand albino rabbits of unspecified sex, size, and housing arrangements.

C. Dosing schedule - 0.1 ml of liquid test material was placed in the conjunctival sac of the right eye of each rabbit.

D. Parameters - The cornea, iris, and conjunctiva were examined and scored for irritation according to the Draize scoring system at 1, 24, 48, and 72 hours, and 4 and 7 days after dosing.

E. Statistics - No statistical tests were performed.

4. REPORTED RESULTS:

The average irritation scores are presented below:

	1 hr	24 hr	48 hr	72 hr	96 hr	7 d
Cornea	0.0	0.0	0.0	0.0	0.0	0.0
Iris	5.0	3.0	3.0	3.0	2.0	1.0
Conjunctiva	6.8	5.2	4.0	4.0	3.2	0.8
Total	11.8	8.2	7.0	7.0	5.2	1.8

No opacity of the cornea was seen in any animal. Irritation of the iris occurred in all animals, with folds above normal, congestion, swelling, and/or circumcorneal injection, and iris still reacting to light. The conjunctiva was also affected in all animals; however, the contribution to the score by redness, chemosis, and discharge was not reported. Irritation in four of the five animals was reversed completely by 7 days but persisted in the remaining rabbit with a score of 5 for the iris and 4 for the conjunctiva.

10. DISCUSSION:

The study is adequate to establish the relatively mild irritation caused by the test compound in the eyes of rabbits, although it does not meet all requirements of the Proposed Guidelines. Unless the effects of washing the eyes 30 seconds after exposure must be known for possible human exposures, the test probably need not be repeated.

11. TECHNICAL REVIEW TIME: 1.0 h

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-936: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-104, prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232178-A)

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary skin irritation.

b. This study relates to the Proposed Guidelines data requirement 163.81-5.

7. CONCLUSION:

This primary skin irritation test in young New Zealand albino rabbits is adequate to establish the severely irritating property of the test material. The mean primary irritation score at 24 and 72 hours for abraded skin sites was 5.95 and for intact skin sites was 5.65, giving an overall mean score of 5.8 of a possible 8.0 points. The test material caused second degree chemical burns in both abraded and intact skin sites of one animal. The other animals had definite

red well-defined erythema at both intact and abraded sites at 24 and 72 hours. Edema varied from barely perceptible to well-defined and raised one mm, and in most cases decreased between the readings at 24 and 72 hours.

The study does not meet the requirements of the Proposed Guidelines as follows: one abraded and one intact site per animal were tested rather than two, observation for irritation, was not continued beyond 72 hours, and the sex of the animals, the size of the patches, and whether the animals were restrained were not specified. The study was audited by the Nalco Chemical Company and no discrepancies were found between the report and the raw data.

Toxicity Category II.

8. MATERIAL AND METHODS:

A. Test substance - BX-936 from the Nalco Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young ~~adult New Zealand~~ albino rabbits of unspecified sex. Housing arrangements unspecified.

C. Dosing schedule - One-half mL of chemical was applied to two sites, one abraded and one intact, on the shaved back of each rabbit. The sites were covered each covered with a gauze patch of unstated size, and then the trunk of each animal was wrapped with plastic sheeting. Following the 24-hour exposure period, the patches, wrapping, and residual compound were removed.

D. Parameters - The skin sites were scored for erythema and edema according to the Draize system at 24 and 72 hours post-application.

E. Statistics - No statistical tests were performed.

9. REPORTED RESULTS:

The mean irritation scores are presented below:

	Abraded Skin		Intact Skin	
	24 hrs	72 hrs	24 hrs	72 hrs
Erythema	3.3	3.3	3.3	3.3
Edema	2.8	2.5	2.5	2.2
Total	6.1	5.8	5.8	5.5

The abraded and intact skin sites on one rabbit had second degree chemical burns that would not result in fibrosis at 24 and 72 hours. The other animals had definite red, well-defined erythema that continued for 72 hours in abraded and intact sites. Edema varied from barely perceptible to well-defined and raised one mm at 24 hours and decreased to barely perceptible or defined and raised less than one mm at 72 hours.

10. DISCUSSION:

Although this test does not conform exactly to the requirements of the Proposed Guidelines, it does adequately establish the severe irritation caused by the test compound. Note that the study has been audited and found to have no discrepancies between the report and raw data.

11. TECHNICAL REVIEW TIME: 0.3 hours

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Emulsifiable Concentrate

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-939: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-105; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL-232176)

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary skin irritation.

b. This study relates to the Proposed Guidelines data requirement: 163.81-5.

7. CONCLUSION:

This primary skin irritation test in young New Zealand albino rabbits is adequate to establish the severely irritating property of the test material. The mean primary irritation score at 24 and 72 hours for abraded skin sites was 6.55 and for intact skin sites was 5.8, giving an overall mean score of 6.2 of a possible 8.0 points. The test material caused second degree chemical burns in abraded skin sites of two animals and intact skin site of one animal. The other animals had well-defined erythema and edema at 24 hours. Erythema persisted but edema was decreased somewhat at 72 hours.

The study does not meet the requirements of the Proposed Guidelines as follows: one abraded and one intact site per animal were tested rather than two; observation for irritation was not continued beyond 72 hours, and the sex of the animals, the size of the patches, and whether the animals were restrained were not specified. The study was audited by the Nalco Chemical Company and no discrepancies were found between the report and the raw data.

Toxicity Category II.

3. MATERIAL AND METHODS:

A. Test substance - BX-939 from the Nalco Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young adult New Zealand albino rabbits of unspecified sex. Housing arrangements unspecified.

C. Dosing schedule - One-half mL of chemical was applied to two sites, one abraded and one intact, on the shaved back of each rabbit. The sites were each covered with a gauze patch of unstated size, and then the trunk of each animal was wrapped with plastic sheeting. Following the 24-hour exposure period, the patches, wrapping, and residual compound were removed.

D. Parameters - The skin sites were scored for erythema and edema according to the Draize system at 24 and 72 hours post-application.

E. Statistics - No statistical tests were performed.

4. REPORTED RESULTS:

The mean irritation scores are presented below:

	Abraded Skin		Intact Skin	
	24 hrs	72 hrs	24 hrs	72 hrs
Erythema	3.5	3.5	3.3	3.2
Edema	3.3	2.8	2.8	2.3
Total	6.8	6.3	6.1	5.5

Abraded skin sites on two animals and the intact skin site on one of these animals had second degree chemical burns that would not result in fibrosis at 24 and 72 hours. The remaining four animals had definite erythema with well-defined area at 24 hours which subsided only in one animal to pale red at 72 hours. Edema was definable and raised less than one to one mm at 24 hours, and decreased slightly to barely perceptible or definable and raised less than one mm at 72 hours.

10. [illegible]:

Although this test does not conform exactly to the requirements of the Proposed Guidelines, it does adequately establish the severe irritation caused by the test compound. Note that the study has been audited and found to have no discrepancies between the report and raw data.

11. TECHNICAL REVIEW TIME: 0. 8 hours

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-933: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-107; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232182-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary skin irritation.

b. This study relates to the Proposed Guidelines data requirement 163.81-5.

7. CONCLUSION:

This primary skin irritation test in young New Zealand albino rabbits is adequate to establish the extremely irritating property of the test material. The mean primary irritation scores for 24 and 72 hours for both abraded and intact skin sites was 8.0 out of a maximum of 8.0 points. The test material caused second degree chemical burns that will not result in fibrosis in all animals at both intervals.

The study does not meet the requirements of the Proposed Guidelines as follows: one abraded and one intact site per animal were tested rather than two, observation for irritation was not continued beyond 72 hours, and the sex of the animals, the size of the patches, and whether the animals were restrained were not specified. The study

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was audited by the Nalco Chemical Company and no discrepancies were found between the report and the raw data.

Toxicity Category II.

8. MATERIAL AND METHODS:

A. Test substance - BX-933 from the Nalco Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young adult New Zealand albino rabbits of unspecified sex. Housing arrangements unspecified.

C. Dosing schedule - One-half mL of chemical was applied to two sites, one abraded and one intact, on the shaved back of each rabbit. The sites were each covered with a gauze patch of unstated size, and then the trunk of each animal was wrapped with plastic sheeting. Following the 24-hour exposure period, the patches, wrapping, and residual compound were removed.

D. Parameters - The skin sites were scored for erythema and edema according to the Draize system at 24 and 72 hours post-application.

E. Statistics - No statistical tests were performed.

9. REPORTED RESULTS:

Intact and abraded sites on all animals had second degree chemical burns, that will not result in fibrosis. Maximum irritation scores of 4 for erythema and 4 for edema were given all animals at 24 and 72 hours.

10. DISCUSSION:

Although this test does not conform exactly to the requirements of the Proposed Guidelines, it does adequately establish the extreme irritation caused by the test compound. Continued observation of the animals past 72 hours would have checked the report's conclusion that the burns would not result in fibrosis. Note that the study has been audited and found to have no discrepancies between the report and raw data.

11. TECHNICAL REVIEW TIME: 0.3 hours

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-936: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-104 prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232178-A).

4. REVIEWED BY: Janette R. Cushman
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801-750-1600

5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary eye irritation.

b. This study relates to the Proposed Guidelines data requirement 163.81-4, Primary eye irritation study.

7. CONCLUSION:

The test establishes the extremely irritating properties of the test chemical to the eyes of New Zealand white rabbits. The maximum mean irritation score was 51.7 points out of a possible score of 110 observed at 72 hours.

However, the study does not meet the requirements of the Proposed Guidelines as follows: the flushing of the eyes of three rabbits following compound administration was not performed, eye examinations

were conducted at three days rather than four days and not at 10 days even though injury persisted, and rabbits' eyes were not examined with fluorescein dye prior to the study.

The eye irritation involved the cornea, iris, and conjunctiva. Scattered or diffuse opacity existed over more than three-quarters of the cornea for 48 hours, and worsened to easily discernible translucent areas with obscured iris in all animals at 72 hours. The signs continued in four animals in a smaller area of the cornea through the 14 day observation period. The iris was congested and swollen, with folds above normal, circumcorneal injection, and positive reaction to light in all animals through 72 hours. The conjunctiva was characterized by redness (noticeable to deep crimson red), swelling (lids completely closed to slight), and discharge (heavy to slight). By 14 days, the iris was normal in all animals and the conjunctiva was normal in all but one animal.

Toxicity Category I.

8. MATERIALS AND METHODS:

A. Test substance - BX-936 from the Nalco Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young New Zealand white rabbits, sex and housing not specified.

C. Dosing schedule - The test material, 0.1 ml, was instilled into the conjunctival sac of the right eye of each rabbit. The eyes of all rabbits were not washed.

D. Parameters - The cornea, iris, and conjunctiva were examined and graded for irritation and injury according to the system of Draize at 1, 24, 48, and 72 hours, and 7 and 14 days.

E. Statistics - No statistics were performed.

9. REPORTED RESULTS:

The average scores for the six rabbits are presented below:

	1 hr	24 hr	48 hr	72 hr	7 d	14 d
Cornea	20.0	20.0	20.0	35.0	18.3	5.8
Iris	5.0	5.0	5.0	5.0	2.5	0.0
Conjunctiva	13.7	14.3	15.0	11.7	4.3	0.3
Total	38.7	39.3	40.0	51.7	25.1	6.1

The eye irritation was the greatest at 72 hours, with easily discernible translucent areas and slightly obscured iris over one-quarter to the

entire area of the cornea in all animals. Diffuse to translucent opacity continued in four animals in one-quarter to one-half of the cornea through the 14 day observation period. The iris had above normal folds with swelling, circumcorneal injection and continued reaction to light in all animals through 72 hours and in three animals through seven days. The conjunctiva was red and swollen in all animals through 72 hours, with redness persisting in all animals through seven days, and in one animal through 14 days. Discharge was heavy at one hour in all animals, and decreased gradually such that two animals at 72 hours, one animal at seven days, and none at 14 days had slight discharge.

10. DISCUSSION:

Although the requirements of the Proposed Guidelines are not met in their entirety, this study is adequate to establish the severe eye irritancy potential of the test compound. The study was audited by a consultant for the Nalco Chemical Company and no discrepancies were found between the report and the raw data. The test does not need to be repeated, unless the effects of immediate washing of the eye must be known for human exposure.

11. TECHNICAL REVIEW TIME: 1.0 h

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-936: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-104 prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232178-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute dermal toxicity.

b. This study relates to the Proposed Guidelines data requirement, 163.81-2, Acute dermal toxicity study.

7. CONCLUSION:

The study does not meet the requirements of the Proposed Guidelines with regard to number of animals, calculations of LD_{50} values separately for ~~animals~~ with intact and abraded skin, concurrent untreated control group, body weights at death, and histology of treated skin.

The LD_{50} for animals of both sexes with abraded or intact skin combined was 1,102 mg/kg with a standard deviation of $\pm$ 158.4 mg/kg.

According to the accompanying Study Audit Report, the majority of the animals received slightly lower doses than expected due to an error in dose calculations.

Rhinitis, salivation, rapid respiration, mydriasis, muscular weakness, prostration, and convulsions were observed in the groups receiving 900 and 1,350 mg/kg. Animals that received 3,000 mg/kg had labored breathing, muscular weakness, and prostration. Skin reactions consisted of well-defined erythema, moderate to severe edema, and second degree burns of 24 hours and escharosis and fissuring at 7 and 14 days. Necropsy revealed red and/or hemorrhaged lungs in 11 animals, and scattered observation of enlarged gallbladder, and a pale kidney. All rabbits dosed at 2,000 mg/kg had vasodilation of the mesenteric capillories. Toxicity Category III.

3. MATERIAL AND METHODS:

A. Test substance - 5X-936 from the Nalco Chemical Company, a clear tan liquid, undiluted.

B. Species - young adult, albino, New Zealand male and female rabbits housed individually in wire-bottomed cages, fed a standard laboratory diet and water ad libitum.

C. Dosing schedule -

rabbits were shaved on backs 24 hours prior to the dermal applications. Shaved area was approximately 30 percent of the total body area. Skin of half the rabbits was abraded (method not described). The test material was applied to the skin, and the test site covered by wrapping the trunk with plastic sheeting. Each rabbit was fitted with collar.

One male and one female rabbit with either intact or abraded skin received the following dose levels: 600, 900, 1,350, and 2,000 mg/kg. After 24 hours, the sheeting and residual material were removed.

D. Parameters -

Test sites were examined at 24 hours. Observations for mortality, local skin reactions, and behavioral abnormalities were continued for 14 days (at unspecified intervals). Initital, 7 and 14-day body weights were recorded. A necropsy examination was conducted on all animals.

E. Statistics - LD_{50} and standard deviation.

9. REPORTED RESULTS:

The following animals died during the study: the female with abraded skin receiving 900 mg/kg, the male with abraded skin and both females receiving 1,350 mg/kg, and all animals receiving 2,000 mg/kg.

The LD_{50} for all animals (with abraded or intact skin) was 1,102 mg/kg with a standard deviation of $\pm$ 158.4 mg/kg. According to the accompanying Study Audit Report, the majority of the animals received slightly lower doses than expected due to an error in dose calculations.

All of the following abnormal signs occurred within 24 hours of dosing: rhinitis, salivation, rapid respiration, mydriasis, muscular weakness, prostration, and convulsions in the 900 and 1,350 mg/kg groups; labored breathing, muscular weakness, and prostration in the 2,000 mg/kg group. No unusual clinical signs were noted in the 600 mg/kg group. Skin reactions consisted of well-defined erythema, moderate to severe edema, and second degree burns at 24 hours and eschorosis and fissuring at 7 and 14 days. Necropsy revealed red and/or hemorrhaged lungs in 11 animals, an enlarged gallbladder in two animals, and a pale kidney in one animal. All rabbits dosed at 2,000 mg/kg had vasodilation of the mesenteric capillaries.

10. DISCUSSION:

The LD_{50} for all rabbits tested is correct as reported. With only one male and female with abraded or intact skin per dose level, it would not be meaningful to calculate separate LD_{50}s for the four groups per dose level represented. The study also does not meet the Proposed Guidelines requirements for an untreated control group, body weight measurements at death, and histology of treated skin. In addition, errors in dose calculations were noted in the Study Audit Report.

This study provides a very rough overall LD_{50} for rabbits of both sexes with intact and abraded skin, and does not provide enough information for LD_{50} calculations by sex and skin treatment as required by the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 1.3 hours

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DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-936:IBT No. 8530-08683. (Unpublished study including letter dated Nov. 2, 1977 from C.W. Wolf to Environmental Protection Agency, received Nov. 9, 1977 under 1706-104; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232178-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinant to toxicology, acute oral toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-1, Acute oral toxicity study.

7. CONCLUSION:

This study establishes the LD_{50} of the test material in rats at 996 mg/kg with a standard deviation of $\pm$ 101.1 mg/kg. Only two male and two female rats were tested per dose level, with one dose level of five producing mortality in the 10 to 90 percent range. Dosing errors noted in a later audit were $\pm$ 1.8 to 7.7 percent of the correct dose. Of the animals that died, all but two had red lungs and three had pale kidneys. Survivors that received 600 mg/kg had no notable signs while those that received 900 mg/kg had necrotic tissue in stomach linings.

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Due to the few animals used, the limited doses tested in the proximity of the LD_{50}, and the errors in doses, the results of this study should be considered only a rough estimate of the LD_{50}. Toxicity Category III.

3. MATERIAL AND METHODS:

A. Test substance - BX-936 from the Nalco Chemical Company, a clear tan liquid, undiluted.

B. Species - young albino rats derived from Sprague-Dawley stock, housed in individual hanging wire cages after dosing, fed a standard laboratory diet plus water ad libitum and fasted for 16 hours prior to dosing.

C. Dosing schedule - a single oral dose by intubation, two female and two male rats each at dose levels of 600, 900, 1350, 4556, and 15,380 mg/kg. The accompanying Study Audit Report states that dose calculations were erroneously rounded off in some cases, so that eight rats received a slightly lower dose and seven rats received a slightly higher dose than stated.

D. Parameters - initial and final body weights, mortalities, clinical observations over a 14 day period, and observations of necropsies.

E. Statistics - LD_{50} and standard deviation.

4. REPORTED RESULTS:

Dose Level (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
600	0/2	0/2	0/4
900	0/2	1/2	1/4
1,350	2/2	2/2	4/4
4,556	2/2	2/2	4/4
15,380	2/2	2/2	4/4

All deaths occurred within 24 hours after dosing. Of the animals that died, all but two had red lungs and three had pale kidneys. Survivors that received 600 mg/kg had no notable signs while those that received 900 mg/kg had necrotic tissue in stomach linings. These observations are given as corrected by the Study Audit Report. The LD_{50} was calculated as 996 mg/kg with a standard deviation of $\pm$ 101.1 mg/kg.

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10. DISCUSSION:

Based on the data presented, the calculated LD_{50} is correct. This study does not follow the Proposed Guidelines with regard to the numbers of rats tested, the presence of more than one group in the range of 10 to 90 percent mortality, and required body weight measurements. In addition, a later audit revealed rounding errors in dose calculations that lead to dosing errors of $\pm$ 1.7 to 7.7 percent for 15 of the 20 rats tested as well as inconsistencies between the recorded and reported observations. At best, this study should be considered a rough estimate of the actual LD_{50} and does not meet the requirements of the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 1.0 hr

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION: Emulsifiable Concentrate

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company; Acute toxicity studies with BX-939: IBT No. 8530-0868 3. (Unpublished study including letter dated Nov. 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov. 9, 1977 under 1706-105; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:23 2176-A).

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5. APPROVED BY:

[BEST AVAILABLE COPY]

6. TOPIC:

a. The study has information pertinant to toxicology, acute oral toxicity.

b. This study relates to the Proposed Guidelines data requirement 162.81-1, Acute oral toxicity.

7. CONCLUSION:

This study establishes the LD_{50} of the test material in rats at 996 mg/kg with a standard deviation of $\pm$101.1 mg/kg. Only two male and two female rats were tested per dose level, with one dose level of five producing mortality in the 10 to 90 percent range. A portion of the animals that died had red lungs, and a pale liver and pale kidneys were each observed in one animal. Survivors dosed at 900 mg/kg had necrotic stomach linings.

Due to the few animals used, the limited doses tested in the proximity of the LD_{50}, and the errors of 1.8 to 7.7 percent in doses administered discovered in a later audit the results of this study should be considered only a rough estimate of the LD_{50}. Toxicity Category III.

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8. MATERIAL AND METHODS:

A. Test substance - [illegible]-39 from the Naico Chemical Company, a clear tan liquid, unalluted.

B. Species - [illegible] albino rats derived from Sprague-Dawley stock, housed in individual hanging wire cages after dosing, fed a standard laboratory diet plus water ad libitum and fasted for 16 hours prior to intubation.

C. Dosing schedule - a single oral dose by intubation, two female and two male rats each at dose levels of 600, 900, 1350, 4556, and 15,380 mg/kg. The accompanying Study Audit Report states that dose calculations were erroneously rounded off in some instances, so that nine rats received a slightly lower dose and five rats received a slightly higher dose than stated.

D. Parameters - initial and final body weights, mortalities, clinical observations over a 14 day period, and observations of necropsies.

E. Statistics - LD_{50} and standard deviation.

9. REPORTED RESULTS:

Dose Level (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
600	0/2	0/2	0/4
900	1/2	0/2	1/4
1,350	2/2	2/2	4/4
4,556	2/2	2/2	4/4
15,380	2/2	2/2	4/4

All deaths occurred within 24 hours after dosing. All animals in the 900 and 1350 mg/kg level group that died had red lungs as did three animals in the 4556 mg/kg group. One rat had a pale liver and one had pale kidneys. These observations are given as corrected by the Study Audit Report. Necrotic stomach linings were seen at the 900 mg/kg level. No gross alterations were seen at the 600 mg/kg level. The LD_{50} was calculated as 996 mg/kg with a standard deviation of $\pm$ 101.1 mg/kg.

10. DISCUSSION:

Based on the data presented, the calculated LD_{50} is correct. This study does not follow the Proposed Guidelines with regard to the numbers of rats tested, the presence of more than one group in the range of 10 to 90 percent mortality and required body weight measurements. In addition, a post-facto audit revealed rounding errors in dose calculations of 2.8 to 7.7 percent of the actual dose for 14 of the 20 rats tested. At best, this study should be considered a rough estimate of the actual LD_{50} and does not meet the requirements of the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 1.4 hr

005281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Emulsifiable Concentrate

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-939: IBT No. 8530-08683. (Unpublisned study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-105; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232176.

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute dermal toxicity.

b. This study relates to the Proposed Guidelines data requirement, 163.81-2, Acute dermal toxicity study.

7. CONCLUSION:

The study does not meet the requirements of the Proposed Guidelines with regard to number of animals, calculation of LD_{50} values separately for animals with intact and abraded skin, concurrent untreated control group, body weights at death, and histology of treated skin.

The LD_{50} for animals of both sexes with abraded or intact skin combined was 1,102 mg/kg with a standard deviation of ± 158.4 mg/kg. However, according to the accompanying Study Audit Report, the animals at the

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600, 900, and 1,350 mg/kg dose levels actually received slightly lower doses than expected due to an error in dose calculations.

Signs of toxicity consisted of labored breathing, loss of righting reflex, muscular weakness, salivation, prostration, rapid respiration, and convulsions. Skin reactions at 24 hours were characterized by red, well-defined to beet-red erythema, moderate edema, and second degree burns. Escharosis and fissuring were noted at the test sites at 7 and 14 days. Hemorrhaged lungs were observed in all but one animal at the 1,350 and 2,000 mg/kg levels. The animals receiving 2,000 mg/kg also had vasodilated mesenteric capillaries and all but one had discolored or pale kidneys. Other gross pathologic findings were limited to one enlarged gall bladder and pale kidneys in two animals.

Toxicity Category III.

8. MATERIAL AND METHODS:

A. Test substance - BX-939 from the Nalco Chemical Company, a clear tan, undiluted.

B. Species - young adult, albino, New Zealand, male and female rabbits housed individually in wire-bottomed cages, fed a standard laboratory diet and water ad libitum.

C. Dosing schedule -

rabbits were shaved on backs 24 hours prior to the dermal applications. Shaved area was approximately 30 percent of the total body area. Skin of half the rabbits was abraded (method not described). The test material was applied to the skin, and the test site covered by wrapping the trunk with plastic sheeting. Each rabbit was fitted with a collar.

One male and one female rabbit with either intact or abraded skin received the following dose levels: 600, 900, 1,350, and 2,000 mg/kg. After 24 hours, the sheeting and residual material were removed.

D. Parameters -

Test sites were examined at 24 hours. Observations for mortality, local skin reactions, and behavioral abnormalities were continued for 14 days (at unspecified intervals). Initial, 7 and 14-day body weights were recorded. A necropsy examination was conducted on all animals.

E. Statistics - LD_{50} and standard deviation.

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9. REPORTED RESULTS:

The following animals died during the study: the female with abraded skin receiving 900 mg/kg, the male with abraded skin and both females receiving 1,350 mg/kg, and all animals receiving 2,000 mg/kg. The LD_{50} for animals of both sexes with abraded or intact skin combined was 1,102 mg/kg with a standard deviation of ± 158.4 mg/kg. According to the accompanying Study Audit Report, the animals at the 600, 900, and 1,350 mg/kg dose levels actually received slightly lower doses than expected due to an error in dose calculations.

Muscular weakness and rapid respiration were seen in some or all animals receiving the 900 mg/kg or higher dose levels. Labored breathing, salivation, and prostration were observed in some animals that received 1,350 and 2,000 mg/kg. In addition, animals that received 1,350 mg/kg had convulsions and those that received 2,000 mg/kg lost their righting reflex. No unusual clinical signs were noted in the 600 mg/kg group.

Skin reactions at 24 hours were characterized by red, well-defined to beet-red erythema, moderate edema, and second degree burns. Escharosis and fissuring were noted at the test sites at 7 and 14 days.

Necropsy revealed hemorrhaged lungs in all but one animal at the 1,350 and 2,000 mg/kg levels. The animals receiving 2,000 mg/kg also had vasodilated mesenteric capillaries and all but one had discolored or pale kidneys. Other gross pathologic findings were limited to an enlarged gall bladder and pale kidneys in one animal that received 600 mg/kg, and pale kidneys in one animal that received 1,350 mg/kg. One animal in the 900 mg/kg group was too badly decomposed for necropsy.

10. DISCUSSION:

The LD_{50} for all rabbits tested is correct as reported. It would not be meaningful to calculate four separate LD_{50}s for males and females with intact or abraded skin based on one animal per group. The study also does not meet the Proposed Guidelines requirements for an untreated control group, body weight measurements at death, and histology of treated skin. In addition, errors in dose calculations were noted in the Study Audit Report.

This study provides a very rough overall LD_{50} for rabbits of both sexes with intact and abraded skin, and does not provide enough information for LD_{50} calculations by sex and skin treatment as required by the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 1.0 hour

005281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-933: IBT No. 8530-08683. (Unpublished study including letter dated Nov. 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov. 9, 1977 under 1706-107; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232182-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinant to toxicology, acute oral toxicity.

b. This study relates to the Proposed Guidelines data requirement 163.81-1, Acute oral toxicity study.

7. CONCLUSION:

This study reports the LD_{50} of the test material in rats at 900 mg/kg with a standard deviation of $\pm$ 105.6 mg/kg. Only two male and two female rats were tested per dose level, with one dose level of five producing mortality in the 10 to 90 percent range. Three dosing errors of 5.6 to 7.1 percent lower than the correct dose in the 600 and 900 mg/kg dose levels were noted in a later audit of the study. Red or hemorrhaged lungs, pale liver, or pale kidneys were each observed in several animals that died. Examination of the survivors revealed necrotic stomach linings of the animals dosed at 900 mg/kg and no notable observations in those that received 600 mg/kg.

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Due to the few animals used, the limited doses tested in the proximity of the LD_{50}, and the errors in doses, the results of this study should be considered only a rough estimate of the LD_{50}. Toxicity Category III.

8. MATERIAL AND METHODS:

A. Test substance - BX-933 from the Nalco Chemical Company, a clear tan liquid, undiluted.

B. Species - young albino rats derived from Sprague-Dawley stock, housed in individual hanging wire cages after dosing, fed a standard laboratory diet plus water ad libitum and fasted for 16 hours prior to dosing.

C. Dosing schedule - a single oral dose by intubation, two female and two male rats each at dose levels of 600, 900, 1350, 4556, and 15380 mg/kg. The accompanying Study Audit Report states that dose calculations were erroneously rounded off in some cases, so that three rats (one in the 900 mg/kg and two in the 900 mg/kg dose level groups) received 5.6 to 7.1 percent lower doses than stated.

D. Parameters - initial and final body weights, mortalities, clinical observations over a 14 day period, and observations made at necropsies.

E. Statistics - LD_{50} and standard deviation.

9. REPORTED RESULTS:

Dose Level (mg/kg)	Number Dead/Number Tested		
	Males	Females	Total
600	0/2	0/2	0/4
900	1/2	1/2	2/4
1,350	2/2	2/2	4/4
4,556	2/2	2/2	4/4
15,380	2/2	2/2	4/4

All deaths occurred within 24 hours after dosing. Red or hemorrhaged lungs were observed in nine, pale liver in four, and pale kidneys in six animals that died. Necrotic tissue in stomach linings were found in the survivors that received 900 mg/kg. Survivors that received 600 mg/kg had no notable signs. The LD_{50} was calculated as 900 mg/kg with a standard deviation of $\pm$ 105.6 mg/kg.

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10. DISCUSSION:

Based on the data presented, the calculated LD_{50} is correct. This study does not follow the Proposed Guidelines with regard to the numbers of rats tested, the presence of more than one group in the range of 10 to 90 percent mortality, and required body weight measurements. In addition, an audit revealed rounding errors in dose calculations resulting in actual doses of 5.5 to 7.1 percent lower than expected in three animals in groups receiving 600 or 900 mg/kg. Inconsistensies between the recorded and reported observations were also found. At best, this study should be considered a rough estimate of the actual LD_{50} and does not meet the requirements of the Proposed Guidelines.

11. TECHNICAL REVIEW TIME: 0.9 hr

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and salts

2. FORMULATION: Unspecified

3. CITATION: Quinn, R.J.; Paa, H. (1976) Report to Nalco Chemical Company: Acute toxicity studies with BX-933: IBT No. 8530-08683. (Unpublished study including letter dated Nov 2, 1977 from C.H. Wolf to Environmental Protection Agency, received Nov 9, 1977 under 1706-107, prepared by Industrial Bio-Test Laboratories, Inc., submitted by Nalco Chemical Co., Oak Brook, Ill.; CDL:232182-A).

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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, primary eye irritation.

b. This study relates to the Proposed Guidelines data requirement 163.81-4, Primary eye irritation study.

7. CONCLUSION:

The test establishes the extremely irritating properties of the test chemical to the eyes of New Zealand white rabbits. The maximum mean irritation score was 57.6 points out of a possible score of 110 observed at 72 hours.

However, the study does not meet the requirements of the Proposed Guidelines as follows: the flushing of the eyes of three rabbits following compound administration was not performed, eye examinations were conducted at three days rather than four days and not at 10 days

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even though injury persisted, and rabbits' eyes were not examined with fluorescein dye prior to the study.

The eye irritation involved the cornea, iris, and conjunctiva. The cornea had scattered or diffuse opacity over more than three-quarters of the area at one hour which progressed to easily discernible translucent areas over more than half of the area with slightly obscured iris at 72 hours. Scattered or diffuse opacity continued in all animals through 14 days. The iris had above normal folds with swelling, circumcorneal injection, and still reacted to light in all animals through 72 hours. The conjunctiva was deep crimson red and swollen (partial progressing to lids completely swollen shut) with discharge in most animals through 72 hours. By 14 days, the iris and conjuctiva of all but one of the animals appeared normal.

Toxicity Category I.

8. MATERIALS AND METHODS:

A. Test substance - BX-933 from the Naico Chemical Company, a clear tan liquid used undiluted.

B. Species - Six young New Zealand white rabbits, sex and housing not specified.

C. Dosing schedule - The test material, 0.1 ml, was instilled into the conjunctival sac of the right eye of each rabbit. The eyes of all rabbits were not washed.

D. Parameters - The cornea, iris, and conjunctiva were examined and graded for irritation and injury according to the system of Draize at 1, 24, 48, and 72 hours, and 7 and 14 days.

E. Statistics - No statistics were performed.

9. REPORTED RESULTS:

The average scores for the six rabbits are presented below:

	1 hr	24 hr	48 hr	72 hr	7 d	14 d
Cornea	20.0	20.0	22.5	38.3	17.5	7.5
Iris	5.0	5.0	5.0	5.0	2.5	0 8
Conjunctiva	14.0	11.3	14.3	14.3	4.3	1.0
Total	39.0	36.3	41.8	57.6	24.3	9.3

The eye irritation was the greatest at 72 hours, with easily discernible translucent areas and slightly obscured iris over one-half to the entire area of the cornea in all animals. Scattered or diffuse opacity continued

in all animals through the 14 day observation period. The iris had above normal folds with swelling, circumcorneal injection and continued reactivity to light in all animals through 72 hours and in three animals through seven days. The conjunctiva was crimson red and very swollen in all animals through 72 hours, with redness persisting in all animals through seven days and in one animal through 14 days. Discharge was heavy at one hour in all animals and decreased gradually such that four animals at 72 hours and one at 7 and 14 days had slight to moderate discharge.

10. DISCUSSION:

Although the requirements of the Proposed Guidelines are not met in their entirety this study is adequate to establish the severe eye irritancy potential of the test compound. The study was audited by a consultant for the Nalco Chemical Company and no discrepancies were found between the report and the raw data. The test does not need to be repeated, unless the effects of immediate washing of the eye must be known for human exposures.

11. TECHNICAL REVIEW TIME: 0.9 hr

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyluracil)

2. FORMULATION: Active Ingredient

3. CITATION: E.I. du Pont de Nemours & Company. (1966) Effect of Enzymatic Hydrolysis on the Concentration of Bromacil and the Principal Bromacil Metabolite in Rat Urine. (Unpublished study received Nov 22, 1966 under 352-67; CDL:002921-E)

4. REVIEWED BY: William M. Draper
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5. APPROVED BY:

6. TOPIC: Metabolism (Guideline Number 163.85-1)

7. CONCLUSIONS:

1. The study augments the findings reported by Gardiner in "Metabolites of Bromacil in Rat Urine", (Unpublished Report).

2. Over 85% of the principal urinary metabolite of bromacil, 5-bromo-3-sec-butyl-6-hydroxymethyluracil is excreted in the form of sulfate and/or glucuronide conjugates. Of the two minor, unidentified uracil metabolites, one was not effected by enzymatic hydrolysis while the second was increased in concentration by a factor of two.

3. Rats ingesting diets containing 1250 ~~mg/kg~~ PPM of bromacil excreted bromacil (20 mg/kg) and 5-bromo-3-sec -butyl-6-hydroxymethyluracil (146 mg/kg, total including "free" and conjugated) in the urine.

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8. ANALYTICAL METHODS:

1. The concentrations of bromacil and its major metabolite, 5-bromo-3-sec-butyl-6-hydroxymethyluracil (6-HMU), were measured in the urine of rats fed an average of three weeks on a diet containing 1250 ppm bromacil. Residue levels were determined before and after hydrolysis at pH 5.0 with beta-glucuronidase/aryl sulfatase enzyme preparation.

2. Bromacil and 6-HMU were determined quantitatively by gas liquid chromatography. The effect of enzymatic hydrolysis on the minor metabolites was examined semi-quantitatively by thin-layer chromatography.

9. REPORTED RESULTS:

1. Urinary residue levels were:

	ppm/kg	
	Before Hydrolysis	After Hydrolysis
Bromacil	20	20
6-HMU	22	140

2. Two unidentified uracil metabolites were estimated at 5-10 mg/kg in rat urine; hydrolysis increased the concentration of the minor metabolites by factors of 1 to 2.

3. No new metabolites were observed following enzyme hydrolysis.

10. DISCUSSION:

1. The study augments the findings described in earlier A.I. "Metabolites of Bromacil in Rat Urine".

2. As before radiolabeled compounds were not employed.

3. The document is a condensed summary in which considerable experimental detail was omitted including:

number, variety, and gender of experimental animals, conditions of enzymatic hydrolysis, kinetic data demonstrating completion of hydrolysis, and details and verification of the analytical methodology employed.

11. TECHNICAL REVIEW TIME: 1.0 hr

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyluracil)

2. FORMULATION: Active Ingredient

3. CITATION: Gardiner, J.A. (19??) Metabolites of Bromacil in Rat Urine. (Unpublished study received Feb 28, 1966 under 352-287; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:107599-C)

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5. APPROVED BY:

6. TOPIC: Metabolism (Guideline Number 163.85-1)

7. CONCLUSION:

1. The study does not meet current guideline requirements for a general metabolism study.

2. A radiolabeled pesticide was not used and analytical methods were inadequate for a cold metabolism study.

3. 5-Bromo-6-hydroxy methyl-3-sec-butyl uracil is a major extractable metabolite in the urine of rats ingesting bromacil. Two minor uracils are present in extracts as well; 5-bromo uracil is not excreted in the urine.

8. MATERIAL AND METHODS:

Preliminary Study

1. Urine was collected from rats maintained for nearly two years on diets containing 1250 mg/kg of bromacil. Chloroform extracts and extracted

Supple

urine were separated on thin-layer chromatography (TLC) plates containing a phosphor. Control rat urine was analyzed in an identical manner.

2. Preparative TLC was used to isolate the major metabolite.

Detailed Study

1. A group of male rats (variety and number unspecified) were fed diets containing 1250 mg/kg of bromacil for one month. A 140 ml, pooled urine sample was collected, extracted with chloroform, and the extract subjected to unspecified cleanup procedures. Preparative TLC was used to isolate metabolites.

2. Metabolites in the pooled urine sample were quantitated by spectrophotometric methods; IR data indicated that each metabolite was a uracil and extinction coefficients were assumed to be identical to bromacil.

3. Metabolites were identified where possible by instrumental methods (IR, NMR, and mass spectrometry).

4. Metabolite structures identified by instrumental methods were verified by synthesis.

5. The pooled urine was analyzed specifically for 5-bromouracil by gas chromatography.

9. REPORTED RESULTS:

1. In the preliminary study metabolites were not detected in the extracted urine; a major metabolite, 5-bromo-6-hydroxy methyl-3-sec-butyluracil, was detected in organic extracts.

2. The detailed study demonstrated the presence of bromacil and two unidentified uracils in the organic extracts; levels were estimated to be between 2 and 3.5 mg/kg. 5-Bromo-6-hydroxymethyl-3-sec-butyluracil was present in the urine at 34 mg/kg.

3. 5-Bromouracil was not detected in the urine; the detection limit was 5 ppm for this compound.

4. Interpretation of spectra used to determine the metabolite structure are provided.

10. DISCUSSION:

1. Radiolabeled bromacil was not used in these studies and metabolites not quenching UV light would have been undetected.

2. Detection limits were provided only for 5-bromouracil.

11. TECHNICAL REVIEW TIME: 2.0 hrs

MRID 13298

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyluracil)

2. FORMULATION: Active Ingredient

3. CITATION: Gardiner, J.A., Reiser, R.W., Sherman, H. (1969). Identification of the metabolites of bromacil in rat urine. J. Agric. Food Chem. 17, 967. Authors affiliated with the Industrial and Biochemicals Dept. E.I. du Pont de Nemours & Company, Inc., Wilimington, Del.

4. REVIEWED BY: William M. Draper
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5. APPROVED BY:

6. TEST TYPE: Metabolism (Guideline Number 163.85-1)

7. CONCLUSION:

1. A major metabolite of bromacil in rat urine is 5-bromo-3-sec-butyl-6-hydroxymethyluracil (6-HMU) which is excreted primarily in conjugated form. Four lesser metabolites were also isolated from rat urine, each resulting from oxidation of the 6-methyl group, oxidation of the 3-sec-butyl group, debromination, or a combination of these reactions.

2. Rats ingesting 1250 mg/kg of bromacil in the diet excreted 20 mg/kg of bromacil, 21 mg/kg of "free" 6-HMU, and 125 mg/kg of 6-HMU in conjugated form in the urine. The minor metabolites varied in concentration from 0.3 to 7 mg/kg. 5-Bromouracil was not detected in urine from dosed rats. There was some evidence that the minor metabolites, like 6-HMU, were conjugated, but, conjugate hydrolysis increased the concentration of minor metabolites by a factor of only 1 to 2.

003281

8. MATERIAL AND METHODS:

1. Male Charles River, CD strain rats were maintained on a diet of ground Purina Lab Chow containing 1250 mg/kg of bromacil. One percent corn oil was used as a carrier for the compound. Rats were maintained on the diet for one month and urine was collected during the third and forth weeks. Control urine was collected from a group of rats maintained on Purina Lab Chow with 1% corn oil added.

2. Bromacil and its metabolites were isolated from urine by concentration of the sample, precipation with ethanol, and extraction into ethylacetate.

   The organic extract was subjected to TLC cleanup twice and the purified extract was again separated by preparative TLC on plates containing a phosphor. Bands not present in control urine were eluted from the adsorbent and identified by instrumental methods (IR, UV, NMR, & mass spectrometry). Some metabolite structures were verified by synthesis of standard materials.

3. Urinary excretion of bromacil, the major urinary metabolite of bromacil, 5-bromo-3-sec-butyl-6-hydroxymethyluracil (6-HMU), and 5-bromouracil were examined using quantitive gas chromatographic procedures. Samples were analyzed before and after enzymatic hydrolysis with a beta-glucuronidase/arylsulfatase enzyme preparation. The concentration of minor metabolites was estimated using a spectrophotometric assay.

9. REPORTED RESULTS:

1. The following compounds were identified as metabolites of bromacil in the urine of rats ingesting diets containing 1250 ppm of bromacil:

Compound	Metabolite
5-bromo-3-sec-butyl-6-hydroxymethyluracil	I[a]
5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil	II[a]
5-bromo-3-(2-hydroxy-1-methylpropyl)-6-hydroxymethyluracil	III
3-sec-butyl-6-hydroxymethyluracil	IV
5-bromo-3-(3-hydroxyl-1-methylpropyl)-6-methyluracil	V
3-sec-butyl-6-methyluracil	VI[a]

[a]standard material synthesized

An unknown bromine-containing compound was isolated as well.

2. The levels of bromacil and metabolite I, the major metabolite, before and after enzymatic hydrolysis were:

99

Compound	Concentration (mg/L) Before Hydrolysis	After Hydrolysis
Bromacil[a]	20	20
Metabolite I[a]	21	146

[a]Undetected in control urine.

3. 5-Bromouracil was not detected in the urine of treated rats; the detection limit was 2 mg/L.

4. Metabolites II, III, IV, V, VI and the unknown were estimated to be approximately 7, < 4, 4, < 4, 0.3, and < 10 mg/L in the urine.

10. CONCLUSION:

It is conceivable that urinary metabolites of bromacil might not be detected in the study described. Volatile metabolites might be lost in the initial 10-fold evaporative concentration of the urine, and in the complex cleanup procedure described; poor UV quenchers would also go undetected in the TLC separation procedure. The data provided is extensive and valuable but confirmation using a radiolabeled compound is desirable.

11. TECHNICAL REVIEW TIME: 2.3 hours

003281

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl)

2. FORMULATION: Active Ingredient

3. CITATION: Pease, H.L. (1964?) Determinacion of Bromacil Residues. Undated method. (Unpublished study received Aug 24, 1965 under 352-287; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:002903-J)

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5. APPROVED BY:

6. TEST TYPE: Development of analytical method for bromacil

7. CONCLUSION:

1. Bromacil can be quantitated in plant and animal tissues, urine, feces, and soil at sub-part per million levels using the method described.

2. The following detection limits for bromacil have been demonstrated: animal tissues and blood, 0.04-0.08 mg/kg; urine and feces, 0.22 mg/kg; citrus fruits and pineapple, 0.05-0.23 mg/kg; sugar cane, 0.10 mg/kg; alfalfa, 0.15 mg/kg.

3. Mean recoveries varied between 85 and 115% in the matrices tested.

8. MATERIAL AND METHODS:

1. Sample extraction for grain, plant or animal tissue, or soil was achieved by grinding, blending or shaking 25 g samples with 1% aqueous sodium hydroxide.

2. The aqueous supernatant a from each matrix was then subjected to clean up as follows:

   a) the extract was acidified, extracted with chloroform, and the organic solvent reduced to dryness,

   b) the residue was redissolved in base, washed with hexane (discarded), extracted with ethyl acetate, and the ethyl acetate extract was reduced to dryness,

   c) the residue was redissolved in nitromethane, washed with hexane (discarded), and the nitromethane volume adjusted to 1 mL for quantition by gas-liquid chromatography (glc).

3. Quantitation was achieved using a microcoulometric detector operating in the oxidation mode

   a) volumes of 25 to 500 uL were injected slowly onto the "cold" glc column (on column concentration).

   b) after a 2 minute pause the column oven was programmed from 100 to 300° C at 10° C/minute; bromacil eluted after 17 minutes from the 2 foot column packed with Diatoport coated with 20% SE 30 and 0.2% epon resin.

   c) the microcoulometric detector was calibrated using external (absolute) calibration. Detector response was equated with peak area.

4. The method was verified by fortifying fruit and foliage, urine, feces, animal tissues, and soil with 0.05 - 5.6 mg/kg of bromacil. Between 2 and 7 replicates of each matrix analysis were performed.

9. REPORTED RESULTS:

1. Bromacil recovery data is summarized as follows:

Matrix	Formulation (mg/kg)	% Recovery	
		Mean	Range
Pineapple fruit	0.04 - 1.4 (7)[a]	102	91-116
Pineapple leaves	0.04 - 1.4 (7)	96	83-109
Oranges	0.05 - 0.92 (3)	104	92-113
Grapefruit	0.05 - 4.8 (7)	95	81-110
Lemon	0.23 - 0.46 (2)	85	81- 89
Sugar Cane	0.10 - 4.8 (5)	89	80- 93
Alfalfa	0.15 - 2.3 (5)	91	76-109
Urine	0.22 - 5.6 (7)	98	91-110
Feces	0.22 - 5.6 (7)	99	79-118
Kidney	0.08 - 0.9 (4)	97	84-107
Liver	0.08 - 0.45 (4)	102	90-110
Muscle	0.04 - 0.9 (4)	97	84-120
Fat	0.04 - 0.22 (3)	115	107-130
Blood	0.04 - 1.2 (2)	94	92- 96
Soil (Keyport)	0.10 - 4.8 (12)	99	84-110

[a]Number of replicates

10. DISCUSSION:

Only one soil type was evaluated (Keyport) and its organic content is not stated. Sandy soils are much more readily extracted than are the high-organic-content soils. As bromacil is applied to soil, it would be worthwile to check its recovery from soils with a range in organic matter content.

The article demonstrates the efficiency of the extraction process as well as the solvent partitioning cleanup. The extensive cleanup is needed as up to one half of the extract may be used in order to obtain a high degree of sensitivity; the coulometric detector is not capable of detecting less than 0.5 ug of bromacil. It is likely that less time consuming glc methods have been published using the more sensitive (and common) electron capture detector. The method described, however, provides data with high precision and accuracy for bromacil determination in an array of matrices.

11. TECHNICAL REVIEW TIME: 2.0 hours

DATA EVALUATION RECORD

1. CHEMICAL: Bromacil and Salts

2. FORMULATION. Wettable powder

3. CITATION: Paynter, O.E. (1966) Final Report: Acute oral toxicity with dogs, Hyvar X Bromacil Weedkiller. (Unpublished study received April 5, 1968 under 352-287 prepared by Hazleton Laboratories, Inc., submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:002921-G).

4. REVIEWED BY Janette R. Cushman
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5. APPROVED BY:

6. TOPIC:

a. The study has information pertinent to toxicology, acute oral toxicity.

b. This study does not relate to any of the Proposed Guidelines data requirements.

7. CONCLUSION:

The oral LD_{50} in dogs could not be determined due to repeated emesis following administration of the compound. A dose of 5 g/kg administered to one mongrel dog either in one dose or in six divided portions 48 hours after the first dose produced repeated emesis, salivation, mydriasis, and diarrhea. The first dose also caused weakness, incoordination, and excitability. A second mongrel dog received two oral doses of 250 and 100 mg/kg five days apart. Both doses caused repeated emesis.

8. MATERIAL AND METHODS:

A. Test substance - Hyvar X Bromacil (Herbicide 976, Batch No. T90524A) from E.I. du Pont de Nemours & Company, Inc., as

Supplementary data

80% wettable powder. Dosages are expressed as to 100% active ingredient.

B. Species - two female mongrel dogs, maintained in the laboratory for at least one month prior to the study, housed individually in metal cages, fed ground Wayne Dog Meal and drinking water ad libitum.

C. Dosing schedule -

Dog No.	Level	No. of Portions and Schedule
1	5 g/kg	1 massive dose
1	5 g/kg	6 divided portions, 48 hrs after previous dose
2	0.25 g/kg	1 dose
2	0.10 g/kg	1 dose, 5 days after previous dose

D. Parameters - gross and ophthalmological examinations.

9. REPORTED RESULTS:

Following the single dose at 5 mg/kg, the first dog vomited 45 min later, and showed excessive salivation, weakness, excitability, incoordination, mydriasis, and lack of pupilar response to light. Diarrhea and emesis continued for two hours; at five hours the dog appeared normal. A second oral dose of 5 mg/kg was administered in six divided portions over a two and one-half hour period two days after the first. The clinical signs noted above were repeated. The dog appeared normal during six days of subsequent observation.

The second dog vomited repeatedly after each of the doses of 250 and 100 mg/kg administered five days apart.

10. DISCUSSION:

As indicated in the report, it appears that emesis limits the acute toxicity of the test material in dogs. The emesis-producing characteristic of the material may be important in acute poisonings in humans.

11. TECHNICAL REVIEW TIME: 1.1 hr

File No. 003281

DATA EVALUATION REPORT

(1) CHEMICAL:

Bromacil (5-bromo-3-sec-butyl-6-methyl)

(2) FORMULATION:

06 - wettable powder

(3) CITATION:

Paynter O.E. (1966) Reproduction study--Rabbits: Project No. 201-163 (Unpublished study including letter dated May 27, 1966 from O.E. Paynter to J. Wesley Clayton, Jr., received November 22, 1966 under 352-287; prepared by Hazelton Laboratories, Inc., submitted by E.I. duPont de Nemours & Co., Wilmington, Del.; CDL:002921-F)

(4) REVIEWED BY:

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Date 20 JUL 81

(5) APPROVED BY:

Signature _____

Date _____

(6) TEST TYPE:

Teratogenicity Studies
Guideline 40 CFR 163.83-3

(7) CONCLUSIONS:

A. The Bromacil teratogenicity study reviewed is inadequate by guideline standards. See the discussion section for itemized variations from recommended study protocols.

(8) MATERIALS AND METHODS:

A. Twenty-six New Zealand white rabbits were divided into control, low and high Bromacil treatment groups. They were bred by a fertile buck and the rabbits were fed Bromacil in the diet (0, 50 or 250 ppm) from the 8th to the 16th days of gestation.

B. On the 28th or 29th day of gestation 3 controls, 3 low dose and 4 high dose rabbits were sacrificed and Caesarean sections were performed. The remainder of the rabbits delivered normally and were then sacrificed within 24 hours.

C. One-third of all the fetuses were prepared for skeletal clearing and staining.

(9) REPORTED RESULTS:

A. All fetuses examined were normal in appearance and behavior.

B. Food consumption was normal during the 9 days of measurement (8th through 16th days of gestation).

C. All skeletal anatomies were found to be normal.

(10) DISCUSSION:

Several deficiencies in the teratogenicity study were noted. Some major variations are listed:

A. Only 1 mammal species was studied and no historical data on the strain was provided.

B. A positive control group was not included in the study.

C. The test compound, Bromacil, was administered only for a selected period during the pregnancies rather than daily.

D. Only control, low and high dose groups were considered--no intermediate dose level was employed. Choice of dose levels was not justified and the doses were not administered according to individual body weights.

E. One-third of the fetuses collected were examined for skeletal abnormalities rather than one-half to two-thirds, and less than 12 pregnant rabbits were included in each dose group.

F. No explanation for administration by diet rather than oral intubation was provided.

G. Maternal and fetal data were brief; expression of data was contrary to guideline protocols.

H. The author's evaluation of the study results was limited since no anomalies were noted that could be related to Bromacil treatments.

The study as presented is unsatisfactory due to inadequate design, execution and reporting. Other than some possible range-finding value, this experiment is without merit for determining the teratogenicity of Bromacil. A new study should be devised and performed after consulting the agency guidelines presented in 40 CFR 163.83-3.

(11) REFERENCES:

None

(12) TECHNICAL REVIEW TIME:

2.25 hours

003281

File No. _____
Page 1 of 4

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl)

(2) FORMULATION: 00 - Active Ingredient

(3) CITATION: Smith, L.W.; Dashiell, O.L.; Barnes, J.R.; et. al. (1978) Long-Term Feeding Study in Mice with 5-bromo-3-sec-butyl-6-methyluracil (Bromacil; INN-976): Haskell Laboratory Report No. 549-78. (Unpublished study received January 17, 1979 under 352-287; submitted by E.I. duPont de Nemours & Co., Wilmington, Del.; CDL:241630-A)

(4) REVIEWED BY: Steven G. Oberg, Ph.D.
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Date 20 Jul 81

(5) APPROVED BY:
Signature _____
Date _____

(6) TEST TYPE: Chronic Feeding Study
ref: 40 CFR 163.83-1

(7) CONCLUSIONS:

A. The experimental design proposed for the long-term Bromacil chronic feeding study appears to be generally well conceived in relation to regulatory compliance.

B. The study, as proposed, was not completed due to an overwhelming systemic bacterial infection that produced high morbidity and mortality among the study population.

C. Due primarily to incompleteness, the tests performed do not comply with existing study guidelines for chronic feeding studies as presented in 40 CFR 163.83-1.

(8) MATERIALS AND METHODS:

A. Test Substance - technical grade Bromacil was characterized by normal HPLC, reverse phase HPLC, GC and anion and cation profiles were obtained. The material contained about 95% active ingredient and about 5% inert materials.

B. Species and strain - Charles River CD-1 mice were used. No justification was given for utilizing mice rather than rats.

C. Sex and age - 320 male and 320 female weanlings were divided into 4 groups of 80 each per sex.

D. Control - untreated control groups were maintained. There was no requirement for a vehicle-only control group.

E. Number of animals - 80/sex/dose level.

F. Duration of testing - a proposed life span study was terminated after 38 weeks due to uncontrollable bacterial infections within the exposed and control populations.

G. Number of dose levels and dose selection - dose levels of 0, 250, 1250 and 5000 ppm were employed. Doses were selected on the basis of range finding studies and literature records.

H. Route of administration - diet (in ground Purina Laboratory Chow).

I. Caging - individual.

J. Observation of animals - mice were observed daily and were weighed weekly for 24 weeks. The protocol called for biweekly weighings for another 24 weeks followed by monthly measurements for the duration. Food consumption was to be monitored on the same schedule as weighings.

K. Clinical laboratory testing - hematology tests were to be performed 1, 3 and 6 months after initiation of dosing; no mention was made in the report of pre-dose or termination measurements. Hematocrit, hemoglobin, red blood cells, total and differential leukocyte values were recorded, but platelets were evidently not counted. No blood chemistry tests were noted other than total protein. Twelve blood chemistry tests listed in the guidelines were not mentioned in these data or in the experimental design of the study. Cholinesterase inhibition tests were not performed but may not have been required for this chemical.

L. Residue analysis - since the study was not successfully completed there was no terminal data regarding analyses of tissue for the test compound or its metabolites.

M. Handling of dead and moribund animals - the study protocol indicated that tissues of dead animals would be saved whenever possible but nothing in the report described that practice during the study.

N. Gross necropsy - examinations of tissues, cavities and orifices were not well described. However, several organs were weighed and preserved in 10% formalin.

O. Histopathology examination - the Bromacil chronic feeding study was terminated prematurely (38th week of lifetime study) due to an overwhelming systemic bacterial (staphylococcal) infection. At termination the mice were sacrificed without pathological examination and no necropsy sheets were filed. Reports were provided that described the disease entity that resulted in the termination of the test.

P. Data reporting and evaluation - reports and evaluations in terms of test protocols, animal records and clinical laboratory data, gross necropsy data, histopathological data and evaluation of results are incomplete or absent.

(9) REPORTED RESULTS:

A. There was a 5% decrease of body weight gain observed in male and female mice fed 5,000 ppm Bromacil.

B. Leukocyte counts were decreased in male mice fed 5,000 ppm Bromacil.

C. Hematocrits of female mice were increased after being fed 5,000 ppm Bromacil.

D. There were no other nutritional, clinical, hematological or pathological evidences of toxicity that could be attributed to the dietary administration of Bromacil (although the time course of the study was shortened due to unrelated infectious diseases among the control and test animals).

(10) DISCUSSION:

A chronic study involving feeding of Bromacil to mice was proposed and initiated. The program was terminated after 38 weeks due to bacterial infections that apparently stemmed from problems with the ear-tagging identification technique.

The technical grade pesticide was characterized very well for active and inert ingredients before administration. Only limited amounts of animal data were collected and/or presented in this report -- average body weights, average daily diet consumption, average food efficiency and average daily intake figures were presented in tabular form for 266 days of the study.

In general the experimental design appeared to be well considered although evidence of performance was necessarily lacking in this incomplete study. Variations in protocols (compared to guidelines) were not explained, e.g. mice were used rather than rats.

Evaluation of the toxicity of Bromacil fed to mice was not accomplished in this study. The study was terminated prematurely

and pathological findings were limited to those attributable to staphylococcal infections. In the 266 day duration of the study, however, no acute clinical toxicological signs that could be credited to Bromacil administration were recorded.

It is recommended that Bromacil be retested ir a chronic feeding study of similar design. Justification should be provided for using test animal species other than rats, and more attention should be given to histopathological reporting requirements.

(11) REFERENCES:

Introductory remarks in the report regarding the results of Bromacil toxicity studies with rats and beagles were not cited adequately enough to locate for review.

(12) TECHNICAL REVIEW TIME:

3.75 hours.

003281

File No. 00022078

Page No. 1 of 3

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Not identified

(3) CITATION: Raltech Scientific Services, Incorporated (1979) Defined Dermal LD50. (Unpublished study received Oct. 25, 1979 under 34704-52; submitted by Platte Chemical Co., Fremont, Nebr.; CDL:241218-B).

(4) REVIEWED BY: David B. Drown
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Logan, Utah 84322
801-750-2760

Signature David B. Drown

Date 7/22/81

(5) APPROVED BY:

Signature _____

Date _____

(6) TEST TYPE: Acute dermal toxicity study. Guideline 40 CFR 163.81-2.

(7) CONCLUSIONS:

1) The data contained in this report were generated according to Proposed Guidelines 40 CFR 163.81-2. The test was conducted as an initial trial using only one dose level 2g/kg Bromacil. All test procedures satisfy the no further testing criterion with the exception of a single mortality observed on day 10 of the observation period.

2) Young adult male and female rabbits (approximately 14 weeks of age) of the New Zealand White Strain were used in the study.

3) Estimated dermal LD50 for both male and female rabbits was reported to be greater than 2.0 g/kg of body weight.

4) With the exception of the single death noted, most animals exhibited only a mild erythema through days 2 to 4. Mild edema was reported on day one for 8 of the 9 animals.

5) Bromacil liquid applied to skin of the experimental rabbits appeared to be mildly toxic.

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(8) MATERIAL AND METHODS:

A) The test material consisted of Bromacil liquid as supplied by the Platte Chemical Co., Fremont, NB. The pathology report refers to the test material as 8.7% Bromacil liquid. The exact formulation was not identified.

B) Testing was performed on young adult (approximately 14 weeks of age) male and female, New Zealand White Strain rabbits. Initial average body weights were 2410 grams and 2376 grams for males and females respectively. The animals were housed in individual screen bottom cages in air conditioned quarters. They were allowed commercial laboratory feed and water continuously.

C) The animals were dosed according to specifications outlined in the Proposed Guidelines 40 CFR 163.81-2. The dose level for males and females was established at 2.0 g/kg. The skin of all animals was abraded prior to application of the test material.

D) Parameters examined in addition to mortality throughout the 14-day observation period included the following: erythema, edema, atonia, disquamation, coriaceous, fissuring, eschar and exfoliation. The animals were observed for pharmacotoxic signs and dermal irritation once daily, and for mortality twice daily for a period of 14 days. Body weights were recorded just prior to dosing and again at 7 and 14 days. A histopathologic study of the dermal application sites was conducted at the close of the study.

(9) REPORTED RESULTS:

One male animal died on day 10 of the study. The remaining 9 rabbits lived until termination on day 14 of the observation period. Most animals exhibited only a mild erythema through day 2 to 4 following the 24-hour exposure. Mild edema was reported on day one for 8 of the 9 animals. Gross necropsies performed on day 14 revealed no visible lesions in all but one animal. One male demonstrated a 5 mm nodule on the left lateral lobe of the liver. The animal that died on day 10 demonstrated no visible lesions.

Histopathologic study of the treated skin revealed that 7 rabbits were considered to be within normal limits. A few inflammatory cells were present in the papillary dermis of 3 rabbits. These were very minimal lesions and were not considered to be significant. A coccidial abscess was observed in the liver of one animal. The estimated dermal LD50 was reported as greater than 2g/kg of body weight in both male and female rabbits.

(10) DISCUSSION:

The conduct of this study has been in accord with the Proposed Guidelines 40 CFR 163.81-2. It was designed on the assumption that the LD50 of Bromacil (test compound) was greater than 2g/kg. That assumption apparently holds true with the exception of one mortality observed on day 10 of the study. Elaboration on that mortality was not included in the report. Pathologic examination, however, revealed nothing unusual. It was difficult to check the raw data against the summarized results. Animal identification numbers did not match up. Apparently, more than one number was assigned to each animal for some reason. The results of the study, however, appear generally acceptable. The estimated dermal LD50 value of greater than 2g/kg for both sexes fits the data as presented here.

(11) TECHNICAL REVIEW TIME:

3.3 hours

003281

File No. 00013227

Page 1 of 1

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Emulsifiable concentrate

(3) CITATION: Cavalli, R.D.; Hallesy, D.W. (1969) Acute Dermal Toxicity of Triox Liquid Vegetation Killer: SOCO 95/II: 134. (Unpublished study received Dec. 1, 1969 under unknown admin. no.; submitted by Chevron Chemical Co., Richmond, CA; CDL:107589-D).

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(6) TEST TYPE: Acute dermal toxicity study. Guideline 40 CFR 163.81-2.

(7) CONCLUSION:

Apparently, there is some inconsistency with this report and the report under file number 00013273, authored by Colburn, C.W., and Frank, K.M. (1969). Skin Absorption LD50: Haskell Laboratory Report No. 276-69. (Unpublished study received Oct. 2, 1969 under 352-87; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL: 002921-C). The data report here, and that in the above citation are identical. Thus, there is no reason to further evaluate this report.

(8) TECHNICAL REVIEW TIME:

0.5 Hours

003281

File No. 00022081

DATA EVALUATION REPORT

(1) CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyl-uracil)

(2) FORMULATION: Active ingredient

(3) CITATION: Raltech Scientific Services, Incorporated (1979) Prim. Skin Initation. (Unpublished study received Oct. 25, 1979 under 34504-52; submitted by Platte Chemical Co., Fremont, Nebr.; DCL:241218-E).

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(6) TEST TYPE: Primary dermal irritation study. Guideline 40 CFR 163.81-5.

(7) CONCLUSIONS:

1) The material reported here was conducted in accord with Proposed Guidelines 40 CFR 163.81-5.

2) Three male and three female young adult New Zealand White Strain rabbits were used.

3) The test material was applied as submitted to the laboratory. An amount of 0.5 ml per area was applied to the experimental animals.

4) Signs of irritation included erythema and edema in about one half of the animals 24-hours after exposure. A dermal irritation score of 0.8 was recorded for the first 24-hour period. Signs of irritation were gone from all animals by the end of the 72-hour observation period. The dermal irritation score for 72 hours was 0. The results of this study indicate a primary skin irritation classification in Catagory IV (no irritation present at 72 hours).

(8) MATERIAL AND METHODS:

A) The test substance (active ingredient) consisted of Bromacil liquid as received for testing. No further information was provided concerning the test material.

B) Male and female young adult rabbits (approximately 14 weeks of age) of the New Zealand White Strain were used in the study. The rabbits ranged from 2000 to 2256 grams at the start of the experiment. The animals were maintained individually in screen bottom cages in air conditioned quarters. The rabbits were collared during the exposure period.

C) The animals were dosed with 0.5 ml of test material per area according to the Proposed Guidelines 40 CFR 163.81-5. Two abraded and two intact areas per animal were treated with the Bromacil liquid. The treated areas were individually covered with gauze patches and overwrapped with Saran wrap and Elastoplast tape to maintain the test material in contact with the skin and decrease the rate of evaporation. After the 24 hours of exposure, the patches were removed and the test substance was wiped from the skin.

D) Parameters examined included the degree of erytherma and edema observed after 24 hours and 72 hours according to the Draize Technique.

(9) REPORTED RESULTS:

The primary dermal irritation scores were 0.8 after 24 hours and 0.0 after 72 hours. The primary dermal irritation index was reported as 0.4 These data place the test results in Category IV which includes those cases where no irritation is present at 72 hours.

(10) DISCUSSION:

This study has been conducted according to the Proposed Guidelines 40 CFR 163.81-5. The Bromacil as received for testing, apparently had a low potential for causing skin irritation according to the test methods of the primary skin irritation test. The results of this study are acceptable as reported here.

(11) TECHNICAL REVIEW TIME:

Three hours

DATA EVALUATION REPORT

1. CHEMICAL: Bromacil (5-bromo-3-sec-butyl-6-methyluracil)

2. FORMULATION: Grade was not specified. 5-bromo-3-sec-butyl-6-methyluracil was in culture medium.

3. CITATION: McGahen, J.W.; Hoffmann, C.E. (1963) Action of 5-bromo-3-sec-butyl-6-methyluracil on Escherichia coli 15T. Nature 200(4906):571-572.

4. REVIEWED BY: Charles F. Luke
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Charles Luke 5-17-81

5. APPROVED BY:

6. TOPIC:

The study has information pertinent to discipline 40, topic 25101010 (mutagenicity). This study does not relate to the Proposed Guidelines data.

7. CONCLUSIONS:

A. This report did not meet the guidelines for mutagenicity.

B. Bromacil was not incorporated as a substitute for thymine into DNA of E. coli 15T . However, because there are so many other possible mechanisms of mutagenicity, this did not fully answer the question of whether or not Bromacil was mutagenic.

C. This test lacked a mammalian metabolic activating system which is necessary to meet the guidelines.

8. METHODS:

A. Medium containing C-14 labelled Bromacil was inoculated with Escherichia coli 15T⁻, a mutant which will only grow in media supplemented with thymine.

B. The cells were then incubated. The length of time of the incubation was omitted.

C. After incubation, DNA from the E. coli was isolated. The total amount of DNA was assayed using the diphenylamine method, and the amount of radiolabelled Bromacil incorporated into DNA as a substitute for thymine was measured.

D. 5-bromouracil, previously found to be incorporated into DNA as a substitute for thymine, was used as a positive control.

9. RESULTS:

A. Bromacil was not incorporated into DNA as 5-bromouracil was.

B. Bromacil, in contrast to 5-bromouracil, did not alter the growth of the E. coli.

C. Bromacil did not decrease the incorporation into DNA of thymine or 5-Bromouracil.

D. Bromacil was not covalently bound to TCA-insoluble components of the cells and was easily washed out with repeated TCA washings.

10. DISCUSSIONS:

A. Bromacil, in contrast to 5-bromouracil (a closely related analog and a known mutagen), did not serve as a substitute for thymine and, therefore, was not incorporated into the DNA of E. coli 15T⁻, a mutant strain requiring medium supplemented with thymine.

B. The study left open the possibility that Bromacil was mutagenic through some other genotoxic mechanism.

11. TECHNICAL REVIEW TIME: 1.5 hours