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

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SEP 23 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Iprodione- Primary eye irritation in rabbits

TO: Kathryn Davis/Barbara Briscoe PM 72
Special Review and Reregistration Division (H7508W)

FROM: K. Clark Swentzel *K. Clark Swentzel 9/9/92*
Toxicology Branch II
HED (H7509C)

THROUGH: Marcia van Gemert, Ph.D. *M van Gemert 9/9/92*
Branch Chief
Toxicology Branch II
HED (H7509C)

ID NO. 109801-000264
CASE: 816345
BARCODE: D179395
MRID NO. 418673-01
SUBMISSION: S419591
PC No. 109801 470 A
CASWELL NO. ~~549C~~
REGISTRANT: Rhone-Poulenc

Requested action

Review subject study

Conclusions

The administration of 0.062 g iprodione to the eyes of rabbits caused mild ocular irritation in 6/6 rabbits which was not seen in any animal at 7 days post dosing. Corneal opacity was seen in 1/6 and conjunctivitis in 6/6. Rinsing treated eyes with physiological saline 30 seconds after instillation of iprodione appeared to decrease the severity of the irritation.

Toxicity category: III

Core classification: minimum. This study satisfies the minimum requirements set forth under the Subdivision F Guidelines for a primary ocular irritation study in rabbits (81-4).

Reviewed by: K. Clark Swentzel *K. Clark Swentzel* 9/9/92
Tox. Branch II, Section II (H7509C)

Secondary Reviewer: Marcia van Gemert, Ph.D.
Tox. Branch II (H7509C) *M van Gemert* 9/9/92

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation in rabbit Tox. Chem. No. 470A

MRID NO. 418673-01

TEST MATERIAL: 3-(3,5-Dichlorophenyl)-N-(1-methylethyl)-2,4-dioxo-1-imidazolidinecarboxamide

SYNONYMS: Iprodione, Iprodine, Glycophene, Chipco 26019, Anfor, RP-26019, Rovral

STUDY NO. 3147.109

SPONSOR: Rhone-Poulenc

TESTING FACILITY: Springborn Laboratories, Inc.

TITLE OF REPORT: Primary Eye Irritation Study in Rabbits with Iprodione

AUTHOR: K. Bonnette

REPORT ISSUED: April 5, 1991

COMPLIANCE STATEMENTS: Signed and dated Quality Assurance and GLP Compliance Statements were included on pages 4 and 3 of the report, respectively.

CONCLUSIONS

The administration of 0.062 g iprodione to the eyes of rabbits caused mild ocular irritation in 6/6 rabbits which was not seen in any animal at 7 days post dosing. Corneal opacity was seen in 1/6 and conjunctivitis in 6/6. Rinsing treated eyes with physiological saline 30 seconds after instillation of iprodione appeared to decrease the severity of the irritation.

MATERIALS AND METHODS

Animals and Animal husbandry

Adult New Zealand white rabbits (5 males/4 females; 2.3 - 2.9 kg at the initiation of the study) were purchased from Mohican Valley Rabbitry (Loudonville, Ohio) for this study. The rabbits were individually housed in suspended stainless steel cages in an environment-controlled room. The test protocol indicated that the environmental parameters were: a 12-hour light cycle, a relative humidity of 40 - 60% and a room temperature of 61 - 70°F. Agway Prolab Rabbit Ration and water were provided to each animal ad libitum. The rabbits were individually identified using plastic ear tags and cage cards. All animals were acclimated to the laboratory environment for a period of five days prior to initiation of the study.

Test Material

The test material was described as a white granular solid (I.D.# S91.001.3147). The Certificate of Analysis indicated a purity of 96.2%.

Protocol

Both eyes of each animal provisionally selected for testing were examined macroscopically for ocular irritation during the 24-hour period preceding the initiation of the test. Also, the corneal surface was examined for retention of fluorescein dye. Only those animals which were free of eye irritation, ocular defects and pre-existing corneal lesions were used.

A dose of 0.062 g of the test material (0.1 ml equivalent) was instilled into the conjunctival sac of the right eye of each animal. Immediately after dosing, the eyelids were held together for approximately one second. The untreated contralateral eye of each rabbit served as the control. At 30 seconds postinstillation, both eyes of three rabbits were rinsed with 50 ml of physiological saline (rinsed group); the remaining six rabbits were called the "no rinse group".

Both eyes of each animal were examined for signs of irritation at 1, 24, 48 and 72 hours and at 7 days (when irritation had not cleared by 72 hours) after dosing using the ocular irritation grading system presented on pages 10 & 11 of the report (Appended pages 1 & 2). Following macroscopic observations at the 24-hour scoring interval, the fluorescein examination was repeated on all control and test eyes. This procedure was repeated at subsequent intervals, if positive fluorescein dye retention was observed, until a negative response was obtained.

Irritation Scores

The ocular irritation scores were added for each animal and the group mean irritation score was calculated for each scoring interval.

RESULTS

Control eyes

The report indicated that normal background fluorescein dye retention (stippling/mechanical abrasion) was seen in 5/9 control eyes but was not considered significant; no irritation was observed in these eyes.

Unrinsed eyes

Corneal opacity was seen in 1/6 rabbits at the 24-hour scoring interval. This effect, which was confirmed by positive fluorescein retention, had cleared by the 72-hour interval. Conjunctivitis (redness, swelling and discharge) was observed in 6/6 test eyes at the 1-hour interval; this effect was not apparent in any animal at day 7.

Rinsed eyes

Conjunctivitis, which was induced in 3/3 test eyes, was not seen in any of these animals at the 72-hour interval.

All ocular irritation scores are appended in Tables 1 & 2 from the report.

Conclusion

The administration of 0.062 g iprodione to the eyes of rabbits caused mild ocular irritation in 6/6 rabbits which was not seen in any animal at 7 days post dosing. Corneal opacity was seen in 1/6 and conjunctivitis in 6/6. Rinsing treated eyes with physiological saline 30 seconds after instillation of iprodione appeared to decrease the severity of the irritation.

Toxicity category: III

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OCULAR IRRITATION GRADING SYSTEM

	<u>Score</u>
<u>CORNEA</u>	
(A) Opacity--degree of density (area most dense taken for reading)	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible . . .	1*
Easily discernible translucent area, details of iris slightly obscured	2*
Opalescent (nacreous) area, no details of iris visible, size of pupil barely discernible	3*
Opaque cornea, iris not discernible through opacity	4*
(B) Area of cornea involved (total area exhibiting any opacity, regardless of degree)	
One quarter (or less) but not zero	1
Greater than one quarter, but less than half	2
Greater than half, but less than three quarters	3
Greater than three quarters, up to whole area	4
Score = A x B x 5	Total Maximum = 80

IRIS

(A) Values	
Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris is still reacting to light (sluggish reaction to positive)	1*
No reaction to light, hemorrhage, gross destruction (any or all of these)	2*
Score = A x 5	Total Maximum = 10

*Positive response.

OCULAR IRRITATION GRADING SYSTEM

	<u>Score</u>
<u>CONJUNCTIVAE</u>	
(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Blood vessels normal	0
Blood vessels definitely injected (hyperemic) above normal (slight erythema)	1
More diffuse, deeper crimson red, individual vessels not easily discernible (moderate erythema)	2*
Diffuse beefy red (marked erythema)	3*
(B) Chemosis	
No swelling	0
Any swelling above normal (includes nictitating membrane, slightly swollen)	1
Obvious swelling with partial eversion of lids	2*
Swelling with lids about half closed	3*
Swelling with lids more than half closed	4*
(C) Discharge	
No discharge	0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to lids	2
Discharge with moistening of the lids and hairs and considerable area around the eye	3
Score = (A + B + C) x 2	Total Maximum = 20

*Positive response.

Table 1
Ocular Irritation Scores
(No Rinse Group)

Animal Number/Sex	Scoring Interval	Cornea			Iris		Conjunctivae			Fluorescein Examination ^a	Comments ^b	
		A	B	Score AXBx5	A	Score AX5	A	B	C			Score (A+B+C)/2
8462/M	1 Hour	0	0	0	0	0	1	1	1	6	6	
	24 Hours	0	0	0	0	0	2	1	0	6	6	
	48 Hours	0	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	0	0	0	0	0	
8492/F	1 Hour	0	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	0	1	1	0	4	4	
	48 Hours	0	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	1	0	0	2	2	
	7 Days	0	0	0	0	0	0	0	0	0	0	
8468/M	1 Hour	0	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	0	2	1	0	6	6	
	48 Hours	0	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	1	0	0	2	2	
	7 Days	0	0	0	0	0	0	0	0	0	0	
8457/M	1 Hour	0	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	0	2	0	0	4	4	
	48 Hours	0	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	1	0	0	2	2	
	7 Days	0	0	0	0	0	0	0	0	0	0	

^aFluorescein examination results: [+] positive retention; [-] negative retention.
^bSee page 12 of 31 for comment code.

Table 1 (continued)

Ocular Irritation Scores
(No Rinse Group)

Animal Number/Sex	Scoring Interval	Cornea			Iris			Conjunctivae			Fluorescein Examination ^a	Total	Examination ^b Comments ^b
		A	B	A+B	A	AX5	Score	A	B	C			
8495/F	1 Hour	0	0	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	0	0	1	0	0	2	2	-
	48 Hours	0	0	0	0	0	0	0	0	0	0	0	
	72 Hours	0	0	0	0	0	0	0	0	0	0	0	
8464/M	1 Hour	0	0	0	0	0	0	2	1	1	8	8	
	24 Hours	1	1	5	0	0	0	2	1	0	6	11	+
	48 Hours	1	1	5	0	0	0	1	1	0	4	9	+
	72 Hours	0	0	0	0	0	0	1	0	0	2	2	-
	7 Days	0	0	0	0	0	0	0	0	0	0	0	

^aFluorescein examination results: [+] positive retention; [-] negative retention.

^bSee page 12 of 31 for comment code.

Group Mean Irritation Scores

1 Hour	-	7.7
24 Hours	-	5.5
48 Hours	-	2.8
72 Hours	-	1.3
7 Days	-	0.0

Table 2
Ocular Irritation Scores
(Rinsed Group)

Animal Number/Sex	Scoring Interval	Cornea		Iris		Conjunctivae			Fluorescein Examination ^a	Total	Comments ^b
		A	B	Score AXB5	Score AX5	A	B	C			
8488/F	1 Hour	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	2	0	0	4	4	+
	48 Hours	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	0	0	0	0	MI
8667/F	1 Hour	0	0	0	0	1	1	0	4	4	
	24 Hours	0	0	0	0	1	0	0	2	0	+
	48 Hours	0	0	0	0	0	0	0	0	0	MI
	72 Hours	0	0	0	0	0	0	0	0	0	
8655/M	1 Hour	0	0	0	0	2	1	1	8	8	
	24 Hours	0	0	0	0	2	1	0	6	6	
	48 Hours	0	0	0	0	1	0	0	2	2	
	72 Hours	0	0	0	0	0	0	0	0	0	

^aFluorescein examination results: [+] positive retention; [-] negative retention.
^bSee page 12 of 31 for comment code.

Group Mean Irritation Scores
 1 Hour - 6.7
 24 Hours - 3.3
 48 Hours - 1.3
 72 Hours - 0.0

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