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**A Preliminary Toxicological Study
of Irganox 1010**

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A PRELIMINARY TOXICOLOGICAL STUDY OF IRGANOX 1010

by

G. A. Drake, J. E. London, D. M. Smith, and R. G. Thomas

ABSTRACT

Acute oral LD_{50/30} values for mice and rats receiving Irganox 1010 were found to be greater than 5 g/kg. According to classical guidelines, this material would be considered slightly toxic or practically nontoxic in both species. Skin application studies in rabbits showed the material to be nonirritating. Eye irritation studies, also in the rabbit, showed that Irganox 1010 was a mild but transitory irritant. The sensitization study in guinea pigs did not show the material to be deleterious.

I. INTRODUCTION

As part of the Los Alamos Scientific Laboratory Mammalian Biology Group's applied toxicology program, Irganox 1010 (Ciba-Geigy Corporation, Ardsley, New York) was tested to determine the following toxic properties: (1) acute oral toxicity; (2) primary skin irritation; (3) skin sensitization; and (4) ocular irritation.

II. EXPERIMENTAL PROCEDURE

A. General

The test material Irganox 1010 was supplied by Group WX-2 of the LASL Design Engineering Division. While in the possession of Group H-4, the material was stored at 25°C in a glass container sealed inside a polyethylene bag. A maximum dose of 5 g/kg was used for testing. Any material showing no mortality at this level in 30 days was reported as having an LD_{50/30} of greater than 5 g/kg and Irganox 1010 was considered to be less than slightly toxic or practically nontoxic.

To determine a suitable vehicle for administration, the following materials or techniques were tried: corn oil alone; DMSO alone; 95% alcohol; agarose; saline; 50% alcohol; 50% chloroform; 100% chloroform; and heating.

None of these approaches was suitable. The best procedure was to dissolve 5 g of Irganox 1010 in 5 ml of DMSO at 50°C. This solution was diluted with 5 ml of corn oil, which formed a suspension of Irganox 1010 in the liquid medium. This suspension was kept at 50°C until administration was completed.

B. Single-Dose Acute Oral Toxicity (LD_{50/30} Days)

1. Rats. Twenty young adult (67-day-old) Sprague-Dawley male rats, weighing 250 to 270 g, were used in the test group to determine the range of toxicity.^{1,2} The material was administered to ether-sedated fasted rats as a suspension in DMSO/corn oil (50/50) heated to 50°C. [Controls were given DMSO/corn oil (50/50) only.] The dose was given intragastrically with a ball-tipped needle and syringe. After treatment, all animals were observed daily for 30 days for aberrant physiological and behavioral responses. These data are on file in the Mammalian Biology Group as Compound H-4-No. 12.

2. Mice. The procedure for single-dose oral-toxicity determination in mice was the same as for rats. Twenty-five young adult (96-day-old) CFW (Swiss-Webster) female mice, weighing 29 to 30 g, were used in this group.

[Controls were given DMSO/corn oil (50/50) only.] As in the rat study, all animals were observed for 30 days for abnormal physiological and behavioral responses.

C. Long-Term Oral Toxicity

1. Mice. Thirty young adult CFW (Swiss-Webster) female mice, weighing 28 to 32 g, were given an intragastric intubation dose of 5 g/kg and will be followed until death when gross and microscopic examination of major organ systems will be performed.

2. Rats. Thirty young adult Sprague-Dawley male rats, weighing 270 to 340 g, were given a single 5 g/kg dose and will be subjected to the same experimental procedures as the mice.

D. Primary Skin Irritation

The Draize test³ was used to assess primary skin irritation. Six New Zealand white rabbits (Keen Ridge Rabbit Ranch, Edgewood, New Mexico) weighing 2.4 to 2.8 kg each, were used. The back of each rabbit was clipped free of hair using Oster electric clippers (Oster Corporation, Racine, Wisconsin) with a No. 40 blade 24 h before application of the mixture. Four sites, two intact and two abraded, were established. The material was applied as a paste (500 mg in 0.5 ml of corn oil) at each location. The test sites were covered with a gauze pad, and the entire back was overlaid with an adhesive plastic surgical drape. Each rabbit was then placed in a rabbit jacket (Alice King Chatham, Los Angeles, California). The jackets and wraps were removed 24 h later, and each test site was scored visually for erythema and edema. Readings were recorded at 24, 48, and 72 h. A final irritation score was calculated for the 24- and 72-h readings.

E. Ocular Irritation

Six New Zealand white rabbits (Keen Ridge Rabbit Ranch, Edgewood, New Mexico) weighing 2.7 to 2.9 kg each, were used in this test. Both eyes were checked for abnormalities before instillation. The material (100 mg) was instilled into the conjunctival envelope of the left eye of each rabbit; the right eye served as a control. Two rabbits had the material washed from the eye with 0.15 M NaCl at 30 s after instillation, two at 5 min after instillation, and two did not have the

material washed from the eye. Each eye was graded for ocular lesions at 1, 4, 24, 48, and 72 h. Of particular interest was whether the cornea, iris, and conjunctivae became inflamed. The procedure and grading systems were taken from the Draize test.³

E. Skin Sensitization

Eight female English guinea pigs (Camm Research Institute, Wayne, New Jersey) weighing 584 to 678 g, were used. The animals were housed individually and fed commercial laboratory stock diets ad libitum supplemented daily by lettuce and cabbage. One hundred mg of the Irganox 1010 was dissolved in 1 ml of DMSO, then diluted to 100 ml with saline to make a 0.1% solution for injection. Saline/DMSO controls were also tested. The material was administered in a series of 10 "sensitizing" injections into the lower back and flanks of the guinea pigs. Before each injection, the test sites were clipped free of hair. Intradermal injections were made randomly over the test area on Sunday, Tuesday, and Thursday with a 1-ml tuberculin syringe fitted with a 25-gauge needle. The volume of the first injection was 0.05 ml, and the remaining nine were each 0.1 ml. At 24 h after each injection, the sites were scored for erythema (redness), height, and diameter. Redness and height were scored as described by Landsteiner and Jacobs.⁴ The diameters of the reactions were measured in millimeters using a micrometer caliper. At 2 wk after administration of the tenth sensitizing injection, the lower back and flanks of each guinea pig were clipped free of hair, and a challenge injection of 0.05 ml was administered. The reaction of each animal was graded 24 h later and compared with results from the sensitizing injections.

III. RESULTS AND DISCUSSION

A. Single-Dose Acute Oral Toxicity (LD_{50/30} Days)

1. Rats. In general, all rat behavioral and physiological responses appeared normal during the 30 day posttreatment period. Because the LD_{50/30} was greater than 5 g/kg, the material was considered to be nontoxic.

TABLE I

EYE IRRITATION RESPONSE IN RABBITS TREATED WITH
IRGANOX 1010^a

Tissue Graded	Average Irritation ^b				
	(hours)		(days)		
	1	4	1	2	3
<u>Wash at 30 s</u>					
Cornea	0	0	0	0	0
Iris	0	0	0	0	0
Conjunctivae	1	2	0	0	0
<u>Wash at 5 min</u>					
Cornea	0	0	0	0	0
Iris	0	0	0	0	0
Conjunctivae	1	1	1	0	0
<u>No Wash</u>					
Cornea	0	0	0	0	0
Iris	0	0	0	0	0
Conjunctivae	3	3	0	0	0

^aTwo rabbits per wash condition.^bMaximum cornea response = 80; maximum iris response = 10; maximum conjunctivae response = 20.

2. Mice. All mouse behavioral and physiological responses appeared normal during the 30-day posttreatment period. The LD_{50/30} was, therefore, greater than 5 g/kg.

B. Primary Skin Irritation

None of the six rabbits exhibited edema or erythema in 24 h; therefore, all animals were judged normal. The total primary irritation score was 0.00.

C. Ocular Irritation

Table I summarizes the eye irritation responses for Irganox 1010. Irritation was observed only in conjunctival tissue. Conjunctival responses were observed at all treatment levels at 1 h and generally consisted of mild redness. All treatment groups were judged normal at 48 h. The eye irritation caused by Irganox 1010 was mild and transitory.

D. Skin Sensitization

Review of the data collected for each guinea pig in the treatment group indicates that all challenge injection reactions were within the limits of sensitizing or within normal limits. The study did not show Irganox 1010 to be a sensitizer.

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