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TOXICOLOGY DEPARTMENT
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Document Processing Center (TS-790)
Office of Toxic Substances
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

8EHQ-92-12602

88920010786

INIT

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company, the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on chlormephos. The CAS number assigned to this compound is 24934-91-6. The CAS name is S-(chloromethyl) O,O-diethyl phosphorodithioate. This chemical was manufactured in Europe and imported for pesticide research and development. To our knowledge, a pesticide application on this chemical has never been submitted to EPA under the Federal Insecticide, Fungicide, and Rodenticide Act.

No claims of confidentiality are made for this submission. The title of the enclosed report is "Acute Subcutaneous Toxicity to Rats of Chlormephos and the Effect of Treatment with: 1. Atropine Sulphate; 2. Atropine Sulphate and PAM". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of the observed clinical signs. In the first experiment, groups of ten female rats received subcutaneous doses ranging from 20 to 50 mg/kg of chlormephos followed by a dose of atropine sulfate. Signs of toxicity consisted of varying degrees of tremors, lethargy, and lacrimation. The onset of tremors occurred between 1.5 and 4 hours after dosing. Death occurred between 22 hours and 5 days of dosing. Recovery of the survivors, as judged by external appearance and behavior, occurred within one week after dosing with chlormephos. The subcutaneous LD50 of chlormephos in rats was 38 mg/kg when administered alone and 34 mg/kg when followed by atropine sulfate.

3/16/95

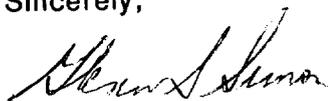
In the second experiment, groups of ten female rats received subcutaneous doses ranging from 32 to 80 mg/kg of chlormephos followed by a dose of atropine sulfate and pralidoxime (2-PAM). Signs of toxicity consisted of tremors, lethargy, and lacrimation. The onset of tremors occurred between 1 and 4 hours after dosing. Death occurred between 22 hours and 69 hours of dosing. Recovery of survivors, as judged by external appearance and behavior, occurred within one week after dosing with chlormephos. The subcutaneous LD50 of chlormephos followed by atropine sulfate and 2-PAM administration was 58 mg/kg with 95% confidence limits of 48 to 70 mg/kg.

One previous TSCA Section 8(e) notice was submitted on this chemical on August 31, 1978. We do not have an EPA Document Control Number for this submission in our records. In addition, approximately 15 submissions will be made on chlormephos under the CAP.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,



Glenn S. Simon, PhD, DABT
Director of Toxicology

CONFIDENTIAL

Report number : 91/71/D16.

18th October, 1971.

ACUTE SUBCUTANEOUS TOXICITY TO RATS
OF CHLORMEPHOS AND THE EFFECT OF TREATMENT WITH :

1. ATROPINE SULPHATE
2. ATROPINE SULPHATE AND PAM

Dr. V. H. Chambers,
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Herts.

Ronald E. Davies,
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Huntingdon Research Centre,
Huntingdon,
England.

SUMMARY

Toxic doses of Chlormephos were administered to groups of female rats treated with atropine sulphate with or without PAM.

Treatment with atropine sulphate alone produced no antidotal effect to rats acutely poisoned with Chlormephos.

When atropine sulphate was given in conjunction with PAM, much larger doses of Chlormephos were required to kill the rats, thus indicating the life-saving potential of antidotal treatment with atropine sulphate together with PAM.

The median lethal dose (LD₅₀) of Chlormephos was previously calculated to be :

38 (33-43)mg/kg bodyweight.

Treatment with Chlormephos and atropine sulphate gave an LD₅₀ value of :

34 (27 to 42)mg/kg bodyweight.

Treatment with Chlormephos atropine sulphate and PAM increased the LD₅₀ value to :

58 (48 to 70)mg/kg bodyweight.

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INTRODUCTION

Previous studies with Chlormephos (P2188) in April 1971 (HRC report number : 85/71/D438) indicated that this compound may be sensitive to the oxime reactivating agent PAM (= 2 - hydroxyiminomethyl-1-methylpyridinium methiodide).

In this present study, the antidotal efficacy of atropine sulphate and atropine sulphate plus PAM were assessed in rats given toxic doses of Chlormephos (P2188). Female rats only were used, since the previous study indicated greater susceptibility in this sex compared with male rats.

The LD₅₀ values obtained under these treatment regimes were compared with the LD₅₀ for female rats treated with Chlormephos alone, namely,

38 (33-43)mg/kg.

(see above report).

The experimental design was based on the recommendations of the Pesticides Safety Precautions Scheme, in Working Document No. 3, "Screening organophosphorus anticholinesterase compounds for response to reactivating agents" (publication address : Pesticides Branch, Great Westminster House, Horseferry Road, London, S.W. 1.)

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EXPERIMENT 1

Acute subcutaneous toxicity of Chlormephos to rats treated with atropine sulphate.

Experimental procedure

The rats used in these tests were of a CFY strain, obtained from Carworth Europe, Alconbury, Huntingdon. At the time of dosing they were in a weight range of 106 to 146g and each animal was identified by earmark. Throughout the subsequent observation period of two weeks, they were kept in groups of five.

Chlormephos was prepared for administration as a 2% suspension in corn oil. The maximum dosage-volume was 2.5ml/kg bodyweight. The atropine sulphate was prepared as a 1.74% solution in water and injected subcutaneously at a dosage volume of 1ml/kg to give a dosage of 17.4mg/kg.

Rats treated with vehicle alone served as controls.

After injections of Chlormephos, the rats were observed closely for the onset of tremoring. At this point the subcutaneous injections of atropine sulphate were given, and repeated at 24 hourly intervals for a further week.

During the observation period of 14 days, a record was kept of all signs of toxicity and mortalities. All rats that died were examined macroscopically in an attempt to identify the target organs, and those animals surviving terminally were similarly examined to detect possible residual damage.

Assessment of the degree of recovery from the initial toxic action of the product was made subjectively from the appearance and behaviour of the animals and, more objectively, by weekly checks on bodyweight.

From the mortality data recorded in Table 2, the LD₅₀ value and its 95% confidence limits were calculated by the method of Litchfield, J.T., and Wilcoxon, F., (1949), J. Pharmac. exp. Ther., 96, 99.

RESULTS

Groups of ten female rats were dosed at varying levels from 20 to 50mg/kg bodyweight (Table 1).

Signs of reaction to treatment consisted of varying degrees of tremoring, lethargy and lacrimation. The onset of tremoring occurred between 1½ and 4 hours after dosing.

Death occurred between 22 hours and 5 days after dosing. Autopsy did not reveal any specific cause of death.

(7)

Recovery of survivors, as judged by external appearance and behaviour, was apparently complete within one week. Bodyweight increases were retarded during the first week, except for rats dosed at 20mg/kg. However, during the second week, they were normal compared with controls (Table 1).

Autopsy revealed a small raised area of tissue reaction measuring approximately 3 x 3mm and pink in colour on the bodywall muscles in the scapular region beneath the injection site.

CONCLUSION

The median lethal subcutaneous dose (LD_{50}) and 95% confidence limits of Chlormephos to rats treated with atropine sulphate were calculated to be :

34 (27 to 42)mg/kg bodyweight

(5)

EXPERIMENT 2

Acute subcutaneous toxicity of Chlormephos to rats treated with atropine sulphate and PAM

Experimental procedure

The experimental procedure was similar to that described for Experiment 1.

In this experiment, each animal received a subcutaneous injection of atropine sulphate and PAM at the onset of tremoring, and subsequently at 24 hourly intervals for seven days.

Atropine sulphate (1.74%) and PAM (5%) were prepared as aqueous dilutions and administered at a constant dosage volume of 1ml/kg bodyweight.

RESULTS

Groups of ten female rats were dosed at varying levels from 32 to 80mg/kg bodyweight (Table 2).

Signs of reaction to treatment consisted of varying degrees of tremoring, lethargy and lacrimation. The onset of tremoring occurred between one and four hours after dosing.

Death occurred between 22 and 69 hours after dosing. Autopsy did not reveal any specific cause of death.

Recovery of survivors, as judged by external appearance and behaviour, was apparently complete within one week. Bodyweight increases were depressed during the first week amongst rats dosed at 50 and 64mg/kg but were normal during the second week. The bodyweight of the one surviving rat dosed at 80mg/kg was depressed compared with controls throughout the observation period (Table 2).

Autopsy revealed a small raised area of tissue reaction measuring approximately 3 x 3mm and pink in colour on the bodywall muscles in the scapular region beneath the injection site.

CONCLUSION

The median lethal subcutaneous dose (LD₅₀) and 95% confidence limits of Chlormephos to rats treated with atropine sulphate and PAM were calculated to be :

58 (48 to 70)mg/kg bodyweight.

TABLE 1

Mortality ratio and group mean bodyweight (g) of rats dosed subcutaneously with Chloromephos and atropine sulphate.

Sex	Dosage (mg/kg)	Bodyweight (g) at			Mortality ratio	(No. deaths) (No. dosed)	Time of death after dosing (hours)
		Dosing	1 week	2 weeks			
♀	0	131	163	192	0/10	-	
	20	128	162	209	2/10		<5 days
	32	124	137	176	3/10		<27
	40	130	147	182	5/10		<29
	50	128	140	180	9/10		<28

TABLE 2

Mortality ratio and group mean bodyweight (g) of rats dosed subcutaneously with Chlormephos and atropine sulphate and PAM.

Sex	Dosage (mg/kg)	Bodyweight (g) at			Mortality ratio	(No. deaths) (No. dosed)	Time of death after dosing (hours)
		Dosing	1 week	2 weeks			
♀	0	131	163	192	0/10	-	
	32	124	157	191	1/10	17	
	50	122	146	199	4/10	251	
	64	124	140	184	5/10	269	
	80	130	132	165	9/10	251	

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: 12602 A

TSCA Inventory:

Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

~~ATOX~~

SBTOX

SEN

w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX

CTOX

EPI

·RTOX

GTOX

STOX/ONCO

CTOX/ONCO

IMMUNO

CYTO

NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only	
entire document: <u>0</u> 1 2 pages <u>12</u>	pages <u>1,2,4,6-8</u>
Notes:	
Contractor reviewer: <u>LPS</u>	Date: <u>5/11/95</u>

#12602A

Chlormephos

~~NP~~ NP

Acute subcutaneous toxicity is of high concern based on a calculated LD₅₀¹⁰ of 38 mg/kg in rats.

Chlormephos + Atropine Sulfate

~~NP~~ NP

Acute subcutaneous toxicity is of high concern based on a calculated LD₅₀¹² of 34 mg/kg in rats. Mortality and corresponding doses (mg/kg) were 2/10 (20), 3/10 (32), 5/10 (40) and 9/10 (50). Signs of toxicity included tremors and lethargy.

Chlormephos Atropine Sulfate + PAM

~~NP~~ NP

Acute subcutaneous toxicity is of moderate concern based on a calculated LD₅₀¹⁵ of 58 mg/kg in rats. Mortality and corresponding doses (mg/kg) were 1/10 (32), 4/10 (50), 5/10 (64) and 9/10 (80). Signs of toxicity included tremors and lethargy.