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Regulation 1910.101 EPA-OTS

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Irrelevant, Filing Date
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Code
Date 3-15-44
Date 3-17-44
Work By V. K. Rowe

Subject

0000495480

COMPARATIVE TOXICITY OF CRUDE DOW
PHENOTHIAZINE AND A SIMILAR DU-
PONT PRODUCT.

26-870002124

To

Edwin Ehlman Dept. By J. K. Rowe

4-22-YY

*Dept.
Distribution*

SEP - 4 1987

Problem:

The Dow Product, Irrelevant, Filing Date is being made in order to compete with a similar DuPont product already on the market.

Is there any significant difference in the toxicity of the two preparations?

Material:

Phenothiazine	Crude preparations.
Irrelevant, Filing Date	Dow Product (Batch 765)
Irrelevant, Filing Date	DuPont Product supplied by 172 Laboratory.

Experimental:

These two preparations were fed to rats in measured single doses by means of a stomach tube and the animals were observed for ill effects for at least two weeks after feeding.

Results:

The tests conducted show that both of these preparations are low in acute oral toxicity and that for practical purposes, there are probably no significant differences between them.

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Biochemical Research Laboratory

Subject TOXICITY OF PHENOTHIAZINE

Irrelevant, Filing Data
Filing Date
Irrelevant, Internal Codes
Rec'd 5-14-40
Filing Date 5-22-44
Work by

To *Irrelevant Distribution*

Irrelevant Distribution
Rept. by

MATERIAL

Name: Phenothiazine
Irrelevant, Filing Data

Formula:
Structural -



Empirical - $C_{12}H_9NS$

M.P. of pure material: Approx. 186°C.

Solubility: Soluble in oils and fat solvents.
Insoluble in water.

Stability: Oxidizes slowly in presence of air and moisture.

PREPARATIONS TESTED

Irrelevant, Filing Data

Ref. No. 308-12-273
M.P. = 184-185°C.
from *Irrelevant 5-16-40 Distribution*

Irrelevant, Filing Data

- Ref. No. 308-14-58
M.P. = 186.0-186.5°C.
from *Irrelevant 12-24-40 Distribution*

Irrelevant, Filing Data

-S-1 - Tar from phenothiazine production
Batch No. 402 of 2-8-44

Irrelevant, Filing Data ~~2-2~~ - M.P. - 185, 400.
Batch No. 402 of 2-2-44
From Mtl. No. 21

Irrelevant, Filing Data ~~2-3~~ - Crude phenothiazine from Dow production.
Batch No. 765 of 3-15-44

Irrelevant, Filing Data ~~2-4~~ - Crude phenothiazine as sold by du Pont.
From 172 sample of 3-15-44

PROBLEM

The first preparations, both obtained from *Irrelevant Distribution* 1940 were studied in an effort to determine something of the toxicity of purified phenothiazine which The Dow Chemical Company was in a position to market.

Irrelevant, Unlisted Chemical

The second two preparations, *Irrelevant, Filing Data* ~~2-2~~ and ~~2-3~~ were studied briefly in order to determine whether or not the presence of the tar would have any effect upon the toxicity of the phenothiazine. In other words, from a practical viewpoint, what physiological properties does the tar from phenothiazine production have?

The third two preparations, *Irrelevant, Filing Data* ~~2-3~~ and ~~2-4~~ were tested in order to reassure the production men that the crude preparation they were planning to market to compete with the du Pont product had no marked difference in acute toxicity.

ACUTE ORAL TOXICITY

Weighed doses of the test materials were suspended in 5-10% gum arabic solution and fed to rats by means of a stomach tube. All of the test materials were found to be low in acute oral toxicity as shown by the figures in Table I.

Table I

Acute Oral Toxicity of Phenothiazine on Rats

<u>Material</u>	<u>100% Survival Dose</u>	<u>100% Lethal Dose</u>
Irrelevant, Filing Data (Ref. #306-12-273)	3.0	5.0
Irrelevant, Filing Data -S-1	5.0	Greater than 15.0 ^{mg}
Irrelevant, Filing Data -S-2	5.0	Greater than 10.0 ^{mg}
Irrelevant, Filing Data -S-3	7.0	Greater than 7.0 ^{mg}
Irrelevant, Filing Data -S-4	5.0	Greater than 7.0 ^{mg}

*It did not seem practical to feed larger doses.

SKIN IRRITATION

Skin irritation tests were conducted in the usual manner on rabbits.

Irrelevant, Filing Data -S-2, a recent product of high purity, failed to exhibit any marked irritant properties. However, a mild irritation developed after prolonged and repeated exposures, indicating that it would be wise to exercise some caution to avoid prolonged exposure.

Irrelevant, Filing Data S-1, the phenothiazine tar, was found to be relatively free of skin irritating properties. It seems doubtful that this material would cause trouble.

TOXIC ABSORPTION

There was no evidence in any case that phenothiazine or the tar was absorbed through the skin in toxic quantities. We do not feel that either of these products presents a skin absorption hazard.

20-DOSE REPEATED ORAL

On Rabbits:

Rabbits were fed repeated doses of phenothiazine (Ref. No. 308-12-273) at the dosage levels of 0.1, 1.0, 2.0, and 5.0 g./kg. The liver, spleen, kidney, adrenal, pancreas, and bone marrow were routinely examined histopathologically. The results were as follows:

Nineteen doses of 0.1 g./kg. failed to cause discernable ill effects.

Twenty doses of 1.0 g./kg. caused slight liver and spleen damage and hyperplasia of the bone marrow.

Fourteen and twenty doses of 2.0 g./kg. caused marked liver and spleen damage and hyperplasia of the bone marrow.

Four and ten doses at 5.0 g./kg. caused marked liver and spleen damage and congestion of the kidneys. No information as to the state of the bone marrow was obtained.

All the animals fed doses of 2.0 and 5.0 g./kg. failed to gain in weight or they lost weight over the experimental period.

On Rats:

Rats were fed repeated doses of phenothiazine (Ref. No. 308-14-58) at the dosage levels of 0.1, 0.5, 1.0, and 2.0 g./kg. The liver, kidney, spleen, pancreas, adrenal, and bone marrow were routinely examined histopathologically, and on the higher doses the heart and testes were also examined. The results were as follows:

Nineteen doses of 0.1 g./kg. failed to cause discernable ill effects.

Nineteen doses of 0.5 g./kg. caused slight spleen and slight to marked liver damage. The bone marrow was slightly hyperplastic.

Five doses of 1.0 g./kg. caused marked liver damage and slight spleen and kidney damage. The bone marrow was again slightly hyperplastic.

Five doses of 2.0 g./kg. caused marked damage to both the liver and the kidney. The bone marrow was again slightly hyperplastic.

DISCUSSION

Our work, as well as published work on small animals (rats), leads us to believe that phenothiazine is relatively low in oral toxicity, particularly when it is administered in single doses. However, there is apparently considerable species variation in susceptibility to phenothiazine poisoning, for untoward results seldom occur following treatment of chickens, dogs, or sheep, while they too frequently occur following treatment of hogs and horses.

For a discussion of studies published before 1940 concerning the hazards and uses of phenothiazine, see the Northwestern Research Laboratory report of 5-11-40, entitled "The Toxicity of Phenothiazine and Its Use as a Urinary Antiseptic — A Literature Survey." Copies of this report were sent to D. K. Billman, W. W. Sunderland, and W. R. Veasey under the file number _____ (since changed to _____).

Apparently the ratio of the effective dose to the toxic dose for horses and hogs is not as favorable as that for the other animals mentioned, thus making the horse and the hog quite susceptible to overdosage.

In looking over some of the more recently published literature describing well controlled studies on the veterinary use of phenothiazine, we feel certain that a high percentage of these untoward effects that have resulted from the use of phenothiazine as an anthelmintic are directly due to overdosage. It appears that safe and effective dosages for several species of livestock are as follows:

horses - 25-30 g./1000 pounds
cattle - 0.1 g./kg.
calves - doses up to 1.0 g./kg. have not caused trouble but would recommend dosage of 0.2 g./kg. as safer
hogs - 5-30 g./hog but as much as 0.5 g./kg. said to be safe
sheep - 25-30 g./animal but as much as 1.0 g./kg. is said to be safe
lambs (up to 60 lbs.) - 15 g.
chickens - 0.5 g./head
puppies - 6-12 g./head

"The wide margin between effective dose and toxic dose probably accounts for the fact that extensive use has not caused trouble in sheep while it has among more susceptible animals. In other words, sheep can tolerate a large overdosage while some other animals cannot.

Phenothiazine has also been used as an anthelmintic in humans but there seems to be a wide divergence of opinion as to whether it is successful or not. Most workers agree that the material is quite effective against some parasites but ineffective against others. In most cases, the investigators have concluded that the side reactions, anemia and hepatitis, make it too dangerous to use except as a last resort. The same opinion seems to be prevalent concerning the use of phenothiazine as a urinary antiseptic.

CONCLUSIONS

(1) Phenothiazine is low in acute oral toxicity for rats. It seems reasonable to conclude that it would be reasonably safe for use as an anthelmintic where single administration is called for or where two administrations several days apart are indicated. It should be kept in mind, however, that certain species of animals, particularly horses, are quite susceptible to overdosage. The use of this material should always be under the direction of a veterinarian.

(2) Phenothiazine is not a marked skin irritant but it may cause irritation if exposures are prolonged or repeated. No evidence that phenothiazine was absorbed through the skin in toxic quantities was observed. Personal cleanliness among men routinely handling this material should be urged to prevent skin troubles.

(3) The repeated oral ingestion of appreciable quantities of phenothiazine may result in liver, kidney, spleen, and/or possible blood changes. The use of this material as a urinary antiseptic should be well controlled.

(4) The tar from the production of phenothiazine at Dow is low in acute oral toxicity and does not seem to be a skin irritant. We would not expect this material to cause trouble.

(5) As far as acute oral toxicity is concerned, there does not seem to be any choice between the crude phenothiazine that Dow expects to market and the comparable product put out by du Pont.

rl-10 copies

Material: Phenothiazine (Ref. #306-12-273)

ACUTE ORAL TOXICITY

Animals Rats

Dose (mg/kilo)	Number of animals that died	Number of animals that survived
0.6	0	1
1.0	0	1
2.0	0	1
3.0	0	5
4.0	4	1
5.0	5	0

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Summary of Chronic Oral Toxicity Experiments

Problem Number	Material	rabbit animal	initial weight	final weight	Dose gm/kg	No. of Doses	Died Hours	Killed Days	Liver	Lung	Spleen	Kidney	Adrenal	Pancreas	Bone marrow	Remarks	
Control		R-6-345	2.04	2.41	0.0	20		26	N		N	+	N	N	N		
		R-6-381	2.74	2.70	0.1	19		26	N		N	N	N	N			
		R-6-382	2.43	-	1.0	5		8								Died	
		R-6-342	2.01	2.36	1.0	20		26	+		+	N	N	N		Hyper.	
		R-6-344	2.41	2.47	1.0	20		26	+		++	N	N			"	
Irrelevant, Internal Codes	Phenothiazine	R-6-341	1.81	1.75	2.0	14		18	+++		++	N	N	N		Died	
		R-6-340	1.64	1.72	2.0	20		26	+++		++	N	N	N		"	
		R-6-337	1.79	1.74	5.0	4		6	++		++	C	N	N			
		R-6-338	1.92	1.74	5.0	9		12									Died
		R-6-339	1.82	1.77	5.0	10		14	+++		++	C	N	N			Died

BIOCHEMICAL RESEARCH LABORATORY

Summary of Chronic Oral Toxicity Experiments

Problem Number	Material	Rat Animal	Initial work Method	final work Method	Dose gm/kg	No. of Doses	Died Hours	Killed Days	Liver	Lung	Spleen	Kidney	Adrenal	Pancreas	Bone Marrow	Remarks
Control Control		4397	186	182	-	15		20								Died. Lung yaws
		4402	155	186	-	19		26	N		N	N	N	N		
		4404	140	183	0.1	19		26	N		N	N	N	N	N	
		4405	192	221	0.5	19		26	++		+	+	N	N		(N) Hyper.
		4400	186	207	0.5	19		26	++		+	N	N	N		(N) Hyper.
		4450	208	170	1.0	5		6	+++		0	+	N	N		Heart: N Testes: N
		4406	165	156	1.0	5		6								Died
		4429	192	-	2.0	5		6								Dead
		4452	164	143	2.0	5		6	+++		N	+++	N	N		Heart: N Testes: N

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Material: Phenothiazine Tartrate (Irrelevant, Filing Data) (8-1)

Irrelevant, Internal Codes

ACUTE ORAL TOXICITY

Animals Rats

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
3.0	0	5
5.0	0	5
7.0	1	4
10.0	1	1
15.0	0	1

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Material: Phenothiazine Tar

Prob. Irrelevant Internal Codes

SKIN IRRITATION _____ Irrelevant, Filing Data ^{-S-1)}

20% Solution in B.C.A. on ear and belly 20 times in 28 days.

Animal # 6-919

Date 3-8-44

Day #	Exp. #	Reaction
	<u>Ear</u>	No appreciable irritation attributable to the test material.
	<u>Belly</u>	Very slight exfoliation of questionable significance.
	<u>Conclusion</u>	No appreciable skin irritation produced by repeated and prolonged contact with this material.

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Irrelevant, Internal Codes

Material: Phenothiazine (Irrelevant, Filing Data -8-2)

ACUTE ORAL TOXICITY

Animals Rats

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
3.0	0	3
5.0	0	5
7.0	3	2
10.0	3	2
No more could handily be fed.		

BIOCHEMICAL RESEARCH LABORATORY

Material: Phenothiazine (Irrelevant, Filing Data -S-3) (Dow Batch 765) Irrelevant, Internal Codes

ACUTE ORAL TOXICITY

Animals Rats

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
3.0	0	2
5.0	0	5
7.0	0	5
No more could conveniently be fed.		

BIOCHEMICAL RESEARCH LABORATORY

Irrelevant, Internal Codes

Material: Phenothiazine (S-4) (DuPonts)

ACUTE ORAL TOXICITY

Irrelevant, Filing Data

Animals Rats

Dose (gm/kilo)	Number of animals that died	Number of animals that survived
3.0	0	2
5.0	0	5
7.0	1	4
No more could conveniently be fed.		

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