MICROFICHE LABEL -- SPECIAL TITLE

ATTENTION DATA ENTRY

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Microfiche # OTS 0206674

Document ID # _____

1A

OFFICE OF TOXIC SUBSTANCES REV. 7/27/82

CODING FORM FOR GLOBAL INDEXING

Microfiche No. (7) • OTS 0206674 1

No. of Pages 2

Doc I.D. 14819 3

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MID No. (7) 19

D & B NO. (11) 20

Contractor 21

Doc Type 22

Doc Title 23

Chemical Name (300 per name) 25

CAS No. (10) 24

P-TERT-BUT... PHENYL ... | ...900-08-7

| 78-...-1

Figure 3. Global Indexing Form

3-11

1B

Chemical Name (300 per name) 25	CAS No. (10) 24
TRI-PHENYL PHOSPHATE	115-86-6
TRI-O-CRESYL PHOSPHATE	9999-08-7
TRI-P-TERT. BUTY PHENYL PHOSPHATE	9999-08-7
MONO-PHENYL DI (P-TERT. BUTYL PHENYL PHOSPHATE)	9999-08-7
DI-PHENYL MONO (P-TERT. BUTYL PHENYL PHOSPHATE)	9999-08-7

1C

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48640

June 29, 1984

Don R. Clay, Director
Office of Toxic Substances (TS-793-I)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Dear Mr. Clay:

We have reviewed your letter of June 6, 1984. As a result we have reviewed the studies submitted under the 8(d) rule about which you have expressed concern.

In view of the public interest in health and safety studies projected by your June 6 letter, we have waived claims of confidential business information in many of the studies submitted. A list of the EPA document control numbers from which CBI claims have been removed or reduced is attached. Copies of these studies have been sent separately to Tim Knutsen's attention. Studies which contain reduced claims of CBI have been re-submitted in duplicate, one copy prepared for the public files and one copy with CBI marked, as directed in the rule. In addition we have undertaken a review of our policy and procedures for asserting CBI claims in 8(d) submissions.

We appreciate your candid and informal approach to dealing with this matter, and trust that our efforts are responsive to your concern.

Very truly yours,

R. L. Hagaman
Research Associate
Regulatory and Legislative Issues
Health and Environmental Sciences
1803 Building

rt

Attachment

cc:Tim Knutsen, US EPA-OTS

1D

HEALTH AND SAFETY STUDIES
FROM WHICH CBI CLAIMS ARE ELIMINATED

Document Control No	Dow Ident	Document Control No	Dow Ident	Document Control No	Dow Ident
878230176	D 657	878230375	D1123	878230377	D1076
878230380	D1047	878230780	D1034	878230791	D 254
878230792	D 433	878230795	D 313	878230796	D 437
878230797	D 320	878230800	D 208	878230805	D 263
878230806	D 264	878230810	D 271	878230812	D 273
878230815	D 301	878230819	D 266	878230821	D 397
878230823	D 511	878230825	D 559	878230828	D 575
878230829	D 580	878230832	D 604	878230838	D 645
878230839	D 250	878230840	D 232	878230841	D 287
878230842	D 549	878230843	D 389	878230844	D 419
878230852	D 613	878230854	D 517	878230857	D 168
878230858	D 169	878230860	D 500	878730861	D 283
878230862	D 365	878230863	D 165	878230864	D 294
878230867	D 185	878230869	D 289	878230872	D 546
878230873	D 383	878230874	D 259	878320875	D 439
878230876	D 199	878230877	D 492	878230878	D 514
878230880	D 577	878230882	D 564	878230883	D 166
878230884	D 167	878230885	D 343	878230886	D 222
878230889	D 336	878230890	D 318	878230891	D 319
878230893	D 223	878230896	D 159	878230897	D 401
878230898	D 256	878230899	D 257	878230900	D 369
878230902	D 175	878230904	D 181	878230905	D 184
878230906	D 187	878230907	D 363	878230908	D 364
878230910	D 377	878230913	D 569	878230914	D 291
878230915	D 230	878230916	D 372	878230920	D 521
878230921	D 367	878230923	D 202	878230925	D 383
878230926	D 385	878230927	D 390	878230929	D 588
878231717	D1138	878231718	D1130	878231778	D1042
878231779	D1041	878231781	D1033	878231782	D1030
878231785	D 596	878231786	D 299	878231788	D 252

1E

878214819

BIOCHEMICAL LABORATORY
Physical Research Laboratory
THE DOW CHEMICAL COMPANY

Subject: ORAL TOXICITY OF P-TERT. BUTYL PHENYL PHOSPHATE (Preliminary Report)

To

From

File No.

Date: 8-21-34

By: D.D.Irish

D-000232

Each dose of material to be tested was suspended in 5% gum acacia and given to a normal healthy rabbit by stomach tube. The preparations which were in the solid state did not form good emulsions. For this reason these tests will be checked in the near future using solutions in Ethanol.

The following table is self-explanatory:

Material Tested	Rabbit No.	Body Wt. Kg.	Dose gm. per Kilo	Effect
Tri-phenyl phosphate	5	2.606	3.0	Slight diarrhea
"	4	2.950	5.0	Diarrhea
Tri-o-cresyl phosphate	2	3.460	0.040	None
"	6	3.595	0.060	None
"	1	2.930	0.110	Very sick. Lost muscular control
Tri-p-tert. butyl phenyl phosphate	3	2.065	1.0	None
Mono-phenyl di (p-tert. butyl phenyl phosphate)	7	[illegible]	1.0	None
"	10	1.6?2	[illegible]	None
Di-phenyl mono (p-tert. butyl phenyl phosphate)	11	1.559	1.0	None
"	8	1.748	3.0	None

No toxic effects were observed with the above doses of the p-tert. butyl phenyl phosphates. It is safe to conclude that under the conditions of the foregoing experiments these materials are relatively nontoxic to rabbits.

:JR

000002

237 5 ISC 1235

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

Subject	**THE TOPICAL ACTION OF TRIPHENYLPHOSPHATE**	File Cop. Rec'd. Fil'd 6-10-38 By:
To	**From**	

SUMMARY

Triphenylphosphate did not have significant action on the skin of the rabbit. It would not be expected to have a greater action on human skin.

EXPERIMENTAL

The dry powdered triphenylphosphate and a saturated solution in pure ethanol (approximately 75%) were tested on the shaven abdomen of rabbits. The dry powder was held in contact with the skin by means of a cloth bandage. Cotton pads were used to hold the alcohol solutions; these also were held in place by a bandage.

The saturated alcoholic solution was applied to the shaven skin of a rabbit 13 times in a period of 16 days. Only a slight fine scale was produced.

When the skin was thoroughly abraded (until it bled), the alcoholic solution produced a denaturation of the skin in 24 hours. Alcohol alone ~~doesn't~~ [illegible] denature the skin as the solution did.

The dry powder had no action upon normal skin. When applied to abraded skin, the powdered solid produced a redness until after the skin healed.

Triphenylphosphate would appear to have no significant action on the skin.

MH

BIOCHEMICAL LABORATORY
THE DOW CHEMICAL COMPANY

Subject ORAL TOXICITY OF CERTAIN PHENYL PHOSPHATES.

To From Aug. 18, 1934

Each dose of material to be studied was suspended in 6% gum acacia and given to a normal healthy rabbit by stomach tube. The rabbit was then observed for a period of several days for toxic symptoms. The data obtained with the phenyl phosphates submitted is tabulated in the following table.

A. Phosphates from Phenol & O-Chlor Phenol -

Material Tested	Rabbit No.	Body Wt. Kg.	Dose gm./Kg.	Observed Effect
Diphenyl mono o-chlor phenyl phosphate	26	1.90	3.0	Dead
	16	1.73	1.0	None
Mono phenyl di (o-chlor phenyl) phosphate	17	2.14	1.0	Dead
	21	1.85	0.5	None
	29	1.86	0.5	None
Tri o-chlor phenyl phosphate	31	1.77	3.0	None
"	19	2.05	1.0	None

B. Phosphates from Phenol & P-Tert. Butyl Phenol -

Di-phenyl mono (p-tert.butyl phenyl) phosphate	8	1.74	3.0	None
"	11	1.89	1.0	None
Mono phenyl di (p-tert. butyl phenyl) phosphate	10	1.85	3.0	None
"	7	1.85	1.0	None

000004

Material Tested	Rabbit No.	Body Wt. Kg.	Dose gm./kg.	Observed Effect
Tri-p-tert. butyl phenyl phosphate	9	2.065	1.0	None

C. Phosphates from Phenol & Ortho Xenol -

Di-phenyl mono (o-xenyl) phosphate	23	3.20	3.0	None
"	14	1.93	1.0	None
Mono-phenyl di (o-xenyl) phosphate	24	2.07	3.0	None
"	15	2.26	1.0	None
Tri (o-xenyl) phosphate	22	2.00	3.0	None
"	12	1.79	1.0	None
Mono-phenyl, mono o-xenyl, mono o-cresyl phosphate	13	2.33	1.0	Dead
"	20	2.38	0.5	Dead
"	39	2.43	0.5	Dead

D. Effect of Varying Substituents on Phenol -

Tri-phenyl phosphate	4	2.95	5.0	Diarrhea
"	5	2.60	3.0	Slight Diarrhea
Tri o-cresyl phosphate	1	2.99	0.11	Very sick. Lost muscular control.
"	6	3.59	0.06	None
"	2	3.46	0.04	None
Tri (2-4 Dichlor phenyl) phosphate	30	1.75	3.0	None
"	21	1.94	1.0	None
"	18	2.04	1.0	None

It is to be observed that no pathological studies were made on the animals that survived without observable toxic symptoms.

Respectfully submitted,

HR

OFFICE OF TOXIC SUBSTANCES REV. 7/27/82

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MID No. (7) 19 D & B NO. (11) 20

Contractor 21

Doc Type 22

• [illegible] • [illegible] • [illegible]

Doc Title 23

[illegible] RESULTS OF RANGE FINDING

TOXICOLOGICAL TESTS ON DOW

[illegible] PLASTICIZER "F-7".

Chemical Name (300 per name) 25	CAS No. (10) 24
FRY- [illegible]	[illegible] 8000-08-7
TRI-(P-TERT BUTYL PHENYL) [illegible]	78-33-1

Figure 3-7. Global Indexing Form
3-11

1A

12 4784

Biochemical Research Laboratory
THE DOW CHEMICAL COMPANY

8782148205

Subject: RESULTS OF RANGE FINDING TOXICOLOGICAL TESTS ON DOW PHOSPHEN PLASTICIZER "P-7". D-287

File
Chg.
Rec'd 1-20-47
Fin'd 8-27-47
Work By L.F.Key

E. M. Adams 8-28-47

Rept. By V. K. Rowe 8-27-47

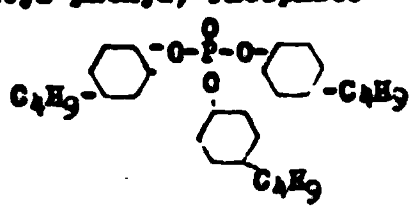
PROBLEM

Dow Phosphen Plasticizer "P-7" is being made by an "alternate process" and might not be as pure as the material made by the old process. What are the handling hazards of this new product and how does it compare from a toxicological viewpoint with the old product.

MATERIAL

Name - Dow Phosphen Plasticizer "P-7"
Tri-(p-tert. butyl phenyl) Phosphate
K No.- K1109-6

Formula - Structural



Empirical - $C_{30}H_{39}O_4P$

Source - D.F. Ponta

Received - 1-27-47

Purity - Probably contains 1 to 2% of p-tert.butyl phenol.

1933

THIS REPORT IS THE PROPERTY OF THE DOW CHEMICAL COMPANY

1319 88 28C 948

878214830

EXPERIMENTAL RESULTS

Acute Oral - The test material as a 20% solution in olive oil was fed in single oral doses to rats. Doses of 5.0 g/kg caused the death of one of the 5 animals treated and doses of 10.0 g/kg caused the death of one of 3 animals tested. These figures indicate that "Alternate Process P-7" is very low in acute oral toxicity.

Skin Irritation - "P-7" as a 10% solution in butyl carbitol acetate was applied repeatedly to the rabbit's ear and hands repeatedly to the shaven belly. No irritation developed on th ..nd only a very slight irritation developed on the belly, and that only after several repeated and prolonged exposures had been made.

CONCLUSIONS

The range finding tests conducted have failed to demonstrate any significant toxicological differences between "Alternate Process P-7" and the old preparation of "P-7".

We do not believe that either of these products present significant handling hazards as far as skin contact is concerned. We do not have information regarding the toxicity of fume or vapors of "P-7" nor do we have any information regarding its chronic oral toxicity.

aj-6

OFFICE OF TOXIC SUBSTANCES REV. 7/27/82

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State 16	MI
Zip 17	[illegible]
Country 18	
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D & B NO. (11) 20	
Contractor 21	
Doc Type 22	[illegible]
Doc Title 23	[illegible]ULTS [illegible] RANGE FINDING TO[illegible]
	[illegible] PHENYL[illegible]

Chemical Name (300 per name) 25	CAS No. (10) 24
[illegible] PHOSPHATE	[illegible] 84Ø-Ø8-7
T[illegible]PHENYL PHOSPHATE	115-[illegible]

Figure 3-7. Global Indexing Form

1A

Chemical Name (300 per name) 25	CAS No. (10) 24
TRIS-(PHENYL ALKYL PHENYL) PHOSPHATE	999800-08-7
TRIS-(ALKYL PHENYL) PHOSPHATE	999804-08-7

1B

8782148 21

Biochemical Research Department D- 000222

The Dow Chemical Company

RESULTS OF RANGE FINDING TOXICOLOGICAL TESTS ON TRIPHENYLPHOSPHATE

File
K No.
Chg.
Rept. By K. J. Olson

Signed K. J. Olson Checked D. D. McCollister

Date Feb. 7, 1957 Date Feb. 7, 1957

PROBLEM

The subject material is being developed as a fire retardent. Are there any problems associated with the laboratory handling or industrial use of this material? This material is being compared with tris-(phenyl alkyl phenyl)phosphate and tris-(alkyl phenyl)phosphate .....) from the standpoint of toxicological properties.

CONCLUSIONS

The subject material has a low acute oral toxicity and should present no problem from ingestion incidental to industrial or general use.

The 100% material and the 10% solution in propylene glycol are but very slightly irritating to the eye. Minimal eye protection should provide adequate precaution for routine laboratory or general handling.

(Continued)

(CONCLUSIONS CONTINUED)

The 100% material is non-irritating to intact or abraded skin. The 10% solution in Dowanol 50B has a very slight effect on intact and abraded skin. Good care and cleanliness should provide adequate precaution for routine handling of this material.

Generally speaking this material is less toxic from the standpoint of eye irritation and skin contact than either of the other two compounds mentioned above. The subject material has a slightly greater acute oral toxicity in rats than the other two compounds in question, but is probably not significantly different from the standpoint of ingestion incidental to laboratory handling or general use.

These conclusions are based upon range finding toxicological tests and are limited to precautions for industrial handling of the material. Development of specific uses will require consideration of the health problems presented and of the need for further toxicological studies.

HAZARDS, PRECAUTIONS FOR SAFE HANDLING, AND FIRST AID MEASURES

Ingestion

The subject material has a low acute oral toxicity and should present no problem from ingestion incidental to industrial or general use. If large amounts of the material are swallowed some injury may result. The likelihood of serious injury is remote.

Eye Contact

The 100% material and the 10% solution in propylene glycol are very slightly irritating to the eye. It would seem advisable to prevent contamination of the eyes simply to avoid any discomfort which might result. Minimal eye protection should provide satisfactory precaution for routine laboratory or industrial handling.

Skin Contact - Irritation

The 100% material is essentially non-irritating to intact or abraded skin. No precautions should be necessary for routine handling of this material. The 10% solution in Dowanol 50B has a very slight effect on intact and abraded skin. The dry nature of the skin and subsequent exfoliation indicated by experimental work may very well be due to the Dowanol 50B used as a solvent. Precautions should be taken to prevent repeated prolonged skin contact with weak solutions of this material. Reasonable care and cleanliness should avert irritation. Any injury or irritation which may develop from handling this material should receive medical attention.

SAMPLE INFORMATION

C.R.I. Name: Triphenylphosphate, Technical

Source:

M.P.: 45-48°C

K No.:

Date Request Received: 7-19-56

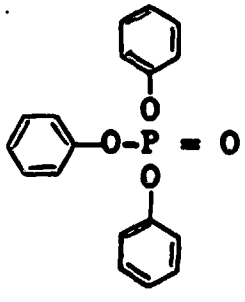
Date Sample Received: 7-19-56

Physical State: Solid

Sol.: Water

Molecular Formula: $C_{18}H_{15}O_4P$

Structural Formula:



Reaction product of alkyl phenol by-product with $POCl_3$ (semiplant product)

SUMMARY OF RANGE FINDING TOXICOLOGICAL DATA

Acute Oral Toxicity

Animal	Preparation Fed	Dose (g /kg.)	No. Died No. Fed	Response-Remarks
Rat	20% solution in corn oil	1.0	0/2	Slight diarrhea and bloody exudate.
Rat	20% solution in corn oil	2.0	1/2	Slight diarrhea and bloody exudate.
Rat	20% solution in corn oil	3.98	1/2	Slight diarrhea and bloody exudate.
				Note: Diarrhea, dehydration, lung congestion, mottled liver and severe kidney necrosis observed in high dose animal at autopsy.

Eye Contact - Rabbit

Material	Treatment	Response-Remarks
100%	Washed and Unwashed	Slight conjunctival irritation, cleared in 24 hours.
10% solution in propylene glycol	Washed and Unwashed	Slight conjunctival irritation, cleared in 24 hours.

Skin Contact - Rabbit

Material	Condition Of Skin	No. Of Appl.	Site	Response-Remarks
100%	Intact	10	Abdomen	No irritation observed.
100%	Abraded	3	Abdomen	No irritation observed.
10% solution in Dowanol 50B	Intact	10	Ear	No irritation observed.
10% solution in Dowanol 50B	Intact	10	Abdomen	Slight to moderate exfoliation increasing after fourth application.
10% solution in Dowanol 50B	Abraded	3	Abdomen	Slight to moderate exfoliation appearing after last application. Healing normal.

Skin Absorption

There is no indication, from the skin irritation tests conducted, that this material is absorbed through the skin in toxic amounts.

UNIT INDEX

Effects resulting from ingestion, eye contact and skin contact are given. Hazards, precautions for safe handling, and first aid measures are discussed.

INDEX HEADINGS

C.R.I. Name: Triphenylphosphate, Technical

DISTRIBUTION

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Contractor	21
Doc Type: • [illegible] • U P • [illegible]	22
Doc Title: [illegible] TOXICITIES OF SOME PHENYL PHOSPHATES	23

Chemical Name (300 per name) 25	CAS No. (10) 24
ARYL PHOSPHATES	800-08-7
DIPHENYL MONO (P-TERTIARY-BUTYLPHENYL) PHOSPHATE	999 800-08-7

1A

Chemical Name (300 per name) 25	CAS No. (10) 24
MONOPHENYL DI(P-TERTIARY-BUTYLPHENYL) PHOSPHATE	illegible
DIPHENYL MONO-O-XENYL PHOSPHATE	illegible
MONOPHENYL DI-O-XENYL PHOSPHATE	illegible

1B

THE COMPARATIVE TOXICITIES OF SOME PHENYL PHOSPHATES

by

E. M. Adams

Problem B7

December 10, 1935

THE DOW CHEMICAL COMPANY

BIOCHEMICAL LABORATORY

MIDLAND, MICHIGAN

INDEX

223-5-15C-1234

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

File B-7
Chg. 1208
Rec'd.
Fin'd. 12-10-35
By E. M. Adams

Subject THE COMPARATIVE TOXICITIES OF
AND SOME PHENYL PHOSPHATES

To S. L. Bass, Organic Lab.
C. E. Rice, First Aid

From Biochemical Laboratory

We examined the following materials:

1.
2.
3. Diphenyl mono (p-tertiarybutylphenyl) phosphate.
4. Monophenyl di (p-tertiarybutylphenyl) phosphate.
5. Diphenyl mono-o-xenyl phosphate. 17.12-9
6. Monophenyl di-o-xenyl phosphate. 17.12-10

SUMMARY:

Acute Oral Tests

None of the materials are very toxic, but the phenyl phosphates are much less toxic than the chlordiphenyls.

Material	MLD gm/kilo	Toxicity Index
	 2	14.5
	 2	14.9
Diphenyl mono(p-tertiary-butylphenyl) phosphate.....>5		___
Monophenyl di)p-tertiary-butylphenyl) phosphate.....>5		___
Diphenyl mono-o-xenyl phosphate .....>5		___
Monophenyl di-o-xenyl phosphate .....>5		___

Chronic Oral Tests

The chronic oral experiments might indicate that the diphenyl mono(p-tertiarybutylphenyl) phosphate are more hazardous than was apparent from the acute oral experiments. Given in small repeated doses, less material was required to kill than when given in single doses.

Topical Tests

The following materials produced a definite irritation on rabbit skin:

Diphenyl mono(p-tertiarybutylphenyl) phosphate. These might be skin hazards. In raboits a resistance is acquired, since during continued topical applications, the irritation disappeared.

EXPERIMENTAL PROCEDURE:

For oral administration, weighed amounts of the materials were emulsified in 5% gum acacia solution and given by means of a stomach tube. In the chronic oral experiments, we gave 0.1 gm. per kilo of body weight.

In the topical experiments, roughly measured amounts of the materials were measured out on the shaved abdomen and rubbed with a glass applicator for a given length of time. The time was two minutes in the case of the rabbits, and five in the case of the cavies.

The topical experiments are necessarily complicated by the fact that there was considerable ingestion, since no attempts were made to prevent the animals' licking themselves. However, this should not necessarily prevent our seeing any local effect upon the skin.

EH

3

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

Subject ACUTE ORAL TOXICITY FOR RABBITS

File
Chg.
Rec'd.
Fin'd 12-10-35
By E. M. Adams

To

From

Diphenyl mono(p-tertiary butyl phenyl) phosphate:

Rabbit #231 received 5.0 gm. per kilo of diphenyl-mono(p-tertiary butylphenyl) phosphate orally. After four days he was killed for examination, at this time showing some reaction. The liver showed a heavy fatty infiltration with a moderate degeneration.

Rabbit #278

received 5.0 gm. per kilo of diphenyl-mono(p-tertiary butylphenyl) phosphate. He was killed for examination after sixteen days, having shown no apparent reactions and having gained 200 gms. in weight. Microscopic examination:

Liver: Severe hydropic degeneration.
Kidney: Degeneration of tubules and congestion.
Stomach: Marked necrosis.

Rabbit #2-11

received 2.0 gm. per kilo of diphenyl-mono(p-tertiarybutylphenyl) phosphate. On the fifth day he was killed for examination. He had shown no reaction and all the organs appeared to be normal.

Microscopic examination:

Liver: Moderate hydropic degeneration.
Kidney: Some swelling.
Stomach: Normal.
Lung: Moderate congestion.

Monophenyl di(p-tertiarybutylphenyl) phosphate:

Rabbit #189

received orally 5.0 gm. per kilo of monophenyl di(p-tertiarybutylphenyl) phosphate. After four days he was killed for examination, having shown no apparent reaction. Microscopically, one found a slight hydropic degeneration in the liver.

Rabbit #271

received 5.0 gm. per kilo of monophenyl di(p-tertiarybutylphenyl) phosphate. After seventeen days, having shown no reaction, he was killed for examination. Nothing appeared abnormal macroscopically.

Microscopic examination:

Liver: Hydropic degeneration.
Kidney: Cloudy swelling.
Stomach: Normal.
Lung: Moderate congestion.

Rabbit #2-10

received 2.0 gm. per kilo of monophenyl di(p-tertiarybutylphenyl) phosphate. After five days he was killed for examination, having shown no reaction. The organs appeared normal.

Microscopic examination:

Liver: Some fatty infiltration and degeneration.
Kidney: Some cloudy swelling.
Stomach: Seems normal.
Lung: Moderate congestion.

Diphenyl mono-o-xenyl phosphate.

Rabbit #210

received 5.0 gm. per kilo of diphenyl mono-o-xenyl phosphate. Having shown no apparent reactions, he was killed on the fourth day. The liver was dark and engorged; otherwise he seemed normal. Microscopically, the liver showed, possibly, a slight hydropic degeneration.

Rabbit #272

received 5.0 gm. per kilo of diphenyl-mono-o-xenyl phosphate orally. He was killed after seventeen days. He had shown no reactions, and macroscopically, all the organs seemed normal.

Microscopic examination:

Liver: Rather severe hydropic degeneration.
Kidney: Moderate cloudy swelling.
Stomach: Necrosis seen in part of section.
Lung: Moderate congestion.

Rabbit #2-14

received 2.0 gm. per kilo of diphenyl mono-o-xenyl phosphate. He was killed on the fifth day.

Microscopic examination:

Liver: Normal.
Kidney: A possible swelling.
Stomach: Normal.

Monophenyl di-o-xenyl phosphate:

Rabbit #212

received orally 5.0 gm. per kilo of monophenyl di-o-xenyl phosphate. He showed no reaction during three days, after which he was killed for examination. All the organs seemed normal. Microscopically, the liver showed a severe, general hydropic degeneration.

Rabbit #274

received 5.0 gm. per kilo of monophenyl di-o-xenyl phosphate. For sixteen days he showed no reaction and gained about 250 gms. of weight. When killed for examination, he appeared quite normal.

Microscopic examination:

Liver: Normal.
Kidney: Normal.
Stomach: Normal.
Lung: Moderate congestion.

Rabbit #2-13 received 2.0 gm. per kilo of monophenyl di-o-xenyl phosphate. He was killed for examination after five days. Microscopically, all the organs appeared normal.

Microscopic examination:

Liver: Normal
Kidney: Not much change.
Stomach: Normal.
Lung: Moderate congestion.

CONCLUSIONS:

1. Acute Oral Toxicity.

Material	MLD gm/kg	Toxicity Index
.....	2	14.5
.....	2	14.9
Diphenyl mono(p-tertiarybutyl-phenyl) phosphate.....	>5	----
Monophenyl di(p-tertiarybutyl-phenyl) phosphate.....	>5	----
Diphenyl mono-o-xenyl phosphate..	>5	----
Monophenyl di-o-xenyl phosphate..	>5	----

The oral M.L.D. for rabbits of the and the is approximately 2.0 gm. per kilo of body weight. The oral M.L.D. of the four is well above 5.0 gm. per kilo; this amount produced no apparent symptoms. None of the materials would seem very toxic, but the phenylphosphates are much less toxic than the chlordiphenyls.

2. Microscopic examination:

The phenylphosphates in doses of 2.0 gm. per kilo of body weight produced some changes in the tissues, but they were not at all severe. In doses of 5.0 gm. per kilo, they produced definite toxic changes, particularly the diphenyl mono(p-tertiarybutylphenyl) phosphate. Their toxic action, however, was not severe enough to produce any visible symptoms in the animals. We are not certain of the significance of the hydropic degeneration seen in many of the livers. However, it does not seem to indicate changes of much significance.

MH

223-5-15C-1234

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

Subject CHRONIC ORAL TOXICITY

File
Chg.
Rec'd.
Fin'd. 12-10-35
By E. M. Adams

To

From

Diphenyl mono(p-tertiarybutylphenyl) phosphate.

Rabbit #243 received the diphenyl mono(p-tertiary-butylphenyl) phosphate nineteen times during twenty-six days. He died; his weight had changed only about one hundred grams. The liver was a greyish color with large yellow areas; the whole of the greater curvature of the stomach was necrotic and ruptured.

Microscopic examination:
Liver: Severe congestion. Some degeneration. Hepatitis.
Kidney: Marked congestion.
Stomach: Degeneration of the mucosa. Necrosis.
Lung: Edema. Marked congestion (terminal).

Rabbit #241 received diphenyl mono(p-tertiarybutylphenyl) phosphate six times during eight days. He died sometime during the evening of the eighth day. The liver showed large yellowish areas and the stomach had ruptured.
Microscopic examination:
Liver: Changes not severe. Congestion.
Kidney: Congestion in tubules.
Lung: Marked congestion. Hemorrhage and hyperplasia of lymphoid tissue. Alveoli collapsed.

Rabbit #287 received diphenyl mono(p-tertiarybutylphenyl) phosphate twenty-three times over a period of thirty-eight days. He received none of the material during the last nine days. He was killed for examination.
Microscopic examination:
Liver: Normal.
Kidney: Cloudy swelling. Congestion. Casts in the tubules.
Lung: Severe congestion.

Monophenyl di(p-tertiarybutylphenyl) phosphate.

Rabbit #244 received monophenyl di(p-tertiarybutylphenyl) phosphate fourteen times during nineteen days. He died on the nineteenth day, and showed a loss in weight of four hundred grams. The lungs appeared to be infected, full of pus.
Microscopic examination:
Liver: Slight congestion.
Kidney: Some cloudy swelling. Casts.
Lung: Much inflammatory exudate and fluid.
This animal undoubtedly died of the lung infection.

Rabbit #290 received monophenyl di(p-tertiarybutylphenyl) phosphate five times during eight days, when he was killed accidentally.
Microscopic examination:
Liver: Some hydropic changes.
Kidney: Congestion in the tubules.
Stomach: Moderate necrosis of the mucosa.

Rabbit #291 received monophenyl di(p-tertiarybutylphenyl) phosphate twenty-three times over a period of thirty-seven days. He was killed for examination having increased in weight from 1.4 kilo to 2.2.

Microscopic examination:
Liver: Moderate hydropic degeneration.
Kidney: Normal.
Stomach: Normal.

Diphenyl mono-o-xenyl phosphate.

Rabbit #246 received diphenyl mono-o-xenyl phosphate ten times during twelve days. He died from injuries made in attempting the stomach tube. He had shown no visible reaction.

Rabbit #289 received diphenyl mono-o-xenyl phosphate nineteen times during thirty-four days. He was killed on account of an infected jaw. For twenty-three days his weight had increased from 1.57 to 1.96 kilo. When killed it had fallen to 1.45 kilo.

Microscopic examination:
Liver: Nothing of importance.
Kidney: Cloudy swelling.
Stomach: Nothing of importance.

This experiment is complicated by the infection, probably the cause of loss in weight.

Rabbit #292 received diphenyl mono-o-xenyl phosphate twenty-four times during thirty-nine days. He was killed for examination, having increased in weight from 1.7 to 2.3 kilo.

Microscopic examination:
Liver: Moderate hydropic degeneration.
Kidney: Cloudy swelling. Casts in tubules.
Stomach: Normal.

Monophenyl di-o-xenyl phosphate.

Rabbit #281 received monophenyl di-o-xenyl phosphate thirty-two times during fifty-two days. His weight had increased from 1.15 to 2.49 kilo. He was killed for examination.

Microscopic examination:
Liver: Rather severe hydropic degeneration.
Kidney: A few casts in tubules.
Stomach: Possibly some changes in the papillae.

Rabbit #249 received monophenyl di-o-xenyl phosphate eleven times during fifteen days. He was killed accidentally.

Microscopic examination:
Liver: Normal.
Kidney: Normal.
Lung: Full of inflammatory exudate.

Rabbit #2-2 received monophenyl di-o-xenyl phosphate twenty times during thirty-seven days. He was killed on account of an infected jaw. During this time his weight had increased from 1.88 to 2.72 kilo.

Microscopic examination:
Liver: Normal.
Kidney: Cloudy swelling.
Stomach: Normal.

CONCLUSIONS:

1. Chronic Oral Toxicity. Again the proved to be more toxic than the phenyl phosphates. Of the latter, diphenyl mono(p-tertiarybutylphenyl) phosphate was definitely the most toxic, but not as much so as the . In particular, it is to be noted that rabbits were killed by the two and by diphenyl mono (p-tertiarybutylphenyl) phosphate in amounts that were definitely smaller than the single doses required to kill. They were killed by the following total amounts:

Material	Total amount in gm./kilo.
	0.9, 0.7, 0.5, 0.4
	2.2, 1.1, 1.2, 0.4 *
Diphenyl mono(p-tertiary-butylphenyl) phosphate	1.9, 0.6 *

* These animals (#234 and #241) probably died of lung infections.

This might indicate that these materials will be more hazardous than was apparent from the acute oral experiments.

3. Microscopic Examination:

Diphenyl mono(p-tertiarybutylphenyl) phosphate produced the most severe reactions of the phenyl phosphates. It was the only phenyl phosphate to kill, producing necrosis and rupture in the stomach with some degeneration and congestion in the liver. Where this ester failed to kill, the principle changes were in the kidney.

The other three phenyl phosphates,
Monophenyl di(p-tertiarybutylphenyl) phosphate,
Diphenyl mono-o-xenyl phosphate, and
Monophenyl di-o-xenyl phosphate, produced some changes indicating an intoxication. On the whole, however, the changes were not severe enough to compare at all with those produced by the first three materials. In many livers one found hydropic degeneration. We are not certain of its significance, but it does not appear to indicate a very severe reaction.

MH

14

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

Subject TOPICAL ACTION

File
Chg.
Rec'd.
Fin'd. 12-10-35
By E. M. Adams

To

From

Diphenyl mono(p-tertiarybutylphenyl) phosphate.

Rabbit #254 received sixteen topical applications of diphenyl mono(p-tertiarybutylphenyl) phosphate during twenty days, after which he was killed for examination. At first the skin showed some irritation (redness), then became "coarse".

Microscopic examination:

Liver: Very little change. Some degeneration.
Kidney: Moderate chronic nephritis.
Skin: Thinning and keratosis.

Rabbit #255 received thirty-three topical applications of diphenyl mono(p-tertiarybutylphenyl) phosphate during a period of forty-three days. He was killed for examination. The skin showed some irritation at first, but less than in the case of the chlordiphenyls. It became quite "coarse".

Microscopic examination:

Liver: Very slight fatty infiltration and degeneration.
Kidney: Slight congestion.
Skin: Definite atrophy and keratosis.

Rabbit #236 received a single topical application of diphenyl mono(p-tertiarybutylphenyl) phosphate, rubbed onto the skin for five minutes using a rubber glove. On the second day the area was quite reddened and swollen. The edema disappeared after four days. The animal received thirteen more applications during eighteen days, after which he was killed for examination.

Microscopic examination:

Liver: Severe central hydropic degeneration. Swelling.
Kidney: Normal.
Skin: Atrophy and keratosis.

Rabbit #2-36 received a single topical application of diphenyl mono(p-tertiarybutylphenyl) phosphate, rubbed onto the skin for five minutes with a glass rod. There was no visible reaction.

Monophenyl di(p-tertiarybutylphenyl) phosphate.

Rabbit #256 received fifteen topical applications of monophenyl di(p-tertiarybutyl-phenyl) phosphate during twenty days, after which he was killed for examination. On this animal the hair grew quite rapidly so that he had to be shaved several times.

Microscopic examination:

Liver: Slight hydropic degeneration.
Kidney: Moderate swelling.
Skin: Definite atrophy and slight keratosis.

Rabbit #257 received thirty-three topical applications of monophenyl di(-tertiarybutylphenyl) phosphate during a period of forty-three days. The animal appeared normal and gained eleven hundred grams in weight. The skin developed only a fine scaliness and showed no irritation.

Microscopic examination:

Liver: Normal.
Kidney: Normal.
Skin: Some atrophy and keratosis.

Rabbit #2-30 had a single application of the monophenyl di(p-tertiarybutylphenyl) phosphate, rubbed with a glass rod for five minutes. There was no reaction.

Diphenyl mono-o-xenyl phosphate.

Rabbit #258 received thirty-three topical applications of diphenyl mono-o-xenyl phosphate during a period of forty-three days, after which he was killed for examination. At first a faint reddening developed, but the principle reaction was a little scaliness. During the experiment he gained over a kilo in weight.

Microscopic examination:

Liver: Normal.
Kidney: A little cloudy swelling.
Skin: Definite atrophy and keratosis.

Rabbit #259 received fifteen applications of diphenyl mono-o-xenyl phosphate during twenty days. A little reddening developed after ten days, but the principle reaction was a scaliness. He gained over five hundred grams in weight.

Microscopic examination:

Liver: Some hydropic degeneration.
Kidney: Normal.
Skin: Some atrophy and keratosis.

Monophenyl di-o-xenyl phosphate.

Rabbit #260 received fifteen topical applications of monophenyl di-o-xenyl phosphate during twenty days after which he was killed for examination. There was no reaction except a little peeling and roughness of the skin. He gained four hundred grams in weight.

Microscopic examination:

Liver: A slight hydropic degeneration.
Kidney: A little swelling.
Skin: Some atrophy and keratosis.

Rabbit #261 received thirty-three applications of monophenyl di-o-xenyl phosphate during forty-three days. There was no apparent reaction and the animal gained twelve hundred grams in weight.

Microscopic examination:

Liver: Moderate hydropic degeneration.
Kidney: Moderate cloudy swelling.
Skin: Marked atrophy.

CONCLUSIONS:

1. Acute Test: At the beginning of the experiments, two animals (#235 and 236) showed marked skin reactions to single treatments with diphenyl mono (p-tertiarybutylphenyl) phosphate. It was impossible to repeat them later, and no such reactions appeared in the chronic experiments. It is impossible to explain these severe reactions.

2. Chronic Tests:

Skin: Macroscopically, there were no marked differences among the six materials in their action on the skin. All produced a scaling or peeling of the outer, keratin layer of the skin. The and the diphenyl mono (p-tertiarybutylphenyl) phosphate produced a small but definite irritation (redness) at the beginning of the experiments. This disappeared after several treatments. Diphenyl mono-o-xenyl phosphate produced this irritation to a very faint degree. This irritation might indicate a possible skin hazard. Microscopically, it was impossible to distinguish any of the materials, all showing atrophy and keratosis.

Other tissues: The kidney and liver showed changes due to intoxication. Since the animals obtained considerable material in licking their abdomens after treatment, it is probable that these changes were produced by oral ingestion and not by absorption through the skin. The most significant changes occured in the cases of the and diphenyl mono (p-tertiarybutylphenyl) phosphate.

WH

Biochemical Laboratory
THE DOW CHEMICAL COMPANY

Subject TOPICAL EXPERIMENTS ON CAVIES

File
Chg.
Rec'd.
Fin'd. 12-10-35
By E. M. Adams

To **From**

Diphenyl mono(p-tertiarybutylphenyl) phosphate.

Cavie #B7-311-3 died after twenty-two applications of diphenyl mono(p-tertiarybutylphenyl) phosphate, made during the course of twenty-nine days. He lost one hundred and forty grams in weight, but showed no particular skin reaction.

Cavie #B7-303-2 was killed for examination after five applications with diphenyl mono(p-tertiarybutylphenyl) phosphate. The skin had no apparent reaction.

Microscopic examination:

Liver: Nothing much.
Kidney: Severe congestion. Some swelling and material in the tubules.
Skin: Some atrophy and keratosis.

Monophenyl di(p-tertiarybutylphenyl) phosphate.

Cavie #B7-165-2 was killed for examination after receiving five applications of monophenyl di(p-tertiary-butylphenyl) phosphate, made during seven days. There had been no apparent reaction.

Microscopic examination:

Liver: Slight congestion.
Kidney: Slight congestion.
Skin: Possibly a little atrophy.

Cavie #B7-323-3 died after receiving fourteen applications of monophenyl di(p-tertiarybutylphenyl) phosphate during the course of nineteen days. The animal lost one hundred and ten grams in weight, but showed no significant skin changes.

Microscopic examination:

Liver: Moderate congestion. Possibly slight fatty changes.
Kidney: Severe congestion and swelling.
Skin: No section. Lost!

Diphenyl mono-o-xenyl phosphate.

Cavie #B7-301-2 was killed for examination after receiving five applications of diphenyl mono-o-xenyl phosphate during six days. There was no apparent change in the skin.

Microscopic examination:

Liver: Some hydropic change.
Kidney: Normal.
Skin: Slight atrophy and keratosis.

Cavie #B7-344-3 died after receiving sixteen applications of diphenyl mono-o-xenyl phosphate during twenty-two days. His weight has decreased from three hundred and twenty to one hundred and ninety-eight grams. The skin showed no significant change.

Microscopic examination:

Liver: Congestion.
Kidney: Congestion.
Lung: Congestion. Inflammatory exudate. Collapsed alveoli.
Skin: Some atrophy and keratosis. This animal seems to have died of a pulmonary infection.

Monophenyl di-o-xenyl phosphate.

Cavie #B7-258-2 was killed for examination after receiving five applications of monophenyl di-o-xenyl phosphate in eight days. There was no apparent skin change.

Microscopic examination:

Liver: Slight congestion.
Kidney: Moderate congestion.
Skin: Some atrophy and keratosis.

Cavie #B7-245-3 died after receiving fourteen applications of monophenyl di-o-xenyl phosphate during nineteen days. There were no significant skin changes.

Microscopic examination:

Liver: Slight congestion.
Kidney: Marked cloudy swelling.
Skin: Lost!

CONCLUSIONS:

1. Action on the skin. All the materials tended to produce the keratosis and atrophy of the skin. We noticed no particularly significant reactions with any of the materials. Cavies do not appear as suitable as rabbits for examining the topical effects of substances.

2. Other actions. The materials examined are apparently more toxic for cavies than for rabbits, since, with one exception, they killed the cavies during the topical treatments. In this one exceptional case, where death was apparently due to a lung infection, there is no reason to expect a lesser toxicity. Since the animals licked considerable amounts of the materials off of themselves, we must assume that the fatal amounts were obtained by oral ingestion and not by absorption through the skin.

MH

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