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March 1st 1939

I hereby recommend that the thesis prepared under my supervision by WILHELM DEICHMANN-GRUEBLER *entitled* "On the Toxic Effects Upon Rabbits of Pentachlorphenol and Sodium Pentachlorphenate".

be accepted as fulfilling this part of the requirements for the degree of Doctor of Philosophy.

Approved by:

Robert A. Kehoe

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TOXIC EFFECTS UPON RABBITS OF PENTACHLORPHENOL AND SODIUM PENTACHLORPHENATE

BY

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TOXIC EFFECTS UPON RABBITS OF PENTACHLORPHENOL AND SODIUM PENTACHLORPHENATE*

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PENTACHLORPHENOL has come to have commercial importance as an agent for the preservation of wood and wood products (1). The wood is dipped for varying periods of time into solutions of pentachlorphenol in one or more solvents which cause the pentachlorphenol to spread and to penetrate. Since the manual handling of the treated lumber cannot be avoided completely, use of the product presents opportunities for injury to the skin as well as for absorption through the skin. For this reason, in our study of the toxicity of pentachlorphenol and its sodium salt, special attention was given to the effects resulting from the cutaneous application of these materials. For purposes of comparison a few observations were made on the sodium salt of tetrachlorphenol. Compounds of a high degree of purity were employed. Effects of the same type were obtained through the use of the corresponding commercial product, with only such slight quantitative differences as arose from the lesser degree of purity of the material.

THE TOXICITY OF PENTACHLORPHENOL

Single Cutaneous Applications

Healthy albino rabbits, both male and female, approximately 4 months of age and weighing from 2 to 3 kg were employed. Single doses of pentachlorphenol in a variety of solvents, ranging in volume from 2 to 12 cc, were applied to the abdominal skin, clipped free of hair in such a manner as to avoid injury to the skin. Each animal was kept under mild but effective restraint on an animal board to prevent his ingesting the solution by licking the skin, and to avoid loss through contact with other objects. In the early experiments, the animals were restrained for $4\frac{1}{3}$ hours, after which the skin was carefully cleaned by the repeated use of the solvent to remove unabsorbed pentachlorphenol. For a variety of reasons this practice was discontinued in favor of a 2 hour period of restraint after which the animals were returned to their cages without any cleansing of the skin. Table 1 gives certain data from experiments in which olive oil, corn oil, pine oil, ethyl alcohol, and a number of petroleum products were used as solvents.

A sublethal dose produced an increase in the respiratory and cardiac rates, these signs becoming apparent about 50 to 70 minutes after cutaneous application. During the period on the animal board, there was a drop in the rectal temperature of the animals to a range between 101°F to 103°F. After release, their temperatures rose

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quickly to the pre-experimental level and higher. The highest temperature observed in surviving animals was 107°F. Fatal effects were associated with higher temperatures, which in individual cases rose as high as 114°F. The fever ran almost parallel with the blood sugar concentration. Table 2 gives typical examples of blood sugar values and fever produced in cutaneously treated rabbits. Together with these signs the animals usually showed some diuresis and increased peristalsis (defecation) during the second, third and sometimes the fourth hour after treatment. The total volume of urine excreted during the first 24 hours was reduced considerably, however, in

TABLE 1

SUMMARY OF THE EFFECTS UPON RABBITS OF THE CUTANEOUS APPLICATION OF SINGLE DOSES OF PENTACHLORPHENOL IN DIFFERENT SOLVENTS

NUMBER OF ANIMALS	SOLUTION	DOSE OF PENTACHLORPHENOL IN RELATION TO EFFECT PRODUCED				INTERVAL BEFORE DEATH
		No apparent ill effects	Acute illness with prompt recovery	Acute illness, local damage, recovery in 2 to 6 weeks	Death	
		mg/kg	*mg/kg*	*mg/kg*	*mg/kg*	*hrs.*
8	5% in olive oil	70, 90, 110, 130, 150, 150, 150, 180				
3	5% in 95% ethyl alcohol	110, 130, 150				
1	10% in 95% " "			1111*		
1	10% in absolute ethyl alcohol	309*				
6	11% in olive oil	200, 250, 350, 450, 450			350	12
1	10% in corn oil	326†				
8	5% in Stanolex fuel oil, no. 1		40, 50, 50		60, 70, 70, 80, 130	1½ to 4
7	5% in Shell Dione oil		70, 80, 90, 100		110, 120, 130	5 to 6½
13	5% in Standard oil (Ind.) pale paraffin oil		60, 70, 80, 90, 100	110, 120, 130, 140, 150, 150, 150		
6	5% in Stanolex furnace oil		70, 80		90, 100, 110, 130	1½ to 3
8	5% in Shell #3 fuel oil			50, 70, 90, 110, 120, 170	130, 150	6
3	1.8% in pine oil			26†	39† 51†	9 to 22

* Applied in repeated small doses over period of 4½ hours, after which skin was cleansed.
† Applied in single dose for period of 4½ hours, after which skin was cleansed.

some instances by so much as one half. During this period the male rabbits excreted glucose, from traces to small amounts, while the females excreted both glucose and lactose. In a few isolated cases, the excretion of sugar persisted until the end of the second day. No protein, bile or red blood cells appeared in the urine. During the day following cutaneous application, the animals showed lack of appetite and a consequent loss of weight. Some rabbits recovered promptly from these acute signs, others continued to lose weight for some time, eventually recovering. Death occurred only during the acute stage of intoxication.

None of the 5 animals that received respectively 200, 250, 350, and 450 mg per kg of body weight, dissolved in olive oil (11% solution), showed more than a slight and temporary increase in the rate of respiration. Rabbit D166, given 350 mg per kg of weight in olive oil, was the only animal of this group that showed signs of pronounced toxemia, followed by death.

The cutaneous application of 326 mg of pentachlorphenol per kg of weight, when dissolved in corn oil (10% solution) produced no illness. Treatment with pentachlorphenol in 95% ethyl alcohol (15% solution) in dosages up to 150 mg per kg, caused no signs of discomfort other than a slight drop in weight during the 24 hours following the application. A dose of 1111 mg per kg applied in successive small doses aggregating 36 cc of a 10% solution, over a period of

TABLE 2

BLOOD SUGAR VALUES AND RECTAL TEMPERATURES OF RABBITS BEFORE AND AFTER CUTANEOUS APPLICATION OF PENTACHLORPHENOL

			BEFORE APPLICATION OF DOSE	HOURS AFTER APPLICATION OF DOSE							FATE
				1	2	3	4	5	6	20	
Rabbit D 42	50 mgm/kg pentachlorphenol in Stanolex fuel oil no. 1	Rectal temp. Blood sugar, mg%	103.4°F 128	101° 130	103.1° 176	105° 218	105° 196	103.1° 157	103.1° 146	103.2° 130	Survived
Rabbit D 35	70 mgm/kg same	Rectal temp. Blood sugar, mg%	103°F 126	100° 134	103.5° 196	106.1° 264	110.5° 346				Died 4 hrs. after treatment
Rabbit D 166	350 mgm/kg pentachlorphenol in olive oil	Rectal temp.	102.7°F	99.7°	99.7°	103.6°	104°	104.8°	105°		Died 12 hrs. after treatment
Rabbit D 170	" "	" "	103.4°F	100°	100.4°	100.4°	103.2°	104.1°	104°		Survived
Rabbit D 167	450 mgm/kg same	" "	104.2°F	99.7°	99.5°	103.5°	103.6°	103.8°	103.6°		"
Rabbit D 171	" "	" "	103°F	102°	101.8°	103°	103.8°	103.8°	103.8°		"

4⅓ hours, caused damage to the skin but no illness; 26 mg per kg dissolved in pine oil (1.8% solution) and applied to the skin, produced illness and loss of weight; doses of the same solution in the amounts of 39 and 51 mg per kg produced death after 9 and 22 hours, respectively.

The signs observed in rabbits after treatment with a lethal dose were those of pronounced toxemia. The onset of fever, increase in respiratory and cardiac rates, diuresis, hyperperistalsis, hyperglycemia and glycosuria became apparent, in some instances, as early as 20 minutes after the application, but these signs progressed much more rapidly when the rabbits had been freed from the animal board. A complete loss of muscle tone became apparent from 30 to 10 minutes before death, and the animals died in a state of complete collapse. In a few cases asphyxial convulsive movements were observed. The lowest and the highest rectal temperatures observed in dying animals were 104.4 and 114°F. Most of the animals died with a fever of 107 or 108°F. It is of interest to note that, with the exception of those treated with pentachlorphenol dissolved in pine oil, no animals died later than 6½ hours after the treatment.

The results obtained from the application of pentachlorphenol to the skin depended to a great extent on the vehicle employed. The mechanisms responsible for the differences in the rate of absorption of the material out of the various solvents are not apparent. The specific gravity of certain solvents, together with their ability to dissolve pentachlorphenol, is shown in table 3. It is evident that there is no parallelism between these properties and their effectiveness as vehicles for the absorption of pentachlorphenol.

The local action on skin and hair was most pronounced with the petroleum solvents, and, among these, was greatest in the case of those mixtures which were least toxic to the organism as a whole. Pentachlorphenol in Standard Oil (Indiana), Paraffin Oil or Shell No. 3 Fuel Oil caused a more or less pronounced edema of the skin, which, about a week later, became dry and wrinkled. Slight cracks developed and the hair was lost completely on some portions of the treated area. Recovery in the most severe

TABLE 3

SPECIFIC GRAVITY AND COMPARATIVE EFFECTIVENESS OF CERTAIN LIQUIDS AS SOLVENTS FOR PENTACHLORPHENOL

SOLVENT	APPROXIMATE WEIGHT-VOLUME SOLUBILITY OF PENTACHLORPHENOL IN SOLVENT AT 25°C	SPECIFIC GRAVITY OF SOLVENT
	%	
Mineral oil	4	0.876 (25°C)
Stanolex furnace oil	5	0.840 (16°C)*
Stanolex fuel oil no. 1	5	0.837 (16°C)*
Shell Dione oil	6	0.898 (16°C)*
Standard oil (Ind.) paraffin oil	5	0.876 (16°C)*
Shell no. 3 fuel oil	5	0.845 (16°C)*
Olive oil	11	0.905 (25°C)
Rabbit fat	17	0.908 (25°C)
Corn oil	30	0.936 (25°C)
Pine oil	34	0.926 (25°C)

* Acknowledgment is made of the receipt of these data from H. K. Nason of Monsanto Chemical Company.

cases was complete in 6 weeks, as judged by the weight curve, complete healing of the skin, and an even growth of new hair. Apparently the deeper structures of the skin and the hair follicles suffered no injury. Ointments were not employed to hasten healing. Pentachlorphenol in Stanolex Furnace Oil, Stanolex Fuel Oil No. 1, and Shell Dione Oil, produced these local changes to a milder degree, while in olive oil and corn oil, it had little or no harmful local effect.

Repeated Cutaneous Applications

Daily doses of 10 cc of a 1% solution of pentachlorphenol in mineral oil (41 mg and 42 mg per kg respectively) were applied to the skin of 2 rabbits. At the end of 4 hours the excess material was wiped off with cotton and, without further washing, the animals were returned to their cages. Both rabbits survived 21 successive daily treatments, without illness, loss of weight or injury to the skin.

Preliminary experiments with low concentrations of pentachlorphenol in other solvents, designed to reveal any chronic systemic effects due to cutaneous absorption of repeated sublethal doses, were inconclusive in that the summation of sublethal doses in several successive days produced characteristic acute manifestations, while injury to the skin produced by the repetition of smaller doses prevented prolonged experimentation. Other experiments carried out in such a manner as to avoid these difficulties have been in progress for some months but are incomplete at this time. It appears, however, from present evidence, that no chronic systemic disease is associated with the repetition of sublethal doses. The local effects of repeated skin applications were of the same type as those induced by a single dose, but were more extensive and slower in healing. Recovery, however, was no less complete, there being no apparent residual damage.

Oral Administration

Rabbits received doses ranging from 70 to 140 mg per kg in the form of an 11% solution of pentachlorphenol in olive oil, administered by means of a stomach tube. The animals had been supplied with food and water up to the time of the experiment. Doses of 70, 80 and 120 mg per kg respectively administered to 3 rabbits, produced acute illness with prompt recovery. Three other animals given 100, 130 and 140 mg per kg, respectively, died from 10.5 to 16 hours after the treatment. They showed an increased rate of respiration, fever, diuresis and increased peristalsis. Their rectal temperatures rose slowly, indicating that the absorption of pentachlorphenol from the gastro-intestinal tract was slow.

Subcutaneous Injections

Various amounts of a 5% solution of pentachlorphenol in olive oil were injected into rabbits subcutaneously. Absorption of the injected material was slow, and often in fatal poisoning the greater part of the dose was found apparently unchanged at the site of injection. In animals that survived, about 2 weeks were required for the disappearance of the local mass. The symptoms observed were the same as those previously described. The time of their onset varied with the dose. A subcutaneous injection of 60 mg per

kg failed to kill one rabbit while 110 mg per kg killed all 5 animals injected with this dose. Table 4 gives the results of these observations.

TABLE 4

THE RESULTS OF THE SUBCUTANEOUS ADMINISTRATION TO RABBITS OF A SOLUTION OF PENTACHLORPHENOL IN OLIVE OIL

NUMBER OF ANIMALS	DOSE OF PENTACHLORPHENOL	DEATHS		TIME TILL DEATH
		Number	Per cent	
	mg/kg			*hours*
1	50		0	
1	60		0	
4	70	1	25	3½
4	80		0	
4	85	1	25	6½
4	90	2	50	7, 12
6	100	5	83	2, 3, 3, 4, 8
5	110	5	100	3, 3½, 4, 4, 5

The Effect Upon the Blood Pressure and the Respiration

The effects of pentachlorphenol on the blood pressure and respiration were studied in 4 rabbits. The results were practically identical. The animals were anesthetized by the intraperitoneal injection of sodium barbital and arrangements were made for recording the blood pressure in the carotid artery and the respiration in the trachea. A lethal dose of pentachlorphenol dissolved in Stanolex Fuel Oil No. 1 was then applied to the skin of the abdomen.

An increase in both the rate and amplitude of the respiration occurred (fig. 1), reaching the maximum in about 43 minutes (fig. 2). The blood pressure, which had remained very nearly constant up to this time, now began to increase, and during the following 6 minutes rose from the normal of 112 to 138 mm Hg; then a gradual but persistent fall ensued, the death of the animal taking place 15 minutes later. Respiration remained quite adequate until the blood pressure dropped to 40 mm Hg. Death was due, therefore, to circulatory failure, a conclusion which is confirmed by the gross pathological picture of fatal poisoning.

The Effect of Starvation on the Action of Pentachlorphenol

The relationship between the height of the fever and the severity of the intoxication in rabbits treated with pentachlorphenol gave rise to considerable speculation as to the mechanisms involved. The high solubility of pentachlorphenol in fats suggested the possibility of central-nervous-system injury or irritation as the explanation. On the other hand if death resulted in part from hyperpyrexia, any measure which would decrease heat production should reduce the incidence of fatalities among the animals. With this possibility in mind, three groups of rabbits were starved, one group for 60 hours, the other two for 7 days, both food and water being withheld from one group, food alone from the others. Along with control animals which had been unrestricted with respect to food and water, they were then given pentachlorphenol. Rectal temperatures and blood sugar concentrations were followed hourly in most of the animals.

The observations are summarized in table 5. Here it may be noted that among the cutaneously treated animals, the five that had been starved survived, while all 6 controls (given

the same dose per kg) died. Of the 8 starved rabbits treated subcutaneously, six survived, while all 5 control animals died. Although these results do not justify definite conclusions, they suggest that the hyperpyrexia, *per se*, may be an important lethal factor.

salt of pentachlorphenol, applied to the abdominal skin (clipped free of hair), in 5 cc quantities from time to time over a period of 4 hours. Rabbit P5 received 8 doses of 2% solution (in terms of pentachlorphenol), equivalent to 257 mg per kg, while Rabbit P1 received 12 doses of 3% solution,

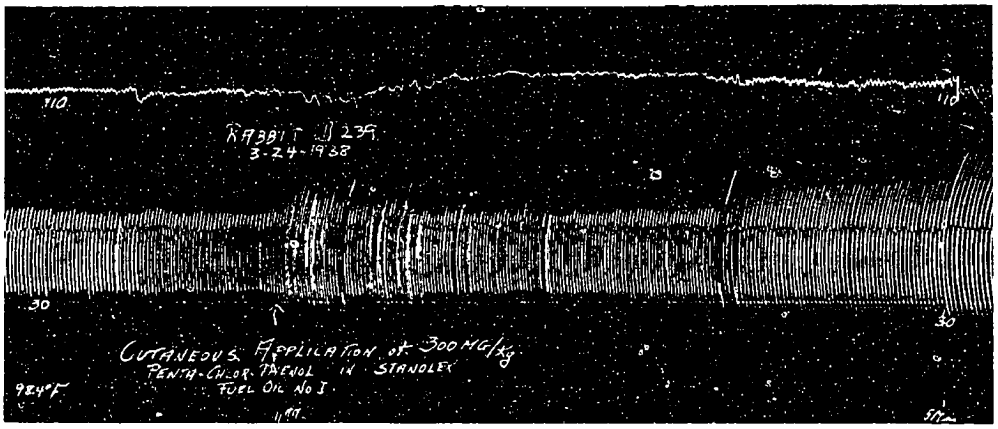

FIG. 1. The effect of pentachlorphenol on the blood pressure and respiration of the rabbit. The upper tracing represents the blood pressure in mm Hg, while the lower shows respiration, the time being shown in 1-min. intervals on the bottom line.

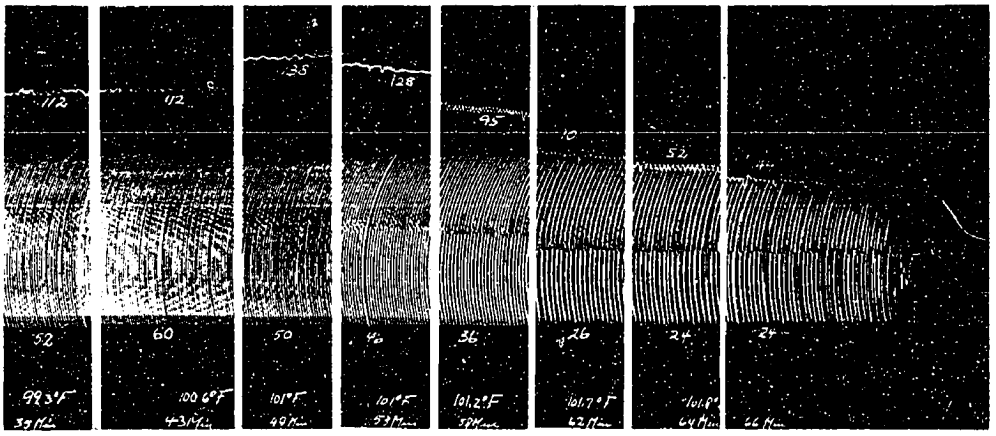

FIG. 2. The entire tracing (a continuation of that in fig. 1) is illustrated by representative sections.

THE TOXICITY OF SODIUM PENTACHLORPHENATE

Single Cutaneous Applications

Two rabbits were treated with a dilute aqueous solution of the sodium

equivalent to 613 mg per kg. Twenty minutes after the administration of the last dose ($4\frac{1}{3}$ hours after the first) the unabsorbed material was removed from the skin with an excess of distilled water and the animals were released

for observation. The 2 animals died in 2½ and 2¼ hours, respectively, after the administration of the last dose.

Similarly, the guinea pigs received 266 and 274 mg respectively, per kg, in the form of 8.5 cc of a 2% solution, applied to the skin in a series of small doses over a period of 90 minutes. The two animals died in 1 and 1⅙ hours, respectively, after the last dose. One had a terminal temperature of 108°F.

Repeated Cutaneous Applications

Rabbit P10 was given 32 daily doses of 63 mg per kg in 10 cc of 2% aqueous solution applied over a period of 4⅓ hours. At no time did this animal show illness or injury to the skin.

TABLE 5

EFFECT OF PRELIMINARY STARVATION OF RABBITS ON FATAL DOSAGE OF PENTACHLORPHENOL

TREATMENT OF ANIMALS		HIGHEST RECTAL TEMP.	HIGHEST BLOOD SUGAR	FATE	
				Survived	Died, hrs. after treatment
		°F.	mg %		hrs.
Starved for 60 hours	Pentachlorphenol in Stanolex fuel oil no. 1 applied cutaneously 70 mg/kg	105.2	284	*	
Starved " " "		105.8	210	*	
Control, not starved		110			3
Control " "		110.6	346		4
Control " "		108.4	276		4
Starved for 7 days	" "	105	210	*	
Starved " " "		105.6		*	
Starved " " "		104	230	*	
Control, not starved		107			3
Control " "		110.5	346		4
Control " "		110	284		3
Starved for 7 days, no water	Pentachlorphenol in olive oil injected subcutaneously 110 mg/kg	105.1		*	
" " " " " "		104.6		*	
" " " " " "		104.1		*	
" " " " " "		108.4			1
" " " " " "		106.8		*	
" " " " " "		105.6		*	
" " " " " "		104.9		*	
" " " " " "		108.2			4
Control, not starved		111.2			3
Control " "		112.5			5
Control " "		112.5			4
Control " "		111.2			4
Control " "		110.4			3

Rabbit P37 received two daily treatments of 113 mg per kg in 15 cc of a 2% aqueous solution applied in 3 doses at 30 minute intervals. This animal died 4 hours after the second daily treatment, with all the previously de-

scribed signs of acute intoxication. Rabbit P38 died with an acute intoxication after the thirteenth application of 111 mg per kg. (After 6 successive daily doses, the treatment of this animal was interrupted for 15 days to allow healing of the skin, and after 4 further daily applications it was discontinued for another 15 days. After 3 additional daily doses the animal became acutely ill, and died with a temperature of 108.4°F.) Guinea pig P10 survived 53 daily doses of 30 mg per kg applied in the form of 1 cc of a 2% aqueous solution, suffering only slight desquamation of the skin. Guinea pigs P9 and P8 died 1½ and 4 hours, respectively, after the second daily application of doses of 65 and 73 mg, respectively, per kg of body weight. Their rectal temperatures rose to 107.5°F.

TABLE 6

EFFECTS OF ORAL ADMINISTRATION TO RABBITS OF SINGLE DOSES OF SODIUM PENTACHLORPHENATE IN AQUEOUS SOLUTION

	WEIGHT	DOSAGE EXPRESSED AS PENTACHLORPHENOL	MG/KG	FATE	REMARKS
	gm				
Rabbit P #22...	2,086	10.0 cc of 1% in 1% NaCl	48	Survived	Slight loss of weight
" P #27...	2,170	10.0 cc " 2% " " "	92	"	Ill for short time
" P #28...	2,329	20.0 cc " " " " "	172	"	Slight loss of weight. Temperature 105.8°
" P #32...	2,686	25.0 cc " " " " "	186	"	Rapid respiration several days
" P #33...	2,753	30.0 cc " " " " "	218	Died in 3¾ hours	Temperature 110.0°F
" P #29...	2,340	30.0 cc " " " " "	256	Died in 6 hours	Temperature 109.0°F

Single Oral Administrations

Doses of sodium pentachlorphenate ranging from 48 to 256 mg per kg (expressed as pentachlorphenol) were administered to 6 rabbits by means of a stomach tube. The compound was dissolved in 1% NaCl in such concentrations that the total volume administered to an animal did not exceed 30 cc. Doses up to and including 186 mg per kg caused an increase in the respiratory rate and a slight loss of weight. Doses of 218 and 256 mg per kg killed 2 animals in 3¾ and 6 hours, respectively. The rectal temperatures of these animals rose to 110 and 109°F (table 6.)

Intravenous Administration

The only available data on the toxicity of sodium pentachlorphenate administered intravenously are those of Bechhold and Ehrlich (2) who give the minimal lethal dose for white mice as 56 mg per kg. It seemed desirable to check and extend these observations.

Solutions of 1 and 2% of sodium pentachlorphenate in distilled water and in 1% aqueous NaCl were injected slowly into 9 rabbits by way of an ear vein.

The injection of 20 and 23 mg per

kg (expressed in terms of pentachlorphenol) in aqueous solution, and 34 and 38 mg per kg in saline solution induced acute illness (temperatures up to 107°F.) but the animals survived. Doses of 22, 33 and 36 mg per kg dissolved in water and 42 mg per kg in NaCl caused increased respiration, urination, defecation, and death in collapse after periods ranging from 1½ to 4 hours from the time of injection. The rectal temperature of one of these animals rose to 111.5°F. The data are given in table 7.

TABLE 7

EFFECTS OF INTRAVENOUS ADMINISTRATION TO RABBITS OF SODIUM PENTACHLORPHENATE IN AQUEOUS SOLUTION

	WEIGHT	DOSAGE EXPRESSED AS PENTACHLORPHENOL	MG/KG	FATE	TEMPERATURE
	gm				*°F*
Rabbit P #17.....	4,447	4.5 cc of 2% in H_2O	20	Survived	106.0
" P #18.....	3,550	8.0 cc of 1% " "	23	"	104.6
" P #23.....	2,336	7.8 cc of 1% in 1% NaCl	34	"	106.0
" P #24.....	2,392	8.2 cc of 1% " " "	34	"	106.8
" P #21.....	2,009	7.5 cc of 1% " " "	38	"	107.0
" P #26.....	2,367	8.5 cc of 1% in H_2O	36	Died in 2 hrs.	107.0
" P #25.....	2,134	4.5 cc of 2% in 1% NaCl	42	Died in 1½ hrs.	111.5
" P #19.....	4,592	10.0 cc of 1% in H_2O	22	Died in 4 hrs.	105.6
" P #16.....	3,057	5.0 cc of 2% " "	33	Died in 2⅓ hrs.	111.2

THE TOXICITY OF SODIUM TETRACHLORPHENATE

Fragmentary data obtained on tetrachlorphenol do not establish the toxicity of this compound, but merely indicate that the lethal dose for rabbits is more than twice that of pentachlorphenol. Rabbits survived oral administration of 160, 262, 302, 360 and 405 mg of tetrachlorphenol per kg given as sodium tetrachlorphenate in the manner previously described. One rabbit, given 529 mg per kg by similar means, died 12 hours later, showing both ante-mortem and post-mortem evidences of acute intoxication similar to those observed in the case of pentachlorphenol.

Intravenous injections of 25, 75, and 96 mg per kg, respectively, as sodium tetrachlorphenate dissolved in 1% NaCl, resulted only in fleeting respiratory changes. The largest volume injected was 14 cc. No further animals were injected.

Pathology of Pentachlorphenol Poisoning in Rabbits

Regardless of the mode of administration, the nature of the material used as a vehicle, or the chemical state in which it was employed (as free pentachlorphenol or as the sodium salt), pentachlorphenol produced a constant group of acute toxic changes in the tissues of fatally poisoned rabbits and guinea pigs.

Animals examined immediately or shortly after death showed a profound rigor, which was the more striking because its onset in some cases coincided with the last respiratory movement. Of the internal organs, the heart, blood vessels, lungs, liver, kidneys and lower genito-urinary tract displayed the most intense injury. The thymus

gland and the mediastinal fat and connective tissue were swollen, deeply congested, and often spotted with petechiae. The heart was hugely dilated, in many instances on both sides, and in every instance on the right side. The lungs, trachea and bronchi were greatly congested and edematous, with localized large and small hemorrhages and with, here and there, islands of marginal emphysema. The liver was enlarged, engorged with blood, and when not too generally edematous, was marked with the lobular picture of passive congestion. The kidneys were swollen and usually tense, varying in appearance to some degree in accordance with the varying predominance of edema, passive congestion, active hyperemia or petechial hemorrhage, in the composite picture. The urinary bladder and the urethra showed variable degrees of irritation and, in some cases, petechial hemorrhage. The mucosa of the stomach was usually passively congested and edematous.

The oral administration of pentachlorphenol usually contributed to the pathologic process by causing local injury to the stomach and by inducing an acute irritation of the intestinal tract. Subcutaneous injections caused edema at the site of injection, but little hyperemia and no hemorrhage.

The microscopic tissue changes confirmed the impression gained by the study of the gross pathology, that the injurious effects of pentachlorphenol resulted from the combination of circulatory failure with direct toxic damage within the tissues. In some instances, evidences of passive congestion of the lungs, liver, and kidneys were foremost in the microscopic picture; generally, however, acute toxic changes predominated. Of the latter, acute vascular damage was most common, as evidenced by varying degrees of swelling and sometimes proliferation of the capillary and arteriolar endothelium, capillary hemorrhage, and perivascular cellular reaction. Hemorrhage and exudation were seen regularly in the lungs, culminating in some instances in well defined lobular pneumonitis; acute toxic parenchymatous (hematogenous) hepatitis, with both albuminous and fatty degeneration of the liver cords, was superimposed on acute passive congestion; likewise, an acute nephritis, characterized by both edema and proliferation of the glomerular endothelium, as well as by edema and necrosis of the tubular epithelium, was found in association with passive congestion; the spleen showed mainly the effects of passive congestion, while the heart muscle changes were chiefly those of interstitial edema and varying degrees of cloudy swelling and necrosis of the muscle fibers, with some swelling of the capillary and arteriolar endothelium and capillary engorgement. (In two cases in which gross rupture of the spinal musculature of the dorsal region resulted from the post-mortem rigor, microscopic examination of the muscle tissue at the site of rupture revealed the presence of an acute inflammatory reaction with necrosis. These inflammatory lesions were assumed to have had no relationship to the acute toxic changes induced by pentachlorphenol.)

Summary and Discussion

1. Pentachlorphenol, as well as its sodium salt, when absorbed into the

tissues of experimental animals in sufficient quantity, produces an acute toxemia characterized by accelerated respiration, hyperpyrexia, hyperglycemia and glycosuria, and by a rapidly developing motor weakness, which in fatal cases, terminates in cardiac and muscular collapse. Rigor mortis is immediate and profound in most cases.

2. The post-mortem evidences of injury consist largely of extensive damage to the vascular system, with heart failure, and with involvement of the parenchymatous tissues in the effects both of heart failure (congestion and edema), and of injury to small blood vessels (edema and proliferation of endothelium, dilatation of arterioles and capillaries, and hemorrhage).

3. The oil-soluble pentachlorphenol, and the water-soluble sodium pentachlorphenate, when dissolved, are capable of absorption through the healthy and intact skin of rabbits and from the subcutaneous tissue.

4. The general and local effects produced by the application of solutions of pentachlorphenol to the skin of animals vary with the solvent employed as the vehicle. With due regard to duration of exposure and the area of skin involved, the minimal lethal dose of the compound for rabbits when dissolved in various materials and applied cutaneously in a single dose was as follows: 39 mg per kg in pine oil; 60 mg per kg in Stanolex Fuel Oil No. 1; 90 mg per kg in Stanolex Furnace Oil; 110 mg per kg in Shell Dione Oil; and 350 mg per kg in olive oil.

5. The smallest dose of pentachlorphenol in olive oil which resulted in the death of a rabbit when administered orally was 110 mg per kg; when injected subcutaneously, 50 mg per kg.

6. The smallest lethal dose of sodium pentachlorphenate in aqueous solution or in 1% NaCl solution, when applied to the skin was 257 mg per kg expressed in terms of free pentachlorphenol; when administered by mouth the corresponding dose was 218 mg per kg, and when given intravenously, 22 mg per kg.

7. No indication has been found that the absorption of repeated small or barely sublethal quantities of pentachlorphenol over periods of some months induces a chronic type of poisoning. Additional and more prolonged observations are required to give conclusive evidence on this point.

Experience in the commercial production and use of pentachlorphenol, up to the present, has not given rise to cases of acute intoxication among workmen. It is evident, therefore, that the actual hazards of technical operations are not so great as might be suggested by the toxicologic properties of the material. The apparent absence of injurious effects of a chronic or slowly developing type among treated animals is also reassuring. It would be surprising, however, if some degree of damage to the skin of workmen did not result from casual or accidental exposure to the dipping solutions. Because of this, precautions should be taken against unnecessary or prolonged contact with such solutions. These solutions, in practice, should not be more highly concentrated than is required for effectiveness, and the solvents should be chosen with reference to their local effects upon the skin as well as their influence upon cutaneous absorption of pentachlorphenol. Mechanical dipping and handling procedures should be used so

far as possible, and suitable protective clothing should be worn by men whose work involves frequent or regular opportunities for contact.

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