EPA No.: 68D80056
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July 15, 1991

DATA EVALUATION RECORD

PHOSPHINE

Subchronic Inhalation in Rats

APPROVED BY:

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Program Manager
Dynamac Corporation

Signature: William L McLellan

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REVIEWED BY:

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DATA EVALUATION RECORD

GUIDELINE § 82-4

STUDY TYPE: Subchronic inhalation toxicity study in rats.

MRID NUMBER: 414131-01.

TEST MATERIAL: Phosphine (PH_3).

SYNONYM(S): N/A.

STUDY NUMBER(S): 87-8030.

SPONSOR: Metal Phosphide Task Force.

TESTING FACILITY: Bio/dynamics Inc., East Millstone, NJ.

TITLE OF REPORT: A Thirteen-Week Inhalation Toxicity Study of Phosphine (PH_3) in the Rat.

AUTHOR: P.E. Newton.

REPORT ISSUED: March 2, 1990.

CONCLUSIONS:

Fischer 344 rats of both sexes were exposed to phosphine 6 hours/day, 5 days/week for 13 weeks at levels of 0, 0.3, 1.0, or 3.0 ppm. Additional groups were exposed at 0 or 10 ppm starting at week 8, and at 0 or 5 ppm starting at week 12. Recovery groups were included in the study at each dose level and sacrificed after 4 weeks of observation. In the groups exposed at levels up to 3.0 ppm, there was a transient decrease in body weight gain accompanied by decreased food consumption. Red blood cell counts, hemoglobin concentration, and hematocrit values were slightly decreased in males but not females after 13 weeks' exposure to 3.0 ppm, but these changes are of doubtful toxicologic importance. Serum urea nitrogen (BUN) was transiently increased in males exposed at 3.0 ppm (4 weeks only), but no effects were observed in these males at 13 weeks or in females at either interval. No exposure-related gross or histologic findings were observed at levels up to and including 3.0 ppm. Exposure at 10 ppm for 3 days caused 40% mortality in females but no mortality in males. Both males and females exposed at 10 ppm had coagulative necrosis in the tubules of the kidneys, and pulmonary congestion was observed in the females that died. No histologic findings related to dosing were apparent in the rats exposed for 2 weeks at 5 ppm; an increase in BUN and alkaline phosphatase was observed in males but not females exposed at 5 ppm.

A LEL for subchronic exposure was not established in this study; the effect level for acute toxicity was 10 ppm. This was not due to inadequate study design, but is the result of the sharp dose-response curve for acute toxicity.

CORE Classification: The study is considered to be CORE Minimum according to Guideline 82-4, since an effect level for subchronic exposure was not achieved.

A. MATERIALS:

1. Test Compound: Phosphine; source: AIRCO Special Gases Riverton, NJ; concentration: 1.04% average active ingredient in nitrogen; impurities--see Appendix (CBI Appendix B-17 and B-18).

2. Test Animals: Species: rat; strain: Fischer 344; age: 7 weeks at receipt and 8 weeks at exposure; mean weight: males--172 g (range 147-194 g), females--137 g (range 127-149 g); source: Charles River Breeding Laboratories, Raleigh, NC.

B. STUDY DESIGN:

1. Animal Assignment: Animals were acclimated for 2 weeks and distributed to the following groups by a random sort method so that body weight means were comparable:

Test Group	Exposure Level (ppm)	Terminal Sacrifice (M/F) (13 Weeks)[c]	Interim[a] Sacrifice (M/F) (4 Weeks)	Recovery Group[b] Sacrifice (M/F) (18 Weeks)
I	0	10/10	10/10	10/10
II	0.3	10/10	10/10	10/10
III	1.0	10/10	10/10	10/10
IV	3.0	10/10	10/10	10/10
V[c]	0	6/6	3/3	3/3
VI[c]	10	10/10	5/1[e]	5/5
VII[d]	0	6/6	3/3	3/3
VIII[d]	5	10/10	5/5	5/5

[a]This group was exposed for 4 weeks and then sacrificed.

[b]The recovery group was exposed for 13 weeks and allowed a 4-week recovery period.

[c]Groups V and VI were started on the study at day 48, and exposure was terminated after 3 days because of the death of four phosphine-exposed females. The groups were initiated since no effects were noted in the groups exposed at up to 3.0 ppm.

[d]Groups VII and VIII were initiated at 75 days, and exposure continued to day 90. Recovery groups were held for an additional 4 weeks.

[e]Four females in this group died prior to the sacrifice.

2. Inhalation Exposure Conditions: The animals were exposed in 10,000-L glass and stainless steel exposure chambers with an airflow rate of 2,010 to 2,130 L/min (2,350 L/min for control) corresponding to four to five air changes/minute. Phosphine was delivered from cylinders through stainless steel tubing to the inlet turret of the exposure chamber. The cylinders had stainless steel regulators equipped with a vent, a purge valve, and a regulatory valve. A Nupro® metering valve and digital mass flowmeter preceded the inlet turret of the exposure chamber where phosphine was mixed with a conditioned air supply. Following exposure, the chambers were flushed with room air for 30 minutes before removing the animals.

Exposure was for 6 hours/day. The chamber concentrations of phosphine in the breathing zone were analyzed by gas chromatography at four intervals during each exposure. Nominal concentration was determined by monitoring the flow of phosphine into the chamber and the flow of air through the chamber. The nominal concentration in ppm was then determined by dividing the total volume of test substance

by the product of volumetric flow rate and total exposure time and multiplying by 10^4.

Particle size distribution measurements were performed once each week with a TSI Aerodynamic Particle Sizer. The chamber temperature was continually monitored as well as relative humidity, flow rate, and negativity in the chamber. The data for temperature, relative humidity, and airflow rate were recorded every half hour during exposure.

Results: The airflow to the chambers averaged 2010 to 2350 L/min for various exposure groups, and there were 4.25 to 4.98 air changes/minute; the time to 99% clearance of the chambers of test compound were between 19.6 and 22.8 minutes.

Table 1 summarizes data on chamber monitoring. Excellent agreement was shown between the target, analytical, and nominal concentrations. Measurements of distribution in various areas of the chamber showed an even distribution with no significant gradients of concentrations. Particle size measurements showed similar particle size in all exposure groups. This indicated that no measurable test compound was present as an aerosol. Temperature and humidity levels were within an acceptable range. Mean chamber temperatures ranged between 67 and 76°F, and the mean relative humidity values ranged between 35 and 49%.

3. Statistics: The following data were analyzed: body weight, food consumption, weight changes from week 0, hematology and clinical chemistry parameters, terminal organ and body weights, and organ-to-body weight ratios. One way analysis of variance to evaluate equality of means was followed by multiple comparisons. If variances were equal using Bartlett's test, parametric procedures were used; one way ANOVA used the F distribution to assess significance, and Dunnett's test was used for pairwise comparisons. For nonparametric data, the Kruskal-Wallis test was used, and the Dunn summed rank test was used to determine which treatment groups differed from the control group. For testing trends, standard regression techniques were used in the parametric case and Jonckheere's test in the nonparametric case.

4. Quality Assurance: A signed quality assurance statement was dated January 29, 1990.

TABLE 1. Chamber Monitoring Results for Phosphine[a]

Group	Target Level (ppm)	Nominal Level (ppm)	Analyzed Level (ppm)	MMAD ± S.D. (μ)
I	0	--	0	3.0 ± 2.7
II	0.3	0.35 ± 0.05	0.37 ± 0.38	4.8 ± 4.0
III	1.0	0.99 ± 0.11	1.0 ± 0.24	4.0 ± 3.1
IV	3.0	3.3 ± 0.6	3.1 ± 1.0	4.6 ± 2.6
V	0	--	0	--[b]
VI	10	9.1 ± 0	10.0 ± 0.07	--[b]
VII	0	--	0	4.0 ± 2.1
VIII	5	5.1 ± 1.2	5.1 ± 0.6	5.7 ± 2.8

[a]Values for nominal and analyzed levels mean/levels for all exposure in ppm ± standard deviation.

[b]Particle size analysis was not performed because exposures were terminated.

C. METHODS AND RESULTS:

1. Observations: Animals were observed twice daily for mortality and clinical signs of toxicity. Animals were also observed daily as a group during the exposure and given detailed individual examinations immediately before exposure on study day 1 and then weekly.

Results: Mortality: Four of 10 females in group VI died after 3 days exposure to 10 ppm, but no deaths occurred in males at this exposure level. As a result of the mortality, exposure at 10 ppm was terminated, five males and females (controls) in group V and one female and five males in group VI were sacrificed on exposure day 3, but the five/sex scheduled for recovery and the corresponding five controls/sex were retained. No deaths occurred during 13 days of exposure at 5 ppm and no deaths occurred in the animals in the main groups, interim sacrifice groups, or recovery groups at the lower exposure levels (groups I to IV; 0, 0.3, 1 or 3 ppm phosphine). During exposure at 0.3, 1, or 3 ppm, mucoid or dried red nasal discharge were observed in a few rats. After 6 weeks of exposure, however, all appeared normal. No similar findings were seen in the "late start" groups exposed at 0, 5, or 10 ppm.

Weekly detailed physical observations did not reveal any indication of exposure-related effects. Only sporadic effects or effects seen equally in all groups were observed.

2. Body Weights: Individual body weights were recorded twice during the pretest period and weekly during the exposure and recovery periods; fasting body weights were recorded just prior to sacrifice. Weekly body weight gains from week zero were calculated.

Results: Table 2 summarizes data on mean body weights at representative intervals during exposure at 0, 0.3, 1.0, or 3.0 ppm phosphine and at the end of the 4-week recovery period. Slight dose-related decreases in mean body weights and weight gains were observed in phosphine-exposed females (0.3, 1.0, and 3.0 ppm) when compared to concurrent controls, particularly during the first 3 weeks of the study. Decreases in weight gain were statistically significant during weeks 1 to 4. At week 1, the decrease compared to control was -4.1% and -3.6% at 1.0 and 3.0 ppm ($p < 0.01$); from weeks 0 to 2, the decrease was -4.8% at 3.0 ppm ($p < 0.01$); and from weeks 0 to 3 the decrease was -4.7% at 1.0 ppm ($p < 0.05$) and -5.4% at 3.0 ppm ($p < 0.01$). There was a recovery from the effect in females after the initial

TABLE 2. Mean Body Weights in Rats Exposed to Phosphine

Exposure Level (ppm)	Mean Body Weight (g ± S.D.) at Week: 0	3	6	13	17 (Recovery)
			Males		
0	181.5 ± 6.3	245.9 ± 8.2	281.3 ± 10.1	313.6 ± 22.6	324.0 ± 23.1
0.3	180.1 ± 6.4	244.3 ± 9.6	288.1 ± 11.5	301.1 ± 19.5	317.1 ± 29.1
1.0	178.4 ± 6.7	246.5 ± 7.1	278.3 ± 9.9	286.4 ± 18.3**	304.1 ± 23.1
3.0	179.8 ± 5.9	245.1 ± 9.1	279.2 ± 11.9	294.2 ± 15.8*	309.6 ± 16.7
			Females		
0	139.5 ± 4.6	168.2 ± 5.5	183.5 ± 5.9	196.2 ± 6.2	195.5 ± 7.2
0.3	137.6 ± 4.4	163.5 ± 5.3*	180.8 ± 5.8	191.5 ± 6.9	190.9 ± 5.7
1.0	137.2 ± 5.6	161.2 ± 5.6**	183.4 ± 5.5	189.3 ± 7.6*	187.5 ± 8.1
3.0	138.8 ± 5.0	162.1 ± 6.2**	182.9 ± 6.5	192.0 ± 7.3	189.2 ± 4.9

*Significantly different from control value, $p < 0.05$.

**Significantly different from control value, $p < 0.01$.

decrease in weight gain. There was a slightly decreased weight gain in dosed males after week 10 compared to controls; the decreases in gain (from week 0) were only significant at week 13 in males exposed at 1.0 ($p < 0.01$) and 3.0 ppm ($p < 0.05$).

In males exposed for 2 weeks at 5 ppm, there were no effects on mean body weights or weight gains. In females exposed at 5 ppm, a decrease in weight gain was observed at weeks 2 and 3 but values were similar to control thereafter and during recovery. In males exposed for 3 days at 10 ppm, a significant decrease in weight gain was observed (-5.8 g) compared to controls (+2.0 g) but weight gain was similar in all groups in the recovery period.

3. Food Consumption: Food consumption was determined weekly for all rats.

   Results: A slight decrease in food consumption was observed in phosphine-exposed groups of both sexes. Decreased weight gains correlated with the food consumption decreases (Table 3). The effects were more marked in females than in males, and there was an apparent dose-related trend in the females.

4. Ophthalmological Examinations: Evaluations were performed at pretest and just prior to terminal and recovery sacrifice using an indirect ophthalmoscope; atropine was used to induce mydriasis.

   Results: Rats with pretest ophthalmologic abnormalities were not included in the study. Conjunctivitis, corneal scars, focal retinopathy, and retinal degeneration were observed in a few rats prior to sacrifices but there was no indication of dose- or compound-related ocular disease.

5. Hematology and Clinical Chemistry: Blood was collected from the retro-orbital sinus or by venipuncture of the abdominal aorta from 10 animals/sex/group for Groups I to IV, from 3/sex/group from Groups V and VII (controls), and 5/sex/group from rats receiving 5 or 10 ppm prior to each sacrifice (5-week, 14-week, recovery, and early terminal sacrifices).

TABLE 3. Mean Weight Gain and Food Consumption Data in Rats Exposed to Phosphine

Exposure Level (ppm)	Weight Gain (g ± S.D.) Weeks 0-3	Weight Gain (g ± S.D.) Weeks 0-13	Food Consumption (g/kg/d) Weeks 1-3	Food Consumption (g/kg/d) Weeks 4-13
		Males		
0	64.4 ± 7.5	129.0 ± 22.5	84.7	61.8
0.3	64.2 ± 6.9	117.5 ± 18.5	83.8	58.8
1.0	68.1 ± 8.1	105.0 ± 19.1**	83.6	58.7
3.0	65.3 ± 7.5	111.9 ± 14.4*	82.9	58.1
		Females		
0	28.7 ± 3.9	54.4 ± 5.2	86.4	74.7
0.3	25.8 ± 4.4*	51.9 ± 6.0	84.7	70.8
1.0	24.0 ± 3.7**	49.2 ± 7.9	85.2	69.0
3.0	23.3 ± 4.3**	50.9 ± 6.3	82.0	68.7

*Significantly different from control values, $p < 0.05$.

**Significantly different from control values, $p < 0.01$.

a. Hematology:

X Hematocrit (HCT)†
X Hemoglobin (HGB)†
X Leukocyte count (WBC)†
X Erythrocyte count (RBC)†
X Platelet count†
X Reticulocyte count (RETIC)
X Red cell morphology
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
Coagulation: thromboplastin time (PT)

Results: No toxicologically important effects on hematology parameters were observed at the end of 4 weeks' exposure. Significant ($p < 0.01$) but slight decreases in hemoglobin concentration (HGB), hematocrit value (HCT), and red cell counts (RBC) were observed at week 14 in males exposed at 3.0 ppm when compared to controls, but no comparable effects were seen for females (Table 4). However, mean RBC level in males exposed at 3.0 ppm were within the normal range at 14 weeks and no effects on mean corpuscular hemoglobin concentration (MCHC) were observed. The hematology changes were reversed after the 4-week recovery period.

No effects on red cell parameters were observed in either sex exposed at 5 ppm for 2 weeks or 10 ppm for 3 days. Mean RBC in males exposed at 10 ppm (7.24 ± 0.10) were slightly lower ($p < 0.05$) than in controls (7.45 ± 0.09) at 14 weeks, but the values were within the normal range.

No effects on leukocyte or platelet counts or other hematology parameters were seen with the exception of a slight increase (4.8%; $p = 0.05$) in platelet counts in 3.0-ppm males at 5 weeks. The effects on the red cell parameters were not considered of toxicologic importance by the reviewers (see Reviewer's Discussion and Interpretation of Results, Section E).

†Recommended by Subdivision F (November 1984) Guidelines.

TABLE 4. Erythrocyte Parameters in Rats Exposed to Phosphine for 13 Weeks and in Recovery Groups (18 Weeks)

	Exposure Level (ppm)							
	Males				Females			
Parameter/Interval	0	0.3	1.0	3.0	0	0.3	1.0	3.0
RBC ($10^6/\mu L$)								
Week 5	8.23 ± 0.19	8.14 ± 0.19	8.31 ± 0.17	8.32 ± 0.12	7.65 ± 0.23	7.83 ± 0.15	7.77 ± 0.26	7.62 ± 0.25
Week 14	7.18 ± 0.13	7.17 ± 0.17	7.07 ± 0.21	6.85 ± 0.15**	6.60 ± 0.22	6.72 ± 0.15	6.68 ± 0.17	6.53 ± 0.14
Week 18	7.86 ± 0.21	7.63 ± 0.19*	7.93 ± 0.42	7.89 ± 0.12	7.49 ± 0.19	7.39 ± 0.18	7.53 ± 0.16	7.46 ± 0.23
HGB (g/dL)								
Week 5	16.9 ± 0.3	16.7 ± 0.3	17.1 ± 0.3	16.9 ± 0.3	16.6 ± 0.5	16.9 ± 0.4	16.8 ± 0.6	16.4 ± 0.6
Week 14	17.3 ± 0.3	17.1 ± 0.4	17.0 ± 0.5	16.4 ± 0.3**	16.7 ± 0.5	16.9 ± 0.4	17.0 ± 0.5	16.5 ± 0.4
Week 18	16.7 ± 0.4	16.3 ± 0.3*	17.0 ± 0.9	16.8 ± 0.3	17.2 ± 0.5	17.1 ± 0.4	17.3 ± 0.3	17.3 ± 0.6
HCT (%)								
Week 5	53 ± 1	52 ± 1	53 ± 1	53 ± 1	50 ± 2	51 ± 1	50 ± 2	49 ± 2
Week 14	45 ± 1	45 ± 1	44 ± 1	43 ± 1**	43 ± 1	44 ± 1	44 ± 1	43 ± 1
Week 18	45 ± 1	44 ± 1	46 ± 3	46 ± 0	46 ± 1	45 ± 1	46 ± 1	46 ± 1

*Significantly different from control value, $p < 0.05$.

**Significantly different from control value, $p < 0.01$.

b. Clinical chemistry:

	Electrolytes		Other
X	Calcium†	X	Albumin†
X	Chloride†	X	Albumin/globulin ratio
	Magnesium†		Blood creatinine†
	Phosphorus†	X	Blood urea nitrogen†
X	Potassium†		Cholesterol†
X	Sodium†	X	Globulins
		X	Glucose†
	Enzymes		Total bilirubin†
X	Alkaline phosphatase (ALP)		Direct bilirubin
	Cholinesterase	X	Total protein†
	Creatine phosphokinase†		Triglycerides
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (SGPT)†		
X	Serum aspartate aminotransferase (SGOT)†		
	Gamma glutamyltransferase (GGT)		

Results: The serum urea nitrogen level (BUN) was significantly increased ($p < 0.01$) in males exposed at 3.0 ppm phosphine at week 5 but there was no increase observed at weeks 14 or 18 (Table 5) or in females at any interval. BUN was also increased in the early sacrifice males exposed at 5 ppm for 14 days (significant) and in the early sacrifice males exposed at 10 ppm for 3 days. No similar effects were observed at any exposure level in females, nor did the effect in males persist after the recovery period. Alkaline phosphatase activity was significantly ($p < 0.05$) increased in the early sacrifice males exposed at 5 or 10 ppm when compared to the respective controls; the increase was 32 and 19% over controls in 5- and 10-ppm males, respectively. The effect did not persist after recovery and no similar response was observed for females. Other changes in clinical chemistry parameters were sporadic and infrequent.

6. Urinalysis: Urinalysis parameters were not examined.

†Recommended by Subdivision F (November 1984) Guidelines.

TABLE 5. Levels of Blood Urea Nitrogen (mg/dL) in Male Rats Exposed to Phosphine

Group	Exposure Level (ppm)	No. Animals	Week 5	Week 14	Week 14[a]	Day 51[b]	Week 18 (Recovery)
I	0	10	17.0 ± 1	21.3 ± 2.7			17.4 ± 2.1
II	0.3	10	17.5 ± 1.5	23.1 ± 1.9			16.6 ± 1.0
III	1.0	10	16.9 ± 0.7	21.0 ± 1.9			17.8 ± 1.8
IV	3.0	10	19.3 ± 1.2**	20.0 ± 2.2			18.0 ± 1.4
VII	0	3			22.8 ± 1.9		18.3 ± 0.8
VIII	5.0	5			30.1 ± 3.6*		19.6 ± 1.8
V	0	3				15.5 ± 1.2	24.1 ± 6.0
VI	10.0	5				19.1 ± 1.9*	22.6 ± 1.7

[a]Fifteen days exposure.

[b]Three days exposure.

*Significantly different from control values, $p < 0.05$.

**Significantly different from control values, $p < 0.01$.

7. Sacrifice and Pathology: All animals that died as well as those sacrificed moribund or by design received a complete gross examination. The CHECKED (X) tissues were collected for histological examination. In addition, the (XX) organs were weighed:

Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta†	XX Brain (3 levels)
X Salivary glands†	XX Heart†	X Peripheral nerve (sciatic nerve)†
X Esophagus†	X Bone marrow†	X Spinal cord (3 levels)
X Stomach†	X Lymph nodes† (mesenteric, peribronchiolar)	X Pituitary†
X Duodenum†	XX Spleen	X Eyes (optic nerve)†
X Jejunum†	X Thymus	
X Ileum†	**Urogenital**	**Glandular**
X Cecum†	XX Kidneys†	XX Adrenals†
X Colon†	X Urinary bladder†	X Lacrimal gland
X Rectum	XX Testes†	X Mammary gland† (right inguinal)
XX Liver†	X Epididymides	X Thyroids†
Gallbladder†	X Prostate	X Parathyroids†
X Pancreas†	Seminal vesicle	Harderian glands
Respiratory	XX Ovaries	
X Trachea†	X Uterus	
XX Lung†	X Clitoral gland	**Other**
X Nasopharyngial		X Bone (sternum and femur)†
		X Skeletal muscle†
		X Skin
		X All gross lesions and masses

Histologic examinations were conducted on groups exposed to 3, 5, and 10 ppm and their respective controls at the interim sacrifice, 14-week sacrifice, and at week 18 after a 4-week recovery period.

Results:

a. Organ weights: At the 5-week interim sacrifice, no effects of toxicologic importance were observed for organ weight data. A slight decrease in mean liver weight ($p < 0.05$) was observed in males exposed at 1.0 ppm, but a dose-related response was not apparent.

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†Recommended by Subdivision F (November 1984) Guidelines.

Table 6 summarizes data for absolute weight and organ-to-body weight ratios of kidneys and liver at the 14-week sacrifice and in the early sacrifice males and females that had been exposed at 10 ppm. In males exposed at 0.3 and 1.0 ppm, a slight but significant decrease in absolute and relative kidney weights was observed; no effect was observed in males exposed at 3.0 ppm or in females at any exposure level up to 3.0 ppm. In males exposed for 3 days to 10 ppm phosphine, absolute kidney weight was increased ($p < 0.05$); there was a corresponding slight but not significant increase in kidney-to-body weight ratio. A slight increase in absolute and relative kidney weight was observed in the surviving female exposed at 10 ppm compared to the appropriate controls. No effects on kidney weights were observed in early sacrifice males or females exposed at 5.0 ppm. Absolute and relative liver weights were significantly decreased in males at all exposure levels and females at 1.0 ppm at the 14-week sacrifice when compared to controls. No similar liver effects were seen in rats exposed at 5 or 10 ppm. No differences in weights of liver or kidney were seen between control and exposed groups after the 4-week recovery period. The biological significance of the decreased liver weights is not apparent, but the increased kidney weight in 10-ppm males was accompanied by histologic kidney pathology.

b. Gross findings: No gross findings were observed that were considered related to dosing. A few pinpoint type foci were observed in the lungs (four control males and six males exposed at 3.0 ppm at the recovery sacrifice, and two control males at the interim sacrifice); these foci were not treatment related. Other gross findings (reddened thymus, discolored skin, small seminal vesicles) were randomly scattered among all groups, there were no dose-related patterns, and the findings were comparable in exposed groups at the interim, terminal, and recovery sacrifices.

c. Microscopic pathology: At the 4-week interim sacrifice, no histopathologic changes related to inhalation of phosphine were observed. Common lesions included the following: slight corneal mineralization (10/10 males and 4/10 females in the control group compared to 7/10 and 5/10 males and females exposed at 3.0 ppm), minimal nonsuppurative myocarditis predominantly in males (7/10 controls and 5/10 at 3.0 ppm), mononuclear cell infiltration of the liver (5/10 control males and 7/10 males exposed at 3.0 ppm), tubular cortical concretions or tubular mineralization of the collecting tubules of the kidneys (39 of 40 rats

TABLE 6. Absolute and Relative Liver and Kidney Weights (± S.D.) in Rats Exposed to Phosphine

Exposure Level (ppm)	Males		Females	
	(g)	(ratio x 1000)	(g)	(ratio x 1000)
		Kidney		
14-Week Sacrifice				
0	2.07 ± 0.16	7.19 ± 0.26	1.33 ± 0.12	7.35 ± 0.61
0.3	1.92 ± 0.10*	6.83 ± 0.32**	1.32 ± 0.08	7.40 ± 0.40
1.0	1.82 ± 0.10**	6.81 ± 0.21**	1.32 ± 0.08	7.49 ± 0.26
3.0	1.99 ± 0.14	7.12 ± 0.20	1.33 ± 0.06	7.55 ± 0.29
Early Sacrifice[a]				
0	1.34 ± 0.05	8.68 ± 0.19	1.10 ± 0.10	8.41 ± 0.69
10	1.50 ± 0.10*	9.83 ± 0.73	1.24 ± 0	10.48 ± 0
		Liver		
14-Week Sacrifice				
0	7.48 ± 0.74	2.59 ± 0.12	4.62 ± 0.19	2.56 ± 0.10
0.3	6.79 ± 0.47*	2.41 ± 0.09**	4.39 ± 0.24	2.47 ± 0.11
1.0	6.31 ± 0.36**	2.36 ± 0.08**	4.20 ± 0.25**	2.39 ± 0.09*
3.0	6.66 ± 0.73*	2.37 ± 0.10**	4.45 ± 0.31	2.52 ± 0.12
Early Sacrifice[a]				
0	5.97 ± 0.53	3.86 ± 0.26	4.60 ± 0.69	3.53 ± 0.46
10	5.94 ± 0.27	3.89 ± 0.22	3.82 ± 0	3.24 ± 0

[a]There were three control males and five males at 10 ppm and three control females and one female exposed at 10 ppm; sacrifice was at study day 78, after three daily exposures.

*Significantly different from control value, $p < 0.05$.

**Significantly different from control value, $p < 0.01$.

examined) and lesions typical of early progressive nephropathy such as regenerative epithelium in the tubules (6/10 control males and 3/10 males exposed at 3.0 ppm; 2/10 female controls and 2/10 exposed at 3.0 ppm). In both exposed animals and controls of each sex, mononuclear cell infiltration was present in the peribronchial, peribronchiolar and/or perivascular regions of the lung of all rats examined at 4 weeks.

Table 7 summarizes histologic lesions in selected tissues (kidneys, lungs, nasopharynx, trachea, heart, liver, and seminal vesicles) at the terminal sacrifice. Exposure-related lesions were observed in kidney sections of both sexes exposed at 10 ppm. Four of 10 females exposed at this level died by day 3 when exposure was terminated; three controls/sex, one surviving female, and five males were sacrificed. Tubular necrosis was observed in all 10 rats exposed at 10 ppm. The lesions were more severe in females (slight to moderate) than in males (minimal to moderate); necrosis was less complete in females that died than in the survivor. Tubular necrosis was not observed after the 4-week recovery period in the rats previously exposed at 10 ppm, nor was it observed at terminal sacrifice in the groups exposed at 5 ppm or 3 ppm phosphine. Other findings in the kidney (pelvic mineralization, tubular concretions, and mineralization) did not appear related to exposure.

Congestion of the lungs was seen histologically in the four females that died after exposure to 10 ppm but not in any of the other animals with the tissues examined. Accumulation of mononuclear cells in the peribronchiolar and perivascular areas of the respiratory tract was a common finding, as was accumulation of alveolar macrophages, but the incidence was generally similar in exposed groups (3.0, 5.0, and 10 ppm) and in their respective controls. Concretions in the submucosal glands were increased in males exposed at 3.0 ppm (terminal sacrifice) as compared to controls, but no increase was seen at 5.0 or 10 ppm. An increased incidence of minimal to slight nonsuppurative myocarditis was noted in the heart of males exposed at 10 ppm and females exposed at 3.0 and 5 ppm when compared to their respective controls, but these findings were considered incidental by the study authors. Findings in other tissues were similar to those found at the 4-week sacrifice.

TABLE 7. Representative Histological Findings in Rats Exposed to Phosphine

Organ/Finding	Exposure Group (ppm)											
	Males						Females					
Group	0 I	3 IV	0 VII	5 VIII	0 V	10 VI	0 I	3 IV	0 VII	5 VIII	0 V	10 VI
Kidneys	(10)[b]	(10)	(3)	(5)	(3)	(5)	(10)	(10)	(3)	(5)	(3)	(5)
Tubular necrosis, cortex	0	0	0	0	0	5	0	0	0	0	0	5
Regeneration, tubular epithelium	7	3	2	1	1	0	0	1	0	1	0	1
Tubular concretions, cortical	10	10	3	4	2	4	7	3	0	1	0	0
Tubular mineralization	5	0	1	1	0	1	10	10	3	5	2	5
Pelvic mineralization	0	3	0	0	0	0	1	2	0	0	0	0
Lungs	(10)	(10)	(3)	(5)	(3)	(5)	(10)	(10)	(3)	(5)	(3)	(5)
Congestion	0	0	0	0	0	0	0	0	0	0	0	4
Pneumonitis, focal	0	2	0	4	1	2	5	1	1	1	0	0
Alveolar macrophages	5	6	3	5	0	3	5	4	2	2	1	0
Perivascular mononuclear cells	10	10	3	5	3	5	10	10	3	5	3	5
Perivascular mononuclear cells	6	3	2	3	0	2	3	2	3	1	2	0
Focal hemorrhage	4	5	0	0	1	0	4	0	0	0	2	4
Trachea	(10)	(10)	(3)	(5)	(3)	(5)	(10)	(10)				
Mononuclear cell infiltrate	3	4	0	2	0	3	1	0	0	3	0	0
Nasopharynx	(10)	(10)	(3)	(5)	(3)	(5)	(10)	(10)	(3)	(5)	(3)	(5)
Submucosal glandular Concretions	1	4	0	1	0	0	1	1	0	1	0	1
Heart	(10)	(10)	(3)	(5)	(3)	(5)	(10)	(10)	(3)	(5)	(3)	(5)
Myocarditis, nonsuppurative	7	8	1	2	0	4	2	7	2	4	1	1
Liver	(10)	(10)	(3)	(5)	(3)	(5)	(10)	(10)	(3)	(5)	(3)	(5)
Mononuclear cell infiltrate	7	7	1	2	1	2	6	7	0	2	3	1
Seminal vesicles	(10)	(10)	(3)	(5)	(3)	(5)	--	--	--	--	--	--
Decreased secretion	2	5	0	0	0	1	--	--	--	--	--	--

[a]Results at the 13-week sacrifice and for females that died or were sacrificed after 3 days at 10 ppm phosphine.
[b]Numbers in parentheses are the numbers of tissues examined histologically.

No exposure-related histologic changes were noted after the 4-week recovery period. All findings in these groups were considered spontaneous. One control female (Group I) had a pituitary adenoma.

D. STUDY AUTHORS' CONCLUSIONS:

Subchronic exposure to 0.3, 1, or 3 ppm of phosphine for 13 weeks and exposure to 5 ppm of phosphine for 13 days, produced a dose-related decrease in body weight at 1 ppm and higher, and decreased food consumption in all phosphine-exposed groups including a transient effect at 0.3 ppm. The females appeared more sensitive. Adaptation was evident in the females as their food consumption returned to normal during the exposures (0.3-ppm group) or completely recovered during the 28-day recovery period. Decreased red blood cells, hemoglobin, and hematocrit were produced in the 3-ppm phosphine group after 13 weeks of exposure. A transient increase in BUN was produced in the 3- and 5-ppm groups. Gross postmortem observations included an increased incidence of small seminal vesicles in the 1- and 3-ppm groups. However, the significance of this observation is equivocal because no microscopic correlate was seen in these vesicles. The effects noted above were reversed after a 4-week recovery period. No important microscopic findings were observed at the 5-week, 13-week, or recovery sacrifices in groups exposed at levels up to 5.0 ppm.

Exposure to 10 ppm of phosphine for 6 hours/day was lethal after only 3 days of exposure to 4 of 10 females and 0 (zero) of 10 males. Increased kidney weights and microscopically, coagulative necrosis of the tubules of the kidneys and pulmonary congestion were noted in the females that died spontaneously. The females appeared more sensitive because of increased severity of the lesions observed when compared to males and because no male animals died spontaneously at this exposure level.

Following a 28-day recovery period, no treatment-related lesions were observed in the kidneys and lungs of survivors that had been exposed to 10 ppm phosphine.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

In the acute toxicity study, a single 6-hour exposure of F344 rats to phosphine at levels of 10 ppm did not cause mortality. However, in the present study, three daily exposures at 10 ppm caused 40% mortality in females. The product of concentration x time was not equal to a constant (Haber's law; $C_0 \times T = k$), since 13 exposures at 5 ppm (210 ppm·hr) or 90 exposures at 3 ppm (1640 ppm·hr) were not equivalent to three exposures at 10 ppm (180 ppm·hr). It may be difficult to approach a dose in a

subchronic or chronic toxicity study that will cause significant toxic effects without causing excessive mortality. Historically, the toxic problems with phosphine have been associated with acute accidental exposures.

The initial decreased body weights in exposed groups were associated with decreased food consumption; the rats adapted to the decrements in food consumption and body weight and reversed the weight gain decrement in the recovery period. Decreased body weight gains were not observed in groups exposed at 5 ppm; however, these groups were older than main-study animals at initiation of dosing, and the mean body weights were closer to the adult plateau body weight.

The reviewers assess that the hematologic changes observed are of doubtful toxicologic importance. The decreases in RBC and HCT in males exposed at 3.0 ppm occurred only at 14 weeks, were reversible, and were not accompanied by changes in derived parameters (MCV, MCH, and MCHC). The changes were not large, and the mean values were within the range of normally encountered historical values for Fischer 344 rats. The individual values were near the lower end of the range for values in concurrent controls. In addition, the effects were seen only in males and not in females. The increases in BUN in males exposed at 3.0 ppm were transient, occurring only at week 4 but not persisting at week 14; a similar increase was not seen in exposed females. Moderate increases in BUN were seen in males exposed at 5.0 ppm for 2 weeks and at 10 ppm for 3 days. The changes may be correlated with kidney histopathology at 10 ppm; however, the histologic changes were more severe in females than males, and no effects on BUN were seen in females.

We agree with the study author's conclusion that the only histopathological lesions associated with exposure were in kidneys of both sexes exposed at 10 ppm; the coagulative tubular necrosis was accompanied by an increase in absolute and relative kidney weight when compared to the appropriate controls.

Phosphine

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