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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

009753

SEP 2 4 1992

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Aluminum Phosphide: Generic Data Registration.
Also applies to Magnesium Phosphide.
EPA #066501. S382268

HED # 1-0039
Chemical No. 31 and 443

TO: Nancy Tompkins (PM 74)
Special Review Branch
Special Review and Reregistration Division (H7508W)

FROM: Stanley B. Gross, PhD, DABT, CIH
Toxicologist/Hygienist
Toxicology Branch I
Health Effects Division (H7509C)

THRU: Joycelyn Stewart PhD
Acting Head, Section II, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Karl P. Baetcke, PhD
Chief, Toxicology Branch I
Health Effects Division (H7509C)

Registrant: Metal Phosphide Task Force
Weyers Cave, Va, 24486

Conclusions:

The following studies have been submitted to support registration of aluminum/magnesium phosphide as indoor fumigants to control insects on food commodities and in structures, and as outdoor fumigants to control rodents and moles. The studies have been reviewed and classified as follows:

A. Ames/Salmonella Mutagenicity Study:

"Ames/Salomonella Plate Incorporation Assy on Hydrogen Phosphide (PH3)". MRID 414343-01 Feb. 10, 1990.

Results. Negative results in repeat testing in Salmonella his-strains to test article up to cytotoxic dose (300 to 900 ppm, both with/without activation).

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Classification-- ACCEPTABLE.

B. Mutagenicity - Chromosome damage -in vitro (CHO).

"Structural Chromosome Aberarations. Chineses Hamster Ovary (CHO) Cell induced by Hydrogen Phosphide (PH3) MRID 414343-02. March 8, 1990.

Results. Positive for inducing chromosome damage directly (i.e., without metabolic activation) in Chinese hamster ovary cells exposed at 2500 and 5000 ppm PH_3 (nominal concentrations; non-cytotoxic doses).

Classification -- ACCEPTABLE.

C. Study: Acute Inhalation in Rats.

" An Acute Inhalation Toxicty Study of Phosphine (PH3) in the Rat. MRID 413770-01. Sept. 5, 1989.

Results. Fischer 344 rats (15/sex/group) were exposed to 0, 2.5, 5.0 and 10 ppm PH3 for 6 hours and observed for 14 days post exposure. There were no signs of toxicity other than nasal discharge.

Classification: SUPPLEMENTARY. The exposure levels were too low. Note: This study was not required nor is it necessary to repeat the study.

D. Study: 13 Week Subchronic Inhalation in Rats.

"A Thirteen Week Inhalation Toxicity Study of Phosphine (PH3) in the Rat. MRID 414131-01. March 2, 1990.

Results: Fischer 344 rats, exposures to 0. 0.3, 1.0 and 3.0 ppm 6 hrs/day, 5 days/week for 13 weeks; 0, 5 ppm for 15 days, and 0, 10 ppm for 3 days. Toxicity observed in 10 ppm rats, mortality in 4/10 females but not males by day 3 of exposure; coagulative necrosis in kidney tubules. BUN and alkaline phosphatase increased in 5 ppm males but not females. No toxic signs and no deaths occurred in rats exposed to up to 3 ppm. The NOEL for subchronic exposure is 3 ppm (HDT).

Classification: Core Minimum.

E. Study: Inhalation Development Study in Rats.

"An Inhaltion Developmental Toxicity Study cf Phosphine (PH3) in Rats". MRID 413770-02 Dec. 5, 1989.

Results. Female rats were exposed to 0.03, .30, 3.0, 5.0 and 7.5 ppm 6 hr/day for days 6 through 15 of gestation. Maternal NOEL was 5 ppm, the maternal LEL was 7.5 ppm (HDT) based on the high incidence of maternal deaths. Fourteen females died between exposure day 3 and exposure day 10, and the 7.5 ppm group was terminated. The 5 ppm group thus became the high dose group. Niether maternal nor developmental toxicity was seen at this dose, therefore the chemical was not a developmental toxicant under the test conditions.

Classification: Minimum. The study satisfies the requirements for developmental toxicity.

The mutagenicity studies were reviewed by Dr. Irving Mauer, the inhalation developmental study was reviewed by Dr. Melba Morrow, and the acute and subchronic studies were reviewed by Dynamac Corporation. The Data Evaluation Records (DER's) are attached for your reference.

CONFIDENTIAL BUSINESS INFORMATION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

EPA No.: 68D80056
DYNAMAC No.: 343-B
TASK No.: 3-43B
July 15, 1991

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DATA EVALUATION RECORD

PHOSPHINE

Subchronic Inhalation in Rats

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L McLellan

Date: July 15, 1991

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DATA EVALUATION RECORD

PHOSPHINE

Subchronic Inhalation in Rats

REVIEWED BY:

William L. McLellan, Ph.D.
Principal Reviewer
Dynamac Corporation
Signature: William L. McLellan
Date: 7/15/91

Margaret E. Brower, Ph.D.
Independent Reviewer
Dynamac Corporation
Signature: Margaret Brower
Date: July 15, 1991

APPROVED BY:

Nicolas P. Hajjar, Ph.D.
Department Manager
Dynamac Corporation
Signature: Nicolas P. Hajjar
Date: 7/15/91

Stanley Gross, Ph.D.
EPA Reviewer, Section II
Toxicology Branch I
(H-7509C)
Signature: Stanley Gross
Date: 4/14/92

~~Marion Copley, D.V.M.~~, ~~D.A.B.T.~~ JOYCELYN STEWART, Ph.D
EPA Section Head, Section II
Toxicology Branch I
(H-7509C)
Signature: Joycelyn Stewart
Date: 4/11/92

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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.

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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.

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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 10⁶.

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 -4.3% 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

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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	278.1 ± 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).

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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, $p < 0.01$.

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a. Hematology:

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

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/µL)								
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, $p < 0.01$.

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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†		
X Cecum†	Urogenital	Glandular
X Colon†	XX Kidneys†	XX Adrenals†
X Rectum	X Urinary bladder†	X Lacrimal gland
XX Liver†	XX Testes†	X Mammary gland† (right inguinal)
Gallbladder†	X Epididymides	X Thyroids†
X Pancreas†	X Prostate	X Parathyroids†
	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.

†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

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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 ± 0.26	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, $p < 0.01$.

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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.

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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.

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APPENDIX

Test Substance Analyses/Impurities

(CBI pp. B-17, 18)

RIN 1108-94

ALUMINUM PHOSPHIDE REVIEW

Page_____ is not included in this copy.

Pages 27 through 28 are not included.

The material not included contains the following type of information:

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____ A draft product label.

____ The product confidential statement of formula.

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✓ FIFRA registration data.

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DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

Acute Fin hal

EPA No.: 68D80056
DYNAMAC No.: 343-A
TASK No.: 3-43A
July 15, 1991

009753

DATA EVALUATION RECORD

PHOSPHINE (AIP)

Acute Inhalation Toxicity Study in Rats

STUDY IDENTIFICATION: Newton, P. E. An acute inhalation toxicity study of phosphine (PH_3) in the rat. (Unpublished study No. 87-8029, performed by Bio/dynamics Inc., East Millstone, NJ, for the Metal Phosphide Task Force; dated September 5, 1989.) MRID No. 413770-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: William L. McLellan for

Date: July 15, 1991

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1. CHEMICAL: Phosphine (PH_3).

2. TEST MATERIAL: 1.06% phosphine in N_2.

3. STUDY/ACTION TYPE: Acute inhalation toxicity study in rats.

4. STUDY IDENTIFICATION: Newton, P. E. An acute inhalation toxicity study of phosgine (PH_3) in the rat. (Unpublished study No. 87-8029, performed by Bio/dynamics Inc., East Millstone, NJ, for the Metal Phosphide Task Force; dated September 5, 1989.) MRID No. 413770-01.

5. REVIEWED BY:

William L. McLellan, Ph.D. Signature: William L McLellan
Principal Reviewer
Dynamac Corporation Date: July 15, 1991

Margaret E. Brower, Ph.D. Signature: Margaret Brower
Independent Reviewer
Dynamac Corporation Date: July 15, 1991

6. APPROVED BY:

Nicolas P. Hajjar, Ph.D. Signature: Nicolas P. Hajjar
Department Manager
Dynamac Corporation Date: 7/15/91

Stanley Gross, Ph.D. Signature: Stanley Gross
EPA Reviewer, Section II
Toxicology Branch I Date: 9/14/92
(H-7509C)

~~Marion P. Copley, D.V.M.~~, ~~D.A.B.T.~~ JOCELYN STERNER Signature: Jocelyn Sterner
EPA Section Head, Section II Date: 9/16/92
Toxicology Branch I
(H-7509C)

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7. CONCLUSIONS:

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Core Classification: CORE Supplementary.

The LC_{50} was not established, since no mortality occurred at the highest exposure level. In addition, an effect level was not established. Phosphine caused no toxic effects other than secretory responses as mucoid nasal discharge.

Toxicity Category: Not established.

8. SUMMARY: Groups of 15 male and 15 female Fischer 344 rats (Charles River Breeding Laboratories, Inc., Kingston, NY) having mean weights of 198 g (males) or 145 g (females) were exposed to phosphine for 6 hours at levels of 0, 2.5, 5.0, or 10 ppm (0, 2.4 ± 0.9, 4.9 ± 1.8, or 11 ± 2.4 ppm, mean analyzed values of samples at four intervals). Each animal was individually caged during exposure in a 1000-L glass and stainless steel exposure chamber and received no food or water. The chamber had an airflow rate of 200 L/min (complete air changes every 5 minutes), and the 99% equilibrium time was 23 minutes. The temperature and relative humidity ranges during exposure were 63-75°F and 45-63%, respectively. All animals were observed prior to exposure, at 15-minute intervals during exposure, and 30 minutes following completion of exposure when the rats were removed from the chambers. Five rats/sex/group were sacrificed at the end of exposure, and 10/sex/group were retained for 15 days. Detailed observations of survivors were performed weekly; body weights were recorded pre-exposure, on day 8, and just prior to sacrifice (day 15). All rats were subjected to a gross necropsy, and brain, heart, kidneys, liver, and lungs were fixed and examined histologically.

All animals survived the exposure. Physical observations during exposure included red or mucoid nasal discharge in some rats in all treated groups; these findings were not present at 7 or 14 days after exposure. There were no adverse effects on body weights, although there were sporadic increases in weight in exposed groups.

No gross findings related to exposure were seen at day 1 or day 14. No histologic findings of importance were observed in the groups sacrificed on the day of exposure. Minimal hyperplasia of the lungs was seen in one low-level male and two mid-level males. Minimal focal alveolitis was observed in one control female, and minimal hyperplasia of the lung was seen in another control female. No lesions of the lungs were seen in any exposed males. Focal mineralization of the kidneys was seen in several females, but there was no difference in incidence between groups (4/5 for controls and 3/5, 3/5, and 4/5 in females exposed at 2.4, 4.9 or 11 ppm). Histologic examination

was not performed on the rats sacrificed 2 weeks after exposure.

9. REVIEWERS' COMMENTS AND QUALITY ASSURANCE MEASURES: The study was adequately conducted and reported. Exposure levels were close to target, and chamber temperature and humidity values were all within an acceptable range. A subchronic inhalation toxicity study (MRID No. 413770-02), found that exposure to 10 ppm phosphine for 6 hours/day caused 40% mortality in Fischer 344 rats on the third exposure. A higher dose should have been tested in the single exposure study. However, it is expected that the dose-response curve for mortality will have an extremely sharp slope; therefore, close spacing of doses will be needed to establish an LD_{50}.

   A Quality Assurance statement was signed and dated June 22, 1989.

10. CBI APPENDIX: Materials and Methods (pp 8-16).

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APPENDIX A

Materials and Methods

RIN 1108-94

ALUMINUM PHOSPHIDE REVIEW

Page_____ is not included in this copy.

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Reviewed By: Irving Mauer, Ph.D., Geneticist
Toxicology Branch I - IRS (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch I - IRS (H7509C)

11-20-90
4/14/92

DATA EVALUATION RECORD 009753

I. SUMMARY

MRID (Acc.) No.: 414343-01
ID No.: 066501
RD Record No.: [S-382263]
Caswell No.: 031
Project No.: 1-0039M

Study Type: Mutagenicity - Ames Test

Chemical: Hydrogen phosphide (PH_3)

Synonym: Phosphine

Sponsor: Degesch America, Inc. (representing the Metal Phosphide Task Force), Weyers Cave, VA.

Testing Facility: Pharmakon Research International (PH) Waverly, PA

Title of Report: Ames/Salmonella Plate Incorporation Assay on Hydrogen Phosphide (PH_3).

Author: Leon F. Stankowski, Jr.

Study Number: PH 301-DA-001-89

Date Issued: February 10, 1990

TB Conclusions:

Negative in repeat testing in Salmonella *his*$^-$ strains exposed to test article up to cytotoxic doses (300 to 900 ppm), both with/without activation.

Classification (Core-Grade): ACCEPTABLE

II. DETAILED REVIEW

A. Test Material - Hydrogen phosphide (10,000 ppm in N_2)

Description: Clear, colorless gas
Batch (Lot): (Not stated)
Purity (%): (Not stated)
Solvent/Carrier/Diluent: Compressed air (medical grade)

B. Test Organism: Bacterial cultures

Species: Salmonella typhimurium LT2
Strains: TA1535, TA1537, TA1538, TA98, TA100, TA102 (all his$^-$)
Source: Dr. Bruce N. Ames, UCal, Berkeley

C. Study Design (Protocol) - This study was designed to assess the mutagenic potential of hydrogen phosphide when administered in vitro to Salmonella his$^-$ strains, according to validated (published) methods.

A Statement of Quality Assurance measures (inspections/audits) was provided, as well as a statement of adherence to Good Laboratory Practice.

D. Procedures/Methods of Analysis - Based upon "an expected lack of toxicity" (as affirmed by the study investigator), triplicate cultures of all six strains were exposed in sealed 250-mm glass dessicators for 48 hours to test article at concentrations of 4.52, 54.7, 190, 488, 1160, and 4340* ppm, both in the absence and presence of an exogenous mammalian metabolic activation mixture consisting of the microsomal fraction (S9) prepared from the livers of male Sprague-Dawley rats pretreated with Aroclor 1254, plus NADP(H)-generating cofactors.

Concurrent bacterial cultures treated with N_2/air served as carrier (negative) controls, while other cultures exposed to strain-specific mutagens** served as positive controls. In addition, 1,3-butadiene, ethylene oxide,

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*Stated by the investigator to have been analytically confirmed by the sponsor.
**Sodium azide (10 ug/plate) for nonactivated TA1535 and TA100.
9-Aminoacridine (150 ug/plate) for nonactivated TA1537.
2-Nitrofluorene (5 ug/plate) for nonactivated TA1538 and TA98; higher (20 ug/plate) in nonactivated TA102.
Mitomycin-C (2.5 ug/plate) for nonactivated TA102.
2-Anthramine for all activated strains (i.e., in the presence of S9).

and methylene chloride were also evaluated concurrently (±S9). After a 24-hour degassing period, revertent "his+" colonies were counted automatically, and individual culture as well as summary data tabulations included in the Final Report.

A confirmatory assay was performed at PH_3 doses of 73.3, 147.0, 228, 360, 378, and 399 ppm, subsequently followed by three additional assays at dose ranges of 99-262, 37-203, and 41-962 ppm (±S9). Standard criteria for evaluation including statistical analyses were presented.

E. Results - In the initial assay, cytotoxicity (characterized by reduced background lawn or revertent counts, and/or the presence of "pin-dot" colonies) was evident in all strains treated at dose levels ≥ 488 ppm PH_3 (see Report Tables attached to this DER). A single positive response was recorded in nonactivated (-S9) TA1535 treated at 190 ppm (statistically significant increased revertent counts approximately 2.5 times control value). In the confirmatory assay, reduced growth was found at all doses above 147 ppm, accompanied by singular increases in revertent counts (3.2 to 4.5-fold controls) in activated (+S9) cultures of TA1537 and TA98 exposed to (only) 360 ppm test article.

No cytotoxicity was apparent in the third assay (employing PH_3 doses of 99, 111, 152, 172, 183, and 262 ppm), but statistically significant nondose-related responses (2.1-fold control) were calculated at all dose levels of PH_3 in activated TA1538.

Hence, the test article was reevaluated in two additional assays with all six bacterial strains exposed to dose levels ranging from 37 to 962 ppm PH_3. The expected cytotoxicity was observed at doses equal to and above 277 ppm, but no significant increases in reversions at any dose level.

The investigator concluded that since the apparent increases in revertent colonies of TA1535, TA1537, TA1538, and TA98 treated with PH_3 in the first three assays were random, nondose-related, and not confirmed in subsequent testing, hence the test article was not mutagenic in this test system.

F. TB Conclusion - ACCEPTABLE. Within the constrictions imposed by the nature of the test compound (difficult to test in vitro, being a gas by nature), the investigator employed rigorous and careful procedures to support his final conclusion that PH_3 was essentially negative for bacterial mutation in repeat assays in Ames testing.

Attachments (Summary Data Tables)

ATTACHMENT I

Summary Data Tables

RIN 1108-94

ALUMINUM PHOSPHIDE REVIEW

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Reviewed by: Irving Mauer, Ph.D., Geneticist
Toxicology Branch-I, HED (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch-I, HED (H7509C)

5/11/92

5/11/92

DATA EVALUATION RECORD

009753

MRID NUMBER No.: 414343-02
ID No.: 066501
RD Record No.: [S-382263]
Caswell No.: 031
Project No.: 1-0039M

I. SUMMARY

STUDY TYPE: Mutagenicity - Chromosome damage in vitro (CHO)

CHEMICAL: Hydrogen phosphide (PH_3)

SYNONYMNS: Phosphine

SPONSOR: Degesch America, Inc. (representing the Metal Phosphide Task Force), Weyers Cave, VA

TESTING FACILITY: Pharmakon Research International (PH) Waverly, PA

TITLE OF REPORT: Structural Chromosome Aberration[s] [in] Chinese Hamster Ovary (CHO) Cell[s] Induced by Hydrogen Phosphide (PH_3).

AUTHOR(S): Juan R. San Sebastian

STUDY NUMBER: PH 320-DA-001-89

DATE ISSUED: March 8, 1990

TB CONCLUSIONS:

Positive for inducing chromosome damage directly (i.e., without activation) in Chinese hamster ovary (CHO) cells exposed at 2500 and 5000 ppm PH3 (nominal concentrations). Although there were limitations in this study, it is considered acceptable for regulatory purposes because of the apparent induction of chromosomal damage by phosphine at non-cytotoxic doses. This activity is supported by other genotoxicity data on phosphine available to OPP.

Classification (Core-Grade): ACCEPTABLE

II. DETAILED REVIEW

A. Test Material - Hydrogen phosphide (PH_3, 10,000 ppm in N_2)

Description: Clear, colorless gas
Batch (Lot): (Not stated)
Purity (%): (Not stated)
Solvent/Carrier/Diluent: Compressed air (medical grade)

B. Test Organism - Mammalian cell strain

Species: Chinese hamster (ovary)
Strain: K_1-BH_4 [Lots A-12 and A-1, doubling time = 12 to 14 hours]
Source: Dr. A.W. Hsie, Oak Ridge, TN

C. Study Design (Protocol) - This study was designed to assess the clastogenic potential of phosphine gas when administered in vitro to cultures of Chinese hamster ovary (CHO) cells, according to recognized (published) methods (referenced in the Final Report).

Statements of both Quality Assurance measures (inspections/audits) as well as of adherence to Good Laboratory Practice were provided.

D. Procedures/Methods of Analysis - Following preliminary cytotoxicity testing utilizing cell proliferation kinetics in cell cultures treated with 10 doses of test article (dose range: theoretically, 0.167 to 5000 ppm, corresponding to sponsor-analyzed actual concentrations of 0.151 to 8775 ppm), duplicate cultures of CHO cells were exposed in sealed 125-mL serum bottles for 5 hours to graded concentrations of PH_3, both in the absence and presence of a mammalian metabolic activation mixture.* Concurrently, other cultures were run untreated, or exposed to the compressed air carrier alone, providing negative controls; or treated with the mutagens N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 1.5 ug/mL = 1.3×10^{-5} M in medium) and 1,3-butadiene (BD, 50%) as positive controls for the nonactivated (-S9) and activated (+S9) series, respectively.

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*Rat S9, consisting of the microsomal fraction of liver homogenates from Sprague-Dawley males pretreated with Aroclor 1254, plus NADP(H)-generating cofactors.

After the 5-hour treatment, cell cultures were washed free of test article and reincubated in fresh medium for three additional periods of time: 8, 18, or 26 hours, in the presence of the metaphase-arresting alkaloid, Colcemid, during the final 2 to 3 hours. At the end of the three harvest times, cells were collected by centrifugation, swollen in hypotonic potassium chloride (0.075M), fixed in Carnoy's, and standard microscope slide preparations made by conventional cytological techniques.

One hundred fifty metaphases per culture (300 per treatment data point), on coded, stained (buffered Giemsa) slides were scored under oil immersion for the conventional array of structural chromosome aberrations. The resulting cytogenetic data were pooled, and analyzed for statistical significance by Chi-Square (for proportion of test cells with any type of aberration at each PH_3 dose, compared to concurrent solvent control), as well as by t-testing (aberrations per cell in treated cultures vs. control).

In this lab, only those CHO assays are considered valid for analysis in which the solvent/carrier controls have < 0.01 total aberrations/cell, and the positive controls bear significant increases over negative control in aberration frequency. A test article would be considered positive if it induces a significant increase in aberrations, preferably in a dose-response manner.

E. Results - PH_3 had no observable cytotoxicity up to and including the HDT, nominally 5000 ppm (by sponsor's analysis, actually 8775 ppm), as determined by apparently normal traverse (no different from negative controls) through the cell cycle (Report Table 1, attached to this DER). Hence, the doses selected for the main assay were (theoretically) 500, 2500, and 5000 ppm (by actual sponsor analysis: 426, 2733, and 4957 ppm for the 8-hour harvest; 634, 468, and 3994 ppm for the later periods).

Small but statistically significant ($p \leq 0.05$) increases in chromosome damage were recorded in cells harvested 8 hours after PH_3 treatment at the two higher concentrations with and without S9 activation (Report Tables 2 and 5 attached here), but not in treated cells harvested later (18 or 26 hours after treatment - Report Tables 3, 4, 6, and 7; also attached). [It should be noted - which the investigator did not! - that none of these statistically significant increases were dose-related, and no dose responsive trends were evident at any treatment levels.]

The author suggested that this positive response at 8 hours should be validated in a second (follow-up) assay.

Whereas the clastogenic response in (nonactivated) MNNG-treated cultures was definitively positive at both indicated harvest times (15 to 30 times background), that of the other (activated) positive control BD was less than satisfactory according to the study author: minimally positive ($p \leq 9.95$) at 8 hours (barely 3 to 4X background - Tables 2 and 5); negative at 18 hours (not significant - Tables 3 and 6). Further, the investigator even discounts the apparent positive registered by BD at 8 hours, as being more probably the result of comparison to a low solvent control, combined with the fact that the mean BD level recorded is within this lab's historical control range for solvent controls.

The study author concluded that PH_3 apparently produced a significantly increased level of chromosome damage in nonactivated cultures (i.e., directly) at concentrations above 2500 ppm 8 hours after treatment, but not at later harvest times (18 and 26 hours). The weak responses of BD (as well as that of the test article) under activation conditions suggest to this investigator a "detoxification" or "inactivation" of the S9 mix, necessitating the need for further investigation.

F. TB Conclusion - ACCEPTABLE. The responses reported in this single assay of the test article suggest that follow-up experimentation would have been appropriate (as was done in the concurrent Ames Assay, MRID No. 414343-01, reviewed above). In the immediate absence of such confirmation, we consider PH_3 to be positive for directly (i.e., not requiring a metabolic activation system for biological activity) inducing chromosome damage in CHO cells at concentrations of 2500 ppm and above. The positive response seen at 8 hours posttreatment (but not later) is consistent with the investigator's conclusion that "first posttreatment metaphases must be scored before they can be lost during the [first] division...reducing the sensitivity of the assay if cells are permitted to cycle through a second mitosis...," given: 1) The normal (unimpeded) cell doubling time = 12 to 14 hours; 2) No cytotoxicity was encountered at any dose level.

Although there were limitations in this study, it is considered acceptable for regulatory purposes because of the apparent induction of chromosomal damage by phosphine at non-cytotoxic doses. This data is further supported by other studies in which phosphine causes chromosomal damage [8(e) submission to the Office of Toxic Substances, #8EHQ-0291-1188]

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Attachments (Summary Data Tables)

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ATTACHMENT I

Summary Data Tables

RIN 1108-94

ALUMINUM PHOSPHIDE REVIEW

Page_____ is not included in this copy.

Pages 63 through 71 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

GUIDELINE: 83-3

Primary Review by: Melba S. Morrow, D.V.M.
Review Section II, Toxicology Branch I/HED

Secondary Review by: Stan Gross, Ph.D.
Review Section II, Toxicology Branch I/HED

4/14/92

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DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: rat
Guideline: 83-3

EPA Identification No.s: EPA MRID No. 413770-02
EPA ID No. 066501
EPA Record No. S382263
Caswell No. 031
HED Project No. 1-0039

Test Material: Phosphine 1% in Nitrogen gas

Synonyms: PH_3

Sponsor: Metal Phosphide Task Force
DEGESCH America, Inc.
Weyers Cave Virginia

Study Number(s): 89-3413

Testing Facility: Bio/Dynamics, Inc.
East Millstone, N.J.

Title of Report: An Inhalation Developmental Toxicity Study of Phosphine in Rats

Author(s): Raymond E. Schroeder

Report Issued: December 5, 1989

Conclusions: Under the conditions of this study, the maternal NOEL is 5 ppm and the maternal LEL is 7.5 ppm based on the high incidence of maternal deaths. The reproductive NOEL is 5 ppm and the developmental NOEL is 5 ppm. Doses tested in this study were 0, 0.3, 0.32, 3.0, 5.0, and 7.5 ppm.
Core Classification: Minimum. The study satisfies the requirements for developmental toxicity as set forth in the Subdivision F Guidelines.

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A. Materials:

Test Compound: Phosphine
Description: Colorless gas with unpleasant odor
Lot Nos.: N-429433, H-70377, N-299593, N-411001

Vehicle(s): 1% Nitrogen gas

Test Animal(s): Species: rat
Strain: CD derived Sprague Dawley
Source: Charles River
Portage, Michigan
Age: Approx. 10 weeks at start of study
Weight: 186 - 281 grams

B. Study Design :
This study was designed to assess the developmental toxicity potential of Phosphine when administered by the inhalation route to female rats on gestation days 6 through 15, inclusive.

Mating
Following a one month acclimation period, female rats were mated with untreated male rats at a ratio of 1M:1F. Matings took place at night and on the morning following cohabitation, the females were examined for the presence of sperm and/or a vaginal plug.

Matings and exposures to phosphine were not conducted on the same day for all animals. Mating was conducted over a period of 19 nights and following each night of mating, females were sorted into groups on the following morning.

Rooms were maintained at temperatures of 67 to 80° F and relative humidity of 30 to 70%.

Group Arrangement:

Test Group	Dose Level (ppm)	Number Assigned
Control	0	24
II	0.03	27[a]
III	0.30	24
IV	3.0	24
V	5.0	24
VI	7.5	19[b]

a= three animals sacrificed on day 2 of exposure were replaced with 3 other females.

b = due to excessive mortality, this group was terminated early in the study.

Dosing

All animals were exposed to levels of phosphine as designated by group number on days 6 through 15 of gestation. Phosphine was administered as a vapor into the breathing zone in 6 m^3 stainless steel and glass chambers. Animals were exposed for six hours each day and remained in the chamber 30 minutes following each exposure to allow the vapors to clear before removing the test animals. Control animals were exposed to room air only during the 6 hour exposure period.

Experimental Chambers

Harford glass and stainless steel exposure chambers with a total volume of 6000 liters were used. The airflow rate, time for air exchange and 99% equilibrium time were measured for each group of animals. Phosphine was delivered by a stainless steel regulator which was connected to a 1/4 swaglock union cross where the test substance was carried to 5 exposure chambers via stainless steel tubing. The test substance was delivered to the top turret of the exposure chamber.

Gas chromatography was used to detect phosphine exposure levels and the nominal concentration of phosphine was determined by dividing the total volume of phosphine metered into the tube by the total volume of air passing through the chamber. Temperature, relative humidity and chamber volumetric air flow were measured every 1/2 hour. (See Table V for chamber monitoring results).

Observations

Maternal animals were observed twice daily for mortality and for clinical signs of toxicity. Physical exams were conducted on days 0, days 6-15 and day 20 of gestation. Body weights were recorded on days 0, 6, 10, 12, 16 and 20 post-coitum. On day 20, actual and corrected body weights were recorded. Food consumption was determined at 4 intervals from day 0 thru day 20. On day 20 post-coitum, animals were sacrificed by exsanguination while under light ether anesthesia.

The ovaries and uterus were removed from each animal and the following parameters were assessed:

- Number of corpora lutea
- Number of implantations
- Number of live fetuses
- Number of early resorptions
- Number of late resorptions
- Number of dead fetuses

Non-pregnant females were immersed in 10% ammonium sulphide to reveal the number of implantation sites. Females with foci in the uterus that were observed after special staining, were considered as having been pregnant.

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Fetuses were identified, sexed and subjected to a gross examination for external malformations/variations. One half of the fetuses were evaluated for visceral abnormalties; the tissues were fixed in Bouin's solution. The remaining half were subjected to a skeletal evaluation after being stained for ossified structures using Alizarin red.

Late resorptions were examined grossly for external malformations. Those with malformations were saved in 10% neutral buffered formalin.

Historical control data were not provided to allow comparison with concurrent controls.

Statistical analysis
Statistics were conducted on data and comparisons were made between control and treated groups. Statistics included Bartlett's test for variance, parametric (ANOVA, Dunnett's test) and non-parametric (Kruskall-Wallis) procedures. Tests for trend included standard regression techniques (parametric) and Jonckheere's test(non-parametric. Arc sine transformation was used on all ratios prior to analysis. $P \leq 0.05$ and $p \leq 0.01$ were determined.

Compliance
A signed Quality Assurance Statement dated 10/24/89 was provided. A statement of compliance with GLPs was also provided.

C. Results

Maternal Toxicity

Mortality
No mortality was reported in groups receiving phosphide up to 5 ppm. At 7.5 ppm, the first 14 females assigned to the group died during the exposure period. The number of exposures that animals in this group received prior to death ranged from 3 to 10. The remaining five animals that had not been exposed to phosphide were sacrificed and the entire 7.5 ppm group was removed from the study.

Clinical Observations
No clinical signs of toxicity were present at doses lower than 7.5 ppm.

Body Weight
Mean body weights and body weight gains were comparable between groups. In terms of absolute weight gains during the study, the treated animals gained more weight than controls. Animals in the 7.5 ppm group were not included in the data analysis. (See Table I, derived from data provided by the sponsor).

Food Consumption:
Food consumption was comparable for all groups for the period prior to dosing and for the period from day 6 to 16. During the post treatment interval, animals in the 5.0 ppm group had significantly higher food consumption. This finding was not believed to be related to the adminstration of phosphine. (See Table II).

Gross Pathology:
Most of the lesions observed in this study were in the 14 animals that were in the 7.5 ppm group. The lungs and the liver were the primary organs with pathology. Discoloration of both of these organs was reported (6/14 lungs and 3/14 livers).

Discolored lungs were observed in 1/24, 2/27, 1/24 and 1/24 animals that received 0, 0.03, 0.3 and 5 ppm , respectively. Dilated renal pelvises were reported in all groups of animals receiving phosphine, but without a dose related increase in the frequency. Emphysema was reported in one animal which received 3 ppm. Lymph node enlargement was reported at the two lowest doses of phosphine but was not present at 3 and 5 ppm. Hair loss was reported in one control animal, in one animal receiving 0.03 ppm and in two animals receiving 5 ppm.

None of these findings were believed to be related to the adminstration of phosphine.

REPRODUCTIVE EFFECTS
In the low dose group (0.03 ppm) the mean number of resorptions and the mean number of litters with resorptions were statistically significantly higher than controls. However, this observation was not made in groups receiving higher levels of phosphine (no data were provided for the animals receiving 7.5 ppm). This increase in the mean number of resorptions is not believed to be compound related since similar findings were not present in animals receiving higher levels of the compound. (See Table III, derived from data provided by the sponsor).

FETAL EFFECTS
No compound related observations were made with regard to the external, visceral or skeletal malformations in fetuses from dams exposed to phosphine. External malformations included one fetus with a filamentous tail in the 0.03 ppm group. In the 0.3 ppm group, one fetus had both micrognathia and a rudimentary tongue; in the 5 ppm group, one fetus was both edematous and had a curly tail. No skeletal malformations were observed in control and 3 ppm dose groups.

Visceral variations in the control group consisted of tortuous

ureters in four fetuses (involving three litters). This abnormality was also present at all doses above 0.03 ppm, but with a lesser frequency than in controls (2 fetuses /2 litters at 0.3 and 3.0 ppm and 2 fetuses /1 litter at 5 ppm).

Malformations included microphthalmia which was observed in 1 fetus in both the 0.03 group and the 3.0 ppm group. Cleft palate was present in the same fetus at 3 ppm . Folded retinas were present in one animal in the lowest and one animal in the highest dose groups. One fetus in the high dose group had abnormalities that were limited to the cardiovascular system and included persistent truncus arteriosus, absence of the ductus arteriosus and the presence of a ventricular - septal defect.

No skeletal malformations were present in the high dose or control fetuses. In the low dose group, one fetus had a variety of skeletal malformations (absent lumbar, sacral and caudal vetebrae and a filamentous tail) At 0.3 ppm, one fetus had a short, thickened mandible and a misshapened palatine process and another fetus from a different litter had a cervical rib. At 3 ppm, skeletal malformations included presence of a cervical rib, branched cervical transverse processes, absent thoracic transverse processes, decrease in the number of thoracic vertebrae, fused ribs and the presence of 5 lumbar vertebrae.

Skeletal variations were present in all groups at similar frequencies and were not associated with the adminstration of the test compound.

Because of the low incidence of malformations and the low number of litters affected, the findings are not believed to be associated with the administration of phosphine. (See Table IV for external, visceral and skeletal malformations).

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Analytical data

Table I: Mean Body Weight Gains (grams)[a]

Group:	Prior to Dosing Period	Dosing Period	Post Dosing Period	Entire Gest'n Period	Corrected Dosing Period	Entire Study
Control	29	44	53	126	-24.5	48.5
0.03	29	45	51	125	-22.3	51.7
0.30	25	45	54	124	-19.1	50.9
3.00	28	43	56	127	-18.8	52.2
5.00	31	43	58	132	-19.5	54.5

a = data extracted from study report.

Food Consumption

Table II: Mean Food Consumption Data (g/kg/day)[a]

Group:	Prior to Dosing Period	Dosing Period*	Post-Dosing Period	Entire Gestation Period
Control	84	152	83	319
0.03	86	151	86	323
0.30	81	155	85	321
3.00	87	150	86	323
5.00	89	153	91**	333

a = data taken from report submitted by sponsor

* = Dosing period covers days 6-15; however, food consumption measured during the interval which covered days 10-16

** = $p \leq 0.05$

Cesarean section Observations

Table III: Cesarean Section observations[a]

Dose:	Control	0.03	0.30	3.0	5.0
#Animals Assigned	24	27	24	24	24
#Animals Mated/Inseminated	24	27	24	24	24
Pregnancy Rate (%)	91.7	87.5	100	95.8	95.8
Maternal Wastage					
#Died (Total)	0	0	0	0	0
#Died/pregnant	0	0	0	0	0
#Non pregnant	2	3	0	1	1
#Aborted	0	0	0	0	0
#Premature Delivery	0	0	0	0	0
Total Corpora Lutea	353	342	383	365	370
Corpora Lutea/dam	16.0	16.3	16.0	15.9	16.1
Total Implantation	339	329	352	346	355
Implantations/Dam	15.4	15.7	14.7	15.0	15.4
Total Live Fetuses	327	296	335	326	338
Live Fetuses/Dam	14.9	14.1	14.0	14.2	14.7
Total Resorptions	12	33*	17	20	17
Resorptions/Dam	0.5	1.3*	0.7	0.9	0.7
# Litters w/resorptns(%)	8(36)	16(76)	9(38)	14(61)	10(44)
Total Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam					
Mean Fetal Weight (gm)	3.24	3.18	3.26	3.28	3.22
Preimplantation Loss(%)	4.0	3.9	8.1	5.2	4.1
Postimplantation Loss(%)	3.5	10.0	4.8	5.7	4.8
Male: female ratio	1.0	0.9	1.1	1.1	1.0

[a] = Data extracted from (study or report number and tables or appendices used)

* $p \leq 0.05$

Developmental Toxicity

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Table IV: External Examinations[a]

Observations	DOSE 0	0.03	0.30	3.0	5.0
#pups(litters) exmnd	327(22)	296(21)	335(24)	326(23)	338(23)
#pups(litters) affctd	0	1(1)	1(1)	0	1(1)
fetal (litter) incidence					
edematous	0	0	0	0	1(1)
filamentous tail	0	1(1)	0	0	0
micrognathia	0	0	1(1)	0	0
rudimentary tongue	0	0	1(1)	0	0
curly tail	0	0	0	0	1(1)

Table IV: Visceral Examinations

Observations	DOSE 0	0.03	0.30	3.0	5.0
#pups(litters) exmnd	161(21)	151(21)	174(24)	167(23)	175(23)
#pups(litters) affctd	4(3)	2(2)	1(1)	1(1)	2(2)
fetal (litter) incidence					
Cleft palate	0	0	0	1(1)	0
microphthalia	0	1(1)	0	1(1)	0
folded retina	0	1(1)	0	0	1(1)
distended 3rd ventr.	0	1(1)	0	0	0
Cardiovascular defects (truncus arteriosus, absent ductus arteriosus ventricular-septal defect)	0	0	0	0	1(1)

Table IV: Skeletal Examinations

Observations	DOSE 0	0.03	0.30	3.0	5.0
#pups(litters) exmnd	158(22)	146(21)	163(24)	159(23)	163(23)
#pups(litters) affected	0	1(1)	2(2)	3(3)	0
fetal (litter) incidence					
short mandible	0	0	1(1)	0	0
misshapen basisphenoid	0	0	1(1)	0	0
misshapen palatine proc.	0	0	1(1)	0	0
cervical rib	0	0	1(1)	1(1)	0
branched cerv.trans proc.	0	0	0	1(1)	0
abs. thor. trans . proc.	0	0	0	1(1)	0
decr. in # of thoracic	0	0	0	1(1)	0
5 lumbar vetebra	0	0	0	1(1)	0
abs. lumbar vert.	0	1(1)	0	0	0
abs. sacral vert.	0	1(1)	0	0	0
abs.caudal vert.	0	1(1)	0	0	0
fused ribs	0	0	0	1(1)	0

a = data taken from study report.

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D. Discussion/Conclusion

Based on the results from this study, phosphine, when delivered via the inhalation route was not associated with maternal, reproductive or developmental toxicity at doses up to 5 ppm. At 7.5 ppm, a high incidence of maternal deaths occurred and this group had to be removed from the study. No analysis was made with regard to the effect that phosphine at 7.5 ppm had on the developmental and reproductive parameters.

All of the reported malformations lack a dose related increase in the frequency of their occurence and are at such a low number that they are not considered to be related to the administration of phosphine.

Maternal, developmental and reproductive NOELs = 5 ppm. The maternal LEL is 7.5 ppm, based on the deaths reported at that dose level.

E. Core Classification: Minimum

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00975303

Date of Entry: 90/01/10 Reviewer: ~~Gross~~ Mazzaw

Tox. Chem. #: 031 Chemical Name: AlP

HED Project #: 1-0039 Date in Section: 10/1/90
Date out of Section:

Beans: 3
TECH: 193T

Tox. Due Date: 12/20/90
RD Due Date: 12/29/90

D - drop for now
H - high RD, SR
M - med. RD, SR
Priority Code: M

Record #'s: S382263
EPA ID #'s: 066501

Comments

Acute inhal(Dyn), inhal terat, 2 muta(dyn), sub chr (dyn)
CECH 133, TECH 87 (was originally 0-80025