NATIONAL TOXICOLOGY PROGRAM

EXECUTIVE SUMMARY OF SAFETY AND TOXICITY INFORMATION

PHOSPHINE

CAS Number 7803-51-2

November 30, 1990

Submitted to:

NATIONAL TOXICOLOGY PROGRAM

Submitted by:

Arthur D. Little, Inc.

Executive Committee Draft Report

TABLE OF CONTENTS

OVERVIEW

Nomination History: *Phosphine was nominated for carcinogenicity (inhalation) testing by the National Cancer Institute in 1989. The nomination was based on its high production, widespread use, and potential for significant human exposure, and the lack of toxicity data.*

Chemical and Physical Properties: *Phosphine is a colorless, flammable gas with a disagreeable odor. It is highly reactive with oxygen and other oxidizing agents, and halogens. Phosphine has a vapor pressure of 760 mmHg @ -87.5°C and a vapor density of 1.17.*

Production/Uses/Exposure: *Phosphine is widely used as a fumigant against insects and rodents in stored grain, leaf tobacco and railroad box cars. Phosphine is also used in the semiconductor industry in the treatment of silicon crystals, and as a vapor-phase dopant gas in the production of organophosphines and phosphonium halides. However, tertiary butyl phosphine is currently being considered as a replacement for phosphine in this usage. No specific production data were found for phosphine. The National Occupational Exposure Survey indicate that 9,234 workers, including 3, 186 female employees, were potentially exposed to phosphine between 1981 and 1983. Consumer exposure to phosphine from rodenticides and fumigants is limited because of legal restrictions on zinc phosphide formulations. The EPA has established a tolerance level of 0.01 ppm for phosphine in or on processed foods. The maximum residue limit for raw cereals is 0.1 ppm. The OSHA permissible exposure limit for phosphine is 0.3 ppm (0.4 mg/m$^{3)}$, and the OSHA short-term exposure limit is 1 ppm (1 mg/m^3). The ACGIH-recommended threshold limit value-time weighted average is 0.3 ppm (0.42 mg/m^3), and the short-term exposure limit is 1 ppm (1.4 mg/m^3).*

Toxicological Effects:

Human: *Many of the case reports described in the literature concern indirect exposure to phosphine from phosphine-releasing aluminum phosphide tablets. Acute symptoms include neurological (headache, dizziness, paresthesia), gastrointestinal (vomiting, diarrhea), and respiratory abnormalities (shortness of breath, pulmonary edema, cardiac arrest) as well as lung and liver congestion, and in some instances coma and death. Symptoms of acute phosphine poisoning following suicide attempts from the ingestion of aluminum phosphide tablets including numbness of the limbs, peripheral vascular failure, renal and hepatic failure, coma and death have reportedly occurred. Chronic exposure to phosphine has reportedly caused anorexia, anemia, and pulmonary edema. In an epidemiological study of grain mill workers, an increased incidence of non-Hodgkins lymphoma, leukemia and pancreatic cancer was found among flour mill workers exposed to pesticides, including phosphine. There are no data available on the reproductive or teratogenic effects of phosphine in humans.*

Animal: *In rat studies, acute and prechronic inhalation of phosphine has been found to cause respiratory irritation (polyuria, dyspnea, loss of muscular coordination, paralysis and lung damage). In the majority of animal studies reported, phosphine was not found to induce chronic effects. In a feeding study, chronic exposure to phosphine caused increased organ weight gain (thymus and lungs), ulceration and necrosis of the colon, and increased development of lymphoid tissue in rats. In this study, no difference in tumor incidence between the control and treated rats was observed. There are no other data available on the carcinogenic effects of phosphine on animals. There are limited data available concerning the reproductive and teratogenic effects of phosphine in animals. In the one study concerning reproductive toxicology described in the literature, phosphine was not found to induce reproductive effects in rats.*

Genetic Toxicology: *In a case study of fumigant applicators, phosphine exposure was found to be associated with an increase in chromosome aberrations, chromosome deletions, and chromosome gaps and breaks. This effect was also demonstrated in vitro by the same authors, using cultured human lymphocytes. No other data were found concerning the genetic effects of phosphine on humans, and there were limited data available on the mutagenic effects of this compound in prokaryotic and eukaryotic systems. In one study reported, phosphine was found to be mutagenic to Drosophila melanogaster.*

Structure Activity Relationships: *No data were found on structure activity relationships for phosphine.*

I. NOMINATION HISTORY AND REVIEW

A. Nomination History

1. Source: National Cancer Institute [NCI, 1989 a,b]

2. Date: March, 1989

3. Recommendations: Carcinogenicity (inhalation)

4. Priority: High

5. Rationale/Remarks:
   - High production
   - Widespread and diverse uses; used in the semiconductor industry and in agricultural products
   - Potential for significant human exposure
   - Limited toxicity data

B. Chemical Evaluation Committee Review

1. Date of Review: September 12, 1990

2. Recommendation: No Testing

3. Priority: --

4. NTP Chemical Selection Principles: --

5. Rationale/Remarks:
   - Chemical is highly reactive and readily decomposes to toxic products even under high vacuum; thus, it is not clear if human exposure is to phosphine or its decomposition products.
   - Generation of pure test material will be difficult.
   - Some human data are available.
   - Chromosomal aberrations observed in fumigant applicators exposed to phosphine and other fumigants.
   - NCI epidemiological study of grain workers indicated an increased incidence of non-Hodgkin's lymphoma, and

suggestions of leukemia and pancreatic cancer. Phosphine or an 80/20 ratio of carbon tetrachloride and carbon disulfide have been routinely used for grain fumigation. Since these are used during the day when most employees are present, they are the most likely agents to be implicated in the increased incidences cited. The EPA has recently curtailed the use of the carbon tetrachloride/carbon disulfide mixture, and this will sharply increase the use of phosphine.

- NCI and EPA are now jointly designing a five year+ prospective study of 150,000 workers in the grain handling industry. Phosphine will be one of the few compounds which will be spotlighted in this study.

C. Board of Scientific Counselors Review

1. Date of Review: October 15, 1990

2. Recommendations: • No testing

3. Priority: --

4. Rationale/Remarks:
   - Phosphine is unstable and decomposes readily; exact nature of decomposition products to which humans are exposed is not known
   - Generation of pure test material would be difficult in animal studies
   - NCI and EPA are collaborating on an epidemiological study of workers in the grain handling industry which will examine the issue of phosphine toxicity

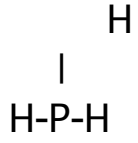
D. Executive Committee Review

1. Date of Review:

2. Decision:

II. CHEMICAL AND PHYSICAL DATA

A. Chemical Identifiers



PHOSPHINE

Molecular formula: H_3P Molecular weight: 34.04

CAS No. 7803-51-2
RTECS No. SY7525000

B. Synonyms and Trade Names

Synonyms: hydrogen phosphide; phosphorated hydrogen; phosphorus trihydride

Trade names: Celphos; Delicia; Detia; Gas-Ex-B; Detia Gas-Ex-T; Delecia Gastoxin; RCRA Waste Number PO96; UN 2199

C. Chemical and Physical Properties

Description: Colorless gas with a disagreeable odor of carbide or decaying fish [Baselt and Cravey, 1989] or garlic [ACGIH, 1986] (odor threshold: 0.02 ppm [NIOSH, 1987])

Melting Point: -133.5°C (-208.3°F) [Weast, 1989]

Boiling Point: -85°C (-121°F) [Sax and Lewis, 1987]

-87.7°C (-125.9°F) [Braker and Mossman, 1980; Weast, 1989]

Specific Gravity/ Density: 0.57 @20 atm [NFPA, 1986]
1.529 g/L [Dean, 1985]

Refractive Index: 1.000 800 @ 25°C [Braker and Mossman, 1980]

Solubility in Water: Slightly soluble in cold water (26 cm^3/100 ml water [Braker and Mossman, 1980]); insoluble in hot water [Sax and Lewis, 1987]

Solubility in OtherSolvents: Soluble in alcohol, ether, cuprous chloride solution [Sax and Lewis, 1987]

Log Octanol/Water Partition Coefficient: No data available

Reactive Chemical Hazards: Explosive in the presence of traces (0.2%) of diphosphane. However, pure phosphine does not spontaneously ignite in air below 150°C unless it is thoroughly dried, when it ignites in cold air [Bretherick, 1985]. Reacts violently with oxygen, other oxidizing agents and halogens [ITII, 1988]; incompatible with acids, halogenated hydrocarbons and moisture [NIOSH, 1987], boron trichloride, bromine, chlorine monoxide, nitrogen trichloride, nitrogen trioxide and silver nitrate [NFPA, 1986]. Decomposition products include oxides of phosphorus, phosphoric acids mist and hydrogen [NFPA, 1986]

Flammability

Hazards:

- Flammable (Dry phosphine is spontaneously flammable in cold air [NFPA, 1986])
- Vapor Pressure: 760 mm Hg @-87.5°C [Hermann, 1983]
- Vapor Density: 1.17 [NFPA, 1986]
- Autoignition Temperature: 100°C (212°F) [NFPA, 1986]; 377°C (100°F]) [Sax and Lewis, 1987]
- Flammable Limits in Air: Lower - 1% [Sax and Lewis, 1989] Upper - no data available
- Flash Point: No data available

III. PRODUCTION/USE

A. Production

1. Manufacturing Process

- Since its original preparation [Gengembre, 1785; Kirwan, 1786] and the subsequent study of its reactions [Davy, 1809] numerous studies of phosphine have been undertaken [Fluck and Novobilsky, 1969].

- Produced by the hydrolysis of an active metal phosphide or from the acid or base catalyzed reaction of elemental phosphorus with water [Baselt and Cravey, 1989; Kirk-Othmer, 1985], or by direct combination of phosphorus and hydrogen under pressure [Braker and Mossman, 1980].

- Formed as a co-product in the manufacture of hypophosphites by the reaction of white phosphorous with alkali [WHO, 1988].
- Produced as a by product in the manufacture of acetylene through the hydrolysis of calcium carbide if calcium phosphide is present as an impurity [WHO, 1988].

2. Producers and Importers

U. S. Producers:

- American Cyanimid Company
  Wayne, New Jersey/Atlanta, Georgia/Charlotte, North Carolina [USEPA, 1990; Chemical Week Buyer's Guide, 1989]

- Atomergic Chemetals Corporation
  Farmingdale, New York [Chemical Week Buyer's Guide, 1989]

- Great Western Inorganics, Inc.,
  Golden, Colorado [USEPA, 1990]

- Hooker Chemicals and Plastics
  Niagara Falls, New York [USEPA, 1990]

- Nashville Plant
  Nashville, Tennessee [USEPA, 1990]

- Matheson Gas Products, Inc.
  Gloucester, Massachusetts [SRI, 1989; USEPA, 1990]

- Phoenix Research Corporation
  La Mesa, California [SRI, 1989; USEPA, 1990]

- Solkatronic Chemicals Inc.
  Fairfield, New Jersey [Chemical Week Buyer's Guide, 1989]

- Synthatron Corporation,
  Parsippany, New Jersey [USEPA, 1990]

- Union Carbide Industrial Gases, Inc., Linde Division
  Somerset, New Jersey [Chemical Week Buyer's Guide, 1989]

European Producers:

- L'Air Liquide SA, Gas Department

France (plant location not specified) [SRI, 1989]

- Albright & Wilson Ltd.,Phosphates Group
  West Midlands, United Kingdom [SRI, 1989]

- Hoechst AG
  Nordrhein Westfalen, Germany [SRI, 1989]

- Ucar Specialty Gases
  Antwerpen, Belgium [SRI, 1989]

Importers:

- Airco Gases
  Murray Hill, New Jersey [Chemical Week Buyer's Guide, 1989]

- Alphagaz Div. Liquid Air Corporation
  Walnut Creek, California [Chemical Week Buyer's Guide, 1989]

3. Volume

Phosphine was not listed in the United States International Trade Commission's publication Synthetic Organic Chemicals for the years 1985-1988 [USITC, 1986-1989].

The volume of phosphine produced at the following plants in 1977 is reported in the public file of the EPA Toxic Substances Control Act (TSCA) Inventory [USEPA, 1990]:

Plant	1977 Production Volume (lbs)
Nashville Plant	1,000,000 - 10,000,000
Synthatron Corporation	1,000 - 10,000
Phoenix Research Corporation	Less than 1,000
Hooker Chemicals and Plastics	100,000 - 1,000,000

4. Technical Product Composition

Phosphine is available as a chemically pure electronic grade with a minimum purity of 99.999% [Braker and Mossman, 1980]. Technical grade phosphine contains substituted phosphines and diphosphine (up to 5%). Depending on the

method of manufacture, other impurities may include methane, arsine, hydrogen and nitrogen [WHO, 1988].

B. Use

- Widely used fumigant against insects and rodents in stored grain and leaf tobacco [Arena, 1986; Baselt and Cravey, 1989; WHO, 1988].

- Treatment of silicon crystals in the semiconductor industry [Arena, 1986] (t-Butyl phosphine is being considered as a replacement for phosphine in this usage [SOEH, 1990]).

- Polymerization initiator and condensation catalyst [Sax and Lewis, 1987].

- Vapor phase dopant gas in the manufacture of organophosphines and phosphonium halides [Sax and Lewis, 1987].

- Acid cleanser for metals [ITII, 1988].

- Used in the preparation of alkyl and aryl phosphonium halides in textile treatment [Mackison, et al., 1981].

- Organic intermediate [Mackison, et al., 1981].

- Curing catalyst for epoxy resins [Mackison, et al., 1981].

- Organophosphines used in oil-additive and pharmaceutical applications [WHO, 1988].

IV. EXPOSURE/REGULATORY STATUS

A. Consumer Exposure

Consumers may be exposed to phosphine from the use of zinc phosphide formulations which are available as rodenticides. However, exposure is limited due to the strict regulation of these products (see Regulatory Status IV. D., p. 8).

B. Occupational Exposure

Data from the National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, indicate that 9,234 workers, including 3,186 female employees, were potentially exposed to phosphine in the workplace. The NOES data base does not contain information on the frequency, level, or duration of exposure to workers of any chemicals listed therein [NIOSH, 1990].

Occupational exposure to phosphine may occur among workers producing phosphine and phosphides, workers employed in operations that can release phosphine, fumigators and pest-control employees as well as workers involved in the transport of phosphine containing products [WHO, 1988].

In industry, exposure to phosphine may result when phosphine is released as a by-product of various processes. Exposures may occur when acid or water comes in contact with metallic phosphides including aluminum phosphide and calcium phosphide. Phosphine may also evolve during the generation of acetylene from impure calcium carbide, as well as during metal shaving, sulfuric acid tank cleaning, rust proofing and ferrosilicon, phosphoric acid and yellow phosphorus explosive handling [Sittig, 1985].

Phosphine is formed during many metallurgical operations including the dissolution of metals containing trace amounts of phosphorus, the reaction of a ferroalloy or intermetallic compound containing traces of phosphorus and the decomposition of carbides containing traces of phosphorus. Exposure to phosphine in the various metallurgical industries (hydrometallurgy, pyrometallurgy, electrometallurgy) has been reported to be a "common phenomenon [Habashi and Ismail, 1975]."

Grain elevator employees' exposure to phosphine during the application of aluminum phosphide in grain elevators has been

evaluated. The data obtained from four industrial hygiene surveys conducted between 1985 and 1986 indicate that the use of aluminum phosphide as a fumigant can result in "demonstrable and occasionally excessive" exposures to phosphine. Based on integrated area and short-term samples analyzed by portable gas chromatography, significant exposure to phosphine may occur during the following processes: charging, recharging, and emptying automatic dispensers as well as during the filling of bins with phosphine-treated grain. In addition, several short-term samples obtained at the start of fumigation runs, indicate that significant applicator exposures to phosphine occur as soon as the original container is opened. This is most likely a result of aluminum phosphide reacting with moisture inside the container, with the subsequent release of phosphine when the flask is opened [Zaebst, et al., 1988]. Recent work indicates that the release of phosphine from aluminum phosphide tablets may occur in as little as 5 minutes [Garry, et al., 1989].

C. Environmental Exposure

Phosphine occurs infrequently in the environment. It may be present transiently in marsh gas and other sites of anaerobic degradation of phosphorus containing matter [WHO, 1988]. In the hydrosphere, bacterial processing of sewage sludge generates phosphine as a byproduct, and is therefore a source of environmental contamination [Garry, et al., 1989].

In addition to natural sources, atmospheric phosphine results from the use of phosphides as rodenticides and fumigants and as a result of emissions and effluents from industry. Phosphine may be emitted from stacks of fossil fuel-burning power plants [Sax, 1984]. In addition, the release of phosphine to the environment near photovoltaic cell plants from stacks, or from leaks in storage, distribution, or process systems has been reported. Quantitative estimates of uncontrolled and controlled pollutant effluents from photovoltaic cell plants during normal operation are presented in Table 1. From plants where phosphine is used only as a dopant gas, only small quantities are expected in the effluent streams. However, the use of

phosphine in the production of zinc phosphide photovoltaic cells may present a large hazard to public and occupational health [Fthenakis and Moskowita, 1987].

TABLE 1
Phosphine Emissions From Thin-Film Photovoltaic Cell Plants

Type of Plant	Emissions (kg/h)[a] Uncontrolled	Controlled[b]
Zn_3P_2 MOCVD[c]	4×10^{-1}	2×10^{-2}
a-Si glow discharge	5×10^{-5}	3×10^{-6}
a-Si reactive sputtering	5×10^{-5}	3×10^{-6}
a-Si chemical vapor disposition	1×10^{-4}	7×10^{-6}

[a]Plant operating 24 h day-[1], 350 days year-[1], with annual production of PV cells
generating 10 MWp.

[b]Based on 95% scrubber efficiency, with NaOCl-KOH scrubber.

[c]Metallorganic chemical vapor deposition

D. Regulatory Status

- The current OSHA permissible exposure limit (PEL) is 0.3 ppm (0.4 mg/m^3), averaged over an eight-hour work shift. The current OSHA short-term exposure limit (STEL) is 1 ppm (1 mg/m^3) [OSHA, 1989].

- Phosphine is regulated by the Environmental Protection Agency (EPA) under the Resource Conservation and Recovery Act (RCRA); The Superfund Amendments and Reauthorization Act (SARA) Title III Section 302, Extremely Hazardous Substances, and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [Roytech, 1989].

- Zinc phosphide formulations, which are a major source of phosphine exposure, are legally restricted in many countries. However, they are available to consumers in some countries

for use as rodenticides. In addition, in most countries there is strict regulation of fumigation to prevent public exposure to phosphine, which limits phosphine exposure [WHO, 1988].

- The United States EPA has established a tolerance level of 0.01 ppm for phosphine in or on processed foods (cereal grains, flour and other milled cereal products, dried foods, fruits, vegetables, spices, cocoa, beans, nuts, peanuts and breakfast cereals). The regulation requires that the finished food should be aerated for 48 hours before it is offered to the consumer, and that the formulation containing aluminum phosphide must not be used so that it, or its unreacted residues, will come into contact with any processed food. The maximum residue limit for raw cereals is 0.1 ppm in the United States. In Canada, the tolerance for raw cereals and processed foods is also 0.1 ppm, and in India the maximum residue limit is 0.05 ppm for whole food grains and 0.01 ppm for milled food grains [WHO, 1988; WHO, 1972].

E. Exposure Recommendations

- The ACGIH - recommended threshold limit value - time weighted average (TLV-TWA) is 0.3 ppm (0.42 mg/m^3). The short-term exposure limit (STEL) is 1 ppm (1.4 mg/m^3)[ACGIH, 1986; ACGIH, 1989].

- There is no NIOSH-recommended exposure limit (REL) reported in the current literature for phosphine.

V. TOXICOLOGICAL EFFECTS

A. Chemical Disposition

1. Human Data

There is limited information on the fate of phosphine in the body. Inhaled phosphine is readily absorbed by the lungs. Ingestion of a metallic phosphide resulted in the release of

phosphine in the acid medium of the stomach, followed by absorption through the gut; a certain portion of this compound may be exhaled unchanged [Baselt and Cravey, 1989].

2. Animal Data

No data were found in the literature on chemical disposition in animals.

B. Acute

1. Human Data

Phosphine gas has been reported to be extremely poisonous, and has been given a toxicity rating of "6" by Gosselin [Gosselin, et al., 1984]. Acute effects observed following exposure to phosphine are a result of central nervous system depression, lung irritation, and damage to the liver and other organs [Sittig, 1985]. In occupational settings, symptoms have been observed to occur as soon as the odor of phosphine is obvious. Acute occupational exposure has been found to cause diarrhea, nausea, vomiting, epigastric pain, tightness of the chest, palpitations, breathlessness, headache, dizziness and staggering gait. Dyspnea, decreased blood pressure, convulsions and coma have also reportedly occurred. Death has been observed to occur within four days to two weeks of exposure [Cooper, 1974], as a result of cardiac arrest or pulmonary edema [Baselt and Cravey, 1989; Sittig, 1985].

Phosphine has not been found to cause ocular or visual abnormalities. However, acute poisoning may result in dilated pupils [Grant, 1986]. Contact with phosphine has reportedly caused skin and eye burns [Dangerous Properties of Industrial Materials, 1986]. However, another source reports that this compound has not been found to cause skin irritation [Sittig, 1985].

The lowest total dose of zinc phosphide known to have caused fatality in humans is 80 mg/kg (LC_{LO}) in a female patient. According to Rodenberg et al., as of 1989, no deaths have been reported in the literature from ingestion of zinc phosphide in the United States. However, in Europe, 25 deaths (average dose of 30 g.), have reportedly occurred from ingestion of this compound [Rodenberg, et al., 1989].

2. Case Reports

The majority of the reports in the literature describe phosphine poisoning from exposure to aluminum phosphide-fumigated grain in India and Western Europe. Other case reports concern suicide attempts from the ingestion of aluminum phosphide or zinc phosphide tablets. In addition, reports of phosphine exposure in industry have been described.

- The effects of acute occupational exposure to phosphine have been investigated in 22 workers engaged in the fumigation of stored grains in India. The mean age of the workers studied was 48 (range 24-60) and their mean duration of exposure prior to the study was 11 years (range 0.5-29). The phosphine concentration in their work environment ranged from 0.17-2.11 ppm.

  During the study period, the workers took 20-30 minutes to place aluminum phosphide tablets on stacks of piled bags of grain before the stacks were covered with a gas-proof plastic cover. After one week, the covers were partially lifted and allowed to aerate for 1 hour before the covers were completely removed. (The workers did not wear personal protective clothing during this procedure, although such clothing was recommended.)

  The workers were given a medical examination immediately after placing the aluminum phosphide tablets on the grain. Symptoms reported by the workers included respiratory abnormalities - cough (18.2%), dyspnea (31.8%), chest tightness (27.3%); and neurological abnormalities- headache

(31.8%), giddiness (13.6%), numbness (13.6%), lethargy (13.6%) and irritability (9.1%). In addition, the following gastrointestinal disturbances were reported: anorexia (18.2%), epigastric pain (18.2%), nausea (9.1%) and dry mouth (13.6%). Fourteen percent of the workers reported having numbness and paresthesia in their fingers after touching the aluminum phosphide tablets, which lasted for 20-30 minutes. All of the reported symptoms appeared to be transient. No significant abnormalities in motor or sensory nerve conduction were observed.

The authors report that in another study involving 67 workers exposed to higher concentrations of phosphine (0-35 ppm), more severe toxic effects were noted. Effects including diarrhea (82%), nausea (73%), epigastric pain (65%), vomiting (29%), chest tightness (52%), breathlessness (34%), chest pain (20%), headache (83%), dizziness (35%) and staggering gait (12%) were observed [Mirsa, et al., 1988].

- A case of fatal phosphine intoxication in Belgium has been reported. Two brothers, four and two years-old, who had played on top of wheat fumigated with aluminum phosphide tablets (1 kg for 2000 tons of wheat), died within 18 hours of exposure. The children reportedly played on the wheat for more than one hour, two and one half days after fumigation. Two days after the death of the children, phosphine was detected at a level of 1 ppm at several locations above the surface of the wheat. Although the wheat was also contaminated with Malathion, phosphine exposure was believed to be the cause of death.

  Post-mortem observation of the two year-old boy revealed ecchymosis of the left side of the forehead, the corner of the right eye, and front side of both knee joints and shins. In addition, congestion of the lungs and slight congestion of the liver was observed. Post-mortem examination of the four year-old boy also revealed ecchymosis of both knees and shins. In addition, lung and slight liver congestion were observed [Heyndrickx, et al., 1976].

- A case of phosphine poisoning caused by the release of the gas from aluminum phosphide-treated grain aboard a Greek freighter has been reported. Measurements of phosphine concentrations aboard the freighter were taken after the incident (six days after fumigation). Phosphine levels were found to range from 0.5 ppm in the living quarters, to 30 ppm in a void space on the main deck.

  The wife and two children of the captain who were on board the freighter became acutely ill two days after the grain was fumigated. One child died before arriving at the hospital. Autopsy findings of this child included congestive heart failure accompanied by pulmonary edema, pleural effusion and an enlarged spleen. Microscopic examination revealed focal myocardial necrosis with mononuclear infiltrates and fragmented fibers, inflamed mitral and aortic valves, desquamated respiratory epithelium with alveoli thickened by hemolyzed red blood cells and congested capillaries.

  The other child's symptoms included nausea, vomiting, dizziness, headache, epigastric pain and fatigue. Physical and neurological examination and results of hematologic, renal and hepatic laboratory studies were normal. However, the child reportedly had transient myocardial injury.

  The captain's wife experienced nausea, vomiting and paresthesia. Physical and neurological examinations gave normal results.

  In addition, 29 of the 31 crew members became ill. The following symptoms were observed:

Shortness of breath	59%
Cough	52%
Sputum production	41%
Nasal drainage	17%
Nausea	72%
Jaundice	52%
Vomiting	45%

Diarrhea	21%
Fatigue	86%
Headache	66%
Drowsiness	62%
Dizziness	62%
Paresthesia	59%
Tremor	31%
Weakness	24%

Results from serum and urine analysis indicated that the crew members also developed urinary tract (occult blood-17%) and liver (bilirubinuria- 10%, elevated SGPT-16%, elevated GGPT-3% and elevated LDH_{5}-16%) abnormalities [Wilson, et al., 1980].

- Eight cases of acute phosphine poisoning in India following suicide attempts from the ingestion of aluminum phosphide tablets have been described. The patients (five males and three females) ranged in age from 14 to 25. Within 5-10 minutes of ingesting the tablets, the patients experienced epigastric pain and vomiting, dryness of the mouth, difficulty breathing and numbness of the limbs. All patients had peripheral vascular failure and neurological abnormalities including stupor, delirium and coma.

  One patient (patient 8, see Table 2) developed jaundice and acute renal failure and ventricular tachycardia. Six patients died after an average of 19 hours in the hospital from peripheral vascular failure, renal and hepatic failure and ventricular tachycardia. (Table 2, Clinical Summary of Aluminum Phosphide Poisoning, contains a summary of the clinical features of the 8 cases.)

  Autopsies which were performed on patients two and four revealed pulmonary edema, gastrointestinal mucosal congestion, and congestion and hemorrhages on the surface of the liver and brain. Histopathological examination of the liver showed vacuolar degeneration of hepatocytes, and dilated central veins and sinusoids filled with proteinaceous fluid and red blood cells. In several focal areas, nuclear

fragmentation was observed. Histopathological examination of the lung revealed marked pulmonary edema and vascular congestion. In some bronchioles, the lining epithelium had been completely desquamated. The spleen, kidney, heart and brain were markedly congested and showed focal areas of exudation and small hemorrhages [Misra, et al., 1988].

- A 36-year-old white male attempted suicide by ingesting a rodenticide, zinc phosphide. The estimated amount of zinc phosphide ingested was approximately 400 mg, and was ingested one to two hours before the patient was examined at the hospital. No acute effects from ingestion of this compound were observed. The patient was treated with ipecac syrup and activated charcoal. At the end of the four-hour observation period, he remained asymptomatic. The patient was discharged and failed to return to the hospital, therefore no follow up could be conducted [Rodenberg, et al., 1989].

Table 2. Clinical Summary of Aluminum Phosphide Poisoning

Patient No.	Age/sex	No. of tablets taken	Clinical Features	Remarks
1	14 (Female)	1	Gastritis, breathing difficulaty, peripheral vascular failure	discharged day2
2	31 (Male)	2	Vomiting, coma, peripheral vascular failure	died 22 h
3	19 (Male)	0.5	Gastritis, peripheral vascular failure	discharged day 5
4	26 (Male)	20	Vomiting, drowsy, peripheral vascular failure	died 5.5 h
5	25 (Male)	4	Vomiting, drowsy	died 2 h
6	25 (Male)	2	Vomiting, unconscious	died 2 h
7	24 (Female)	?	Vomiting, unconscious	died 5.5 h
8	20 (Female)	3	Vomiting, delirium, peripheral vascular failure, renal failure, jaundice, ventricular tachycardia	died 72 h

- A 43-year-old female electronics worker suffered an acute, overexposure to phosphine in a U.S. semiconductor plant. The woman opened the cover of a wafer diffusion apparatus in which an exhaust tube had become plugged. She subsequently experienced a strong odor with accompanying dizziness, shortness of breath, and a "pressure sensation in the head". She was taken to a hospital and observed

overnight and examined. Her physical examination was within normal limits, and no signs of overexposure were observed [Shusterman, et al., 1988].

- An acetylene worker who was exposed to phosphine (approximately 8 ppm) reportedly died from pulmonary edema. No other details were reported [Wald and Becker, 1986].

- A case of fatal phosphine exposure in a Japanese cargo boat carrying ferro-silicon containing a trace of calcium phosphide impurity has been reported. One of the three male crew members experienced headache, vertigo, vomiting and abdominal pain, before lapsing into a coma and dying. Congestion of "various" organs and fatty degeneration of the liver was observed during autopsy. No other details were provided [Furuno, et al., 1976].

3. Animal Data

   The acute effects of phosphine exposure have been investigated in rats. The following two studies were reported in the literature:

- The acute inhalation toxicity of phosphine has been studied in ChR-CD male rats. Six young adult male rats were used for each 4-hour exposure. All exposures to phosphine gas were conducted in an 18-liter borosilicate glass bell jar. The four-hour LC_{50} value of phosphine was determined to be 11 ppm (15 μg/liter or 0.44 μM/liter). The range of experimental doses used was not reported. At all dose levels tested, signs of mild respiratory irritation were observed including red ears, salivation, lacrimation, face pawing and dyspnea.

  Gross, pathologic examination was performed at necropsy on rats exposed for sacrifice at one, two and seven days post-exposure. Lungs, liver, spleen, kidney, testes and thymus were trimmed and weighed. Brain, heart, trachea, hilar lymph node, pancreas, epididymis, esophagus, stomach, duodenum, bone marrow, skin and eyes were also removed

and examined. No effects attributable to phosphine exposure were found in any of the tissues examined [Waritz and Brown, 1975] .

- In another acute inhalation toxicity study, phosphine gas generated from aluminum phosphide preparations was tested on adult female albino rats (CFT-Wistar). Six rats were exposed per dose. Aluminum phosphide pellets were dropped into a beaker containing distilled water located in the center of the chamber, causing an evolution of phosphine gas. Two aluminum phosphide preparations, A and B were used. By varying the number of pellets and exposure times, different concentration-time products (0.190 to 0.410 mg/h/L) could be obtained. The LC_{50} value for phosphine was determined to range from 0.22 mg/ h/L to 0.36 mg/ h/L with related exposure periods of 5.2 to 7.4 hours respectively for products A and B. The results obtained correspond to a 4-hour LC_{50} of 55 mg/m^3. The LC_{95} was found to range from 0.42 -0.49 mg/hr/L with exposure periods of 6.2 and 8.8 hours respectively for products A and B.

  The rats were observed for four weeks post-exposure. Polyuria and dyspnea were observed during exposure and the affected rats appeared listless and gasped heavily. Some rats experienced reduced muscular coordination, resulting in loss of balance. In addition, many rats became paralyzed. There was an overall decrease in body weight at the end of the first week, after which time the weights returned to normal. Seventy five percent mortality occurred during exposure and 20% of the rats died within 1-2 hours post-exposure. The survivors were autopsied at the end of the fourth week, and the weights of liver, lung, kidney, heart, spleen, ovary and adrenals were recorded. No marked morphological changes were observed, but the relative weights of the lungs increased slightly.

  Histopathological examination revealed lung damage with symptoms ranging from mild to severe cellular infiltration

around the bronchioles. Some lungs were mildly edematous [Mathu, et al., 1980].

C. Prechronic

1. Human Data

No information was found concerning the prechronic effects of phosphine on humans.

2. Animal Data

The prechronic inhalation toxicity of phosphine has been studied in ChR-CD rats. Six young, adult male rats were used per four-hour exposure during a 10-day exposure period. In the control group, 6 rats were similarly exposed to a nitrogen/oxygen atmosphere. The average concentration during the test was 0.163 μM/liter phosphine. The clinical signs observed during exposure were indicative of mild respiratory irritation-lacrimation, salivation, dyspnea, and red ears. Phosphine also reportedly caused a slight, transient decrease in weight gain during the exposure period.

For all exposures, three test and three control rats were sacrificed for gross and histopathologic examination immediately after the last exposure. In addition, three test and three control rats were sacrificed fourteen days after the final exposure. The lungs, liver, spleen, kidney, testes, thymus, brain, heart, trachea, hilar lymph node, pancreas epididymis, esophagus, stomach, duodenum, bone marrow, skin and eyes were examined microscopically. No gross or histopathologic effects attributable to phosphine expose were observed [Waritz and Brown, 1975].

D. Chronic/Carcinogenicity

1. Human Data

Chronic inhalation of phosphine at sub-toxic doses (exposure levels not reported) has been observed to cause toothache, swollen jaw, and mandibular necrosis. Other symptoms

include anorexia, weight loss, anemia, tendency toward spontaneous bone fractures, restlessness, fatigue, coughing and thirst. Headache and dizziness may be associated with disturbances of speech, vision and gait [Cooper, 1974]. Prolonged inhalation of phosphine gas had been found to cause vomiting, decreased blood pressure, dyspnea, pulmonary edema, circulatory collapse, convulsions and coma [Arena, 1986].

2. Epidemiological Evidence/Case Reports

An epidemiological study of cancer mortality in the U.S. flour industry has been reported. The mortality experience among 22,939 white male workers who were current or former members of the American Federation of Grain Millers' life insurance program was assessed for the period 1955 through 1985 in a cohort mortality analysis and in a nested case-control analysis. Members in the life insurance program included employees at grain elevators, flour mills, animal feed-processing plants, soybean-processing plants, plants that blended flour and other ingredients, a beet sugar-processing plant, a prepared foods plants, and a potato-processing plant.

Workers in flour mills had a slightly non-significantly elevated risk of developing non-Hodgkin's lymphoma (SMR=149), leukemia (SMR=136) and pancreatic cancer (SMR=133) compared to the general population of U.S. white males. SMRs for non-Hodgkin's lymphoma increased by the number of years since first employment. Flour millers with 20 or more years of follow-up since first employment in the industry were at a statistically significant (P=.03) excess risk of developing non-Hodgkin's lymphoma. The SMRs for pancreatic cancer also increased significantly with time since first employment in flour mills (P=0.03), but the risk of leukemia did not seem to be related to time since first employment (P=.89). Within the flour mills, employees who had worked in the maintenance department (OR=8.1) or in the grain elevator department (OR=2.8) were at particularly elevated risk of developing non-Hodgkin's lymphoma.

A survey of current and retired workers in the cohort revealed that twice as many flour mill employees applied pesticides including carbon tetrachloride, malathion, ethylene dibromide, methyl bromide, pyrethrum and phosphine, during normal work operations than workers in other subdivisions in the industry. Flour mill employees in the grain elevator department are likely to have the greatest chemical exposure from the application of grain fumigants. However, the authors report that it is difficult to assess historical exposures to pesticides for individual workers in the grain industry, as actual measurements of pesticide exposure are rare, and the records documenting worker application of pesticides are not available [Alavanja, et al., 1990].

2. Animal Data

- The effects of phosphine-releasing tablets composed of aluminum phosphide have been examined during a 2-year feeding study using albino Wistar rats. The experimental animals were divided into 2 groups, comprised of 30 males and 30 females. The control group received untreated basal diet for the duration of the study. The experimental group received diets treated with Phostoxin® at a level of 48 g/metric ton from week 1 through week 16, and 90 g/metric ton from week 17 through week 104 (6 grams of Phostoxin® pellets per metric ton of feed were used. Three grams of Phostoxin® pellets contain approximately 2 grams of aluminum phosphide which yields 1 gram of phosphine when decomposed). The diet was fumigated for 48-72 hours and aerated for 48 hours prior to consumption. Quantitative analysis of phosphine concentrations indicated that the levels ranged from 0.377 mg/kg to 7.50 mg/kg.

  No discernible toxicologic effects were observed concerning the behavior, general appearance, survival and body weight of the animals. In addition, there were no significant differences between the experimental and control groups regarding hematology, blood chemistry, urine and bone

marrow smear evaluations. Significant pathologic changes were not observed microscopically or at necropsy, that were attributable to the treated diet [Hackenberg, 1972].

- The effects of chronic ingestion of a phosphine-fumigated diet have been studied on 120 Sprague-Dawley rats. The control group received a standard laboratory diet, while the treated group received the same diet fumigated with phosphine at a constant level of 2000 ppm. The diet was aerated for 48 hours before consumption and the average residual level of phosphine was 5 ppb. The levels of phosphorus were 6946 ppm for the treated diet and 7139 ppm for the control diet. Thirty males and thirty females comprised both the control and experimental groups.

  Daily records of the general condition of the animals were maintained. In addition, blood and urine samples were taken every 3 months from 10 males and 10 females in each group. The rats receiving the phosphine fumigated diet showed no particular behavioral abnormalities or modification of growth or food intake changes, compared with rats on the untreated diet. In addition, no significant hematological differences were observed between the treated and untreated groups. Furthermore, none of the plasma or urinary measurements showed consistently significant variations between treated and control rats.

  After 1 year of feeding, 19 male and 20 female control rats and 20 male and 19 female treated rats were sacrificed. The survivors of the remaining 40 animals were sacrificed after 2 years for histopathological examination. No significant organ weight differences were noted between the control and treated groups after 1 year, with the exception of the thymus which was slightly heavier in the treated females (mean body weight of 0.35 g/100 g in the control group versus 0.47 g /100 g body weight in the treated group {$P<0.05$}). Macroscopic examination of the organs after one year revealed no abnormalities, although several histopathological changes were observed after one year, including congestion of the duodenum (1 of the 18 controls

versus 6 of the 15 treated rats), ulcerous and necrotic zones in the colon (1 of the 18 controls versus 3 of the 15 treated rats) and pigmentation indicative of degeneration of the lung (none of the 18 controls versus 1 of the 15 treated rats) and thymus (none of the 17 controls versus 5 of the 13 treated rats). P values were not reported for these results.

In the rats sacrificed after two years, a significant difference in organ weight of the thymus and lungs was observed between treated and untreated females. The mean thymus weight of 10 female rats in the control group was 0.10 g /100 g body weight versus 0.13 g/100 g in the treated group {P<0.05}, and the mean lung weight in the control group was 0.48 g/100 g body weight versus 0.41 g/100 g body weight in the treated group {P<0.01}). In addition, the colons of some treated male rats had an increase in ulceration and necrosis (none of the control males versus 2 of the 10 treated males), and a greater development of lymphoid tissue (none of the controls versus two of the treated males).

No differences in tumor incidence were observed between the control and treated groups [Cabrol, et al., 1985]. No other information was available in the literature concerning the carcinogenic effects of phosphine on animals.

- From an abstract of a German study, it was reported that chronic inhalation experiments were carried out on cats, guinea pigs and rats exposed to phosphine at concentrations of 1 and 2.5 ppm (1.4 or 3.5 mg/m^3) for 4-6 hours per day, for a total of more than 800 hours over a 24 week period. There was no evidence of chronic toxicity at either dose level. No other information was reported [Klimmer, 1969].

E. Reproductive Effects and Teratogenicity

1. Human Data

No data were found on the reproductive and teratogenic effects of phosphine in humans.

2. Animal Data

- In the abstract from a French study, it was reported that a phosphine -fumigated diet (5 ppb phosphine) fed to Sprague-Dawley rats did not cause reproductive effects or cumulative toxicity in three generations of rats. Various parameters were analyzed including fertility index, viability index and nutritional index [Cabrol, et al., 1986]. No other data were found.

F. Genetic Toxicology

1. Human Data

The following study concerning the genetic toxicology of phosphine in humans has been described. No other data were found in the literature.

- A group of 24 fumigant applicators participated in an *in vivo* study of the genotoxic effects of phosphine and other pesticides. Nine of the applicators were exposed to phosphine alone, 11 to phosphine and other pesticides, while 4 were not exposed to phosphine. Average exposure levels for the fumigant applications was 2.97 mg/m^3 for workers engaged in enclosed space application. For workers involved in open-air application, exposure levels ranged from 0.1 to 0.90 mg/m^3. Community control subjects were selected from a range of occupations. Agricultural industry control subjects were also chosen who were engaged in the inspection and processing of grain, but not routinely exposed to phosphine in their work. Only males were included in the study population. Blood specimens were obtained at least twice during the application season and again six weeks to three months after the season's work was completed. Specimens from the control subjects were obtained throughout the season, within three days of receipt of test specimens. One hundred metaphase

lymphocytes from each sample were analyzed yielding the following results:

Fumigant applicators (exposed to phosphine alone and exposed to phosphine and other pesticides) were found to have 3.58 times more total chromosome aberrations (excluding gaps) than control subjects ($P<0.001$). In addition, phosphine-exposed workers had a five-fold increase in chromosome deletions compared to control subjects ($P<0.001$). Chromosomal gaps and breaks were significantly increased among phosphine workers compared to control subjects ($P<0.02$ and $P<0.01$, respectively). There were no significant differences in sister chromatid exchanges between the applicator groups and control subjects. Among workers who used phosphine and other pesticides or who used other pesticides and fumigants, there were more deletions and breaks than in control subjects ($P<0.05$).

The same pattern of chromosomal aberrations in the phosphine exposed workers observed *in vivo* was demonstrated *in vitro* by the same authors. Specifically, a dose-related increase in gaps and deletions was observed ($P<0.01$), following the treatment of cultured lymphocytes with phosphine at doses ranging from 0.26 μg/liter to 4.50 μg/liter. Lymphocytes treated with phosphine *in vitro* were not found to have an increase in sister chromatid exchanges. In addition, other agents to which the workers were exposed (malathion, methyl bromide, chloropicrin or carbon disulfide) were not found to induce this pattern of chromosome aberrations in lymphocytes treated *in vitro* with these pesticides.

After completion of the fumigation season, Garry et.al. investigated whether the chromosomal aberrations that were observed in the applicator group could still be detected. Specimens were obtained from 12 of the same group of workers (6 from the phosphine group, 6 from the phosphine and other pesticides group and 10 control subjects) 6 weeks to 3 months after the end of the fumigant application season.

Nonbanded 48-hour cell culture preparations and 72-hour banded cultures were examined. Results from the nonbanded 48-hour cultures indicate that the frequency of gaps and breaks among the exposed workers did not differ from the control group, suggesting that the phosphine induced deletions and breaks previously observed represent a transient chromosome abnormality. On the other hand, banded analysis of 72-hour cultures demonstrated that chromosome rearrangements were found to be more than six times more frequent in the population that had been exposed to phosphine than in the control subjects ($P<0.05$). The authors reported that preliminary analysis and comparison of chromosome breakpoints and rearrangements in banded chromosomes from exposed versus control subjects, and of lymphocytes treated with phosphine *in vitro*, suggest that the chromosome rearrangements observed in this study are a specific effect of phosphine [Garry, et al., 1989].

2. Prokaryotic Data

No data were found on the genotoxic effects of phosphine in prokaryotic systems.

3. Eukaryotic Data

- Phosphine has been found to induce sex-linked recessive lethal mutations in *Drosophila melanogaster*. Phosphine exposure was carried out at a concentration of 0.8 mg/l at 10, 30 and 60-minute time intervals. A statistically significant increase in the frequency of mutation ($P<0.05$) was observed following the 60 minute treatment only [Al-Hakkak, 1988].

4. Other Data

- The cytogenic effect of phosphine gas has been studied in seeds of the red onion (*Allium Cepa* L.). Seeds at 6% and 15% moisture content were fumigated with phosphine for

either 2 or 4 weeks. Phosphine fumigation was carried out at two dose levels (7 and 14 mg/l) for each moisture content. At 6% moisture content, significant increases were observed in the frequency of aberrant cells in the root tips of phosphine fumigated seeds at 7 mg/l phosphine ($P<0.05$) and 14 mg/l phosphine ($P<0.001$), following two weeks of treatment. After 4 weeks of exposure, similar effects were observed with an increase in chromosomal aberrations at phosphine concentrations of 7 mg/l ($P<0.001$) and 14 mg/l ($P<0.001$).

Phosphine was found to have a more pronounced clastogenic effect on seeds at 15% moisture content. Following two weeks of treatment, the number of chromosome aberrations was significantly greater at both dose levels (7 and 14 mg/l {$P<0.001$ at both dose levels}). After four weeks of treatment, a similar increase in chromosomal aberrations was observed ($P<0.001$ at both dose levels) [Younis, et al., 1989].

- Phosphine has been found to induce forward mutation in the fungus *Neurospora sitophila.* Seven day-old cultures were fumigated at a concentration of 0.36 or 0.72 mg/l of phosphine for 48 hours. The mutagenic effects of phosphine were characterized by inoculating the fumigated fungus into flasks containing media supplemented with four surface-active drugs. Three different patterns of resistance to the set of drugs were observed at both concentrations, indicating that phosphine is a "moderate" mutagen to this fungus [Al-Saqur, 1989].

G. Other Toxicological Effects

1. Immunotoxicity

No data were found on the immunotoxic effects of phosphine on animals or humans.

2. Neurotoxicity

- In the abstract from a Polish study, it was reported that nervous system damage (objective changes, EEG abnormalities) continued for 18 months following acute phosphine exposure. No other information was available [Kurzbauer and Kiesler, 1987]. In addition, acute exposure to phosphine has been found to cause neurological abnormalities including headache, giddiness, numbness, lethargy and irritability (See Section V.B.).

3. Biochemical Toxicology

- In the abstract of a Russian study, it was reported that prolonged exposure to phosphine resulted in alterations in phospholipid composition of the membranes of the rat liver nucleus, mitochondria and microsomes. No other data was reported [Tazhibaev, et al., 1986].

VI. STRUCTURE/ACTIVITY RELATIONSHIPS

No information was found on structure activity relationships for phosphine.

VII. REFERENCES

Alavanja, M.C.R., Blair, A., and Masters, M.N., "Cancer Mortality in the U.S. Flour Industry." Journal of the National Cancer Institute, Vol. 82, No. 2 (May, 1990).

Al-Hakkak, Z.S., "Mutagenicity of Phosphine Gas In *Drosophila melanogaster*." Journal of Biological and Scientific Research, Vol. 19 (1988), pp.739-745.

Al-Saqur, A. M.,"Mutagenicity of Phosphine Gas In *Neurospora sitophila*." Journal of Biological and Scientific Research, Vol. 20 (1989), pp.1-7.

American Conference of Governmental Industrial Hygienists, Documentation of the Threshold Limit Values and Biological Exposure Indices, Fifth Edition. Cincinnati: ACGIH, 1986.

American Conference of Governmental Industrial Hygienists, Threshold Limit Values and Biological Exposure Indices for 1989-1990. Cincinnati: ACGIH, 1989.

Arena, J.M., Poisoning: Toxicology, Symptoms, Treatment, Fifth Edition. Springfield, Illinois: C.C. Thomas, 1986, pp. 210-211.

Baselt, R.C., and Cravey, R.H., Disposition of Toxic Drugs and Chemicals in Man, Third Edition. Littleton, Massachusetts: Year Book Medical Publishers, Inc., 1989, pp. 693-694.

Budavari, S., ed., The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, Eleventh Edition, Rahway, New Jersey: Merck, 1989, p. 7314.

Bretherick, L., Handbook of Reactive Chemical Hazards, Third Edition, Boston: Butterworths, 1985, pp. 59, 976, 1123, 1185-1189.

Braker, W. and Mossman, A.L., Matheson Gas Data Book, Sixth Edition. Secaucus, New Jersey: Matheson Gas Products, 1980, pp. 601-605.

Cabrol, A., de Saint Blanquat, G., and Derache, R., "Reproduction in the Rat With Phosphine Fumigated Diet." Microbiologie-Aliments-Nutrition (abstract), Vol.4 (1986),pp.241-246.

Cabrol Telle, A., de Saint Blanquat, G., and Derache, R., "Nutritional and Toxicological Effects of Long-Term Ingestion of Phosphine - Fumigated Diet By The Rat." Food Chemical Toxicology, Vol. 23, No. 11 (1985), pp.1001-1009.

Chan, L.T.F., Crowley, R.J., Delliou, D. and Geyer, R., " Phosphine Analysis in Post Mortem Specimens Following Ingestion of Aluminum Phosphide." Journal of Analytical Toxicology, Vol. 7 (July-August, 1983), pp. 165-167.

Chefurka, W., Kashi, K.P., and Bond, E.J., "The Effect of Phosphine on Electron Transport in Mitochondria." Pesticide Biochemistry and Physiology, Vol. 6 (1976), pp. 65-84.

Chemical Week Buyer's Guide 1990, Chemical Week, (October, 1989), pp.9,10,11,12,27,28,36,38,39,376.

Clayton, G.D. and Clayton, F.E., eds., Patty's Industrial Hygiene and Toxicology, Vol. 2A, Third Revised Edition. New York: Wiley-Interscience, 1981, pp. 2359-2375.

Cooper, P., Poisoning by Drugs and Chemicals, Plants and Animals. Chicago, Illinois: Year Book Medical Publishers, Inc., 1974, p. 176.

Dangerous Properties of Industrial Materials Report, Vol.6, No. 2 (March/April, 1986), pp.103-107.

Davy, H., Phil. Trans. Roy. Soc. (London), Vol. 39 (1809), p. 450.

Dean, J.A., Lange's Handbook of Chemistry, Thirteenth Edition, New York: McGraw-Hill, 1985, p. 4.87.

Dhaliwal, G.S., "Recent Developments On the Mode of Action of Phosphine." Pesticides, Vol. 11, No.6 (June,1977), pp.40-41.

Dreisbach, R.H., Handbook of Poisoning: Prevention, Diagnosis and Treatment. Los Altos, California: Lange Medical Publications, 1980, pp. 239-245.

Finkel, A.J., Hamilton and Hardy's Industrial Toxicology, Fourth Edition. Boston: John Wright, PSG Inc., 1983, pp. 116-118.

Fluck, E. and Novobilsky, "Die Chemie des Phosphins," Fortschr. Chem. Forsch., Vol. 13 (1969), p. 125.

Furuno, J.,Sugawara, N. and Ikeda, H., "A Fatal Case Poisoned by Hydrogen Phosphide and the Simultaneous Separation of Inorganic Gases by Gas Chromatography." Bulletin Yamaguchi Medical School, Vol.23, No.1-2 (1976), pp.57-58.

Fthenakis, V. M. and Moskowitz, P.D., "Characterization and Control of Phosphine Hazards in Photovoltaic Cell Manufacture." Solar Cells, Vol. 22 (1987), pp.303-317.

Garry, V.F., Griffith, J., Danzl, T.J., Nelson, R.L., Whorton, E.B., Krueger, L.A., and Cervenka, J., "Human Genotoxicity: Pesticide Applicators and Phosphine." Science, Vol.246 (October, 1989), pp. 251-255.

Gengembre, P., Hist. Mem. Acad. Roy. Soc., Vol. 10 (1785), p. 651.

Goodman, L.S. and Gilman, A.G., The Pharmacological Basis of Therapeutics, Seventh Edition. New York: Macmillan, 1985, p. 1643.

Gosselin, R.E., Smith, R.P. and Hodge, H.C., Clinical Toxicology of Commercial Products: Acute Poisoning, Fifth Edition. Baltimore: Williams & Wilkins, 1984, pp. II-119, III-348-351.

Grant, W.M., Toxicology of the Eye, Third Edition. Springfield, Illinois: C.C. Thomas, 1986, p. 733.

Habashi, F. and Ismail, M.I., "Health Hazards and Pollution In The Metallurgical Industry Due to Phosphine and Arsine." CIM Bulletin, (August, 1975), pp. 99-103.

Hackenberg, U., " Chronic Ingestion by Rats of Standard Diet Treated with Aluminum Phosphide." Toxicology and Applied Pharmacology, Vol. 23 (1972), pp.147-158.

Hermann, H., "Phosphine." Encyclopedia of Occupational Health and Safety, Vol. 2 (1983), pp. 1681-1684.

Heyndrickx, A., Van Peteghem, C., Van Den Heede, M. and Lauwaert, R., "A Double Fatality With Children Due to Fumigated Wheat." European Journal of Toxicology, Vol. 9 (March-April, 1976), pp.113-118.

The International Technical Information Institute, Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal: With Toxicity and Hazard Data, Revised. Tokyo: The International Technical Information Institute, 1988, pp. 413-414.

Kirk-Othmer, Concise Encyclopedia of Chemical Technology. New York: Wiley-Interscience, 1985, pp. 872-874.

Kirwan, R., Phil. Trans. Roy. Soc. (London), Vol. 76 (1786), p. 118.

Klimmer, O.R., "Beitrag zur Wirkung des Phosphorwasserstoffes (PH_3)." Archives of Toxicology, Vol. 24 (1969) pp.164-167.

Kurzbauer, H., and Kiesler, A., "Occupational Phosphine Poisoning." Neurol. Neurochir. Pol. (abstract), Vol. 21, No. 4-5 (1987), pp. 415-417.

Mackison, F.W., Stricoff, R.S., and Partridge, L.J. Jr., eds., Occupational Health Guidelines for Chemical Hazards, DHHS (NIOSH) Publication No. 81-123. National Institute for Occupational Safety and Health. Cincinnati, Ohio 1981.

Misra, U.K., Bhargava, S.K., Nag, D., Kidwai, M.M. and Lal, M.M. "Occupational Phosphine Exposure in Indian Worders." Toxicology Letters, Vol. 42 (1988) , pp.257-263.

Misra, U.K., Tripathi, A.K., Pandey, R. and Bhargwa, B., "Acute Phosphine Poisoning Following Ingestion of Aluminum Phosphide." Human Toxicology, Vol. 7(1988), pp.343-345.

Muthu, M., Krishnakumari, M.K. and Majumder, S.K., "A Study on the Acute Inhalation Toxicity of Phosphine to Albino Rats." Bulletin of Environmental Contamination and Toxicology," Vol. 24(1980), pp. 404-410.

Nakakita, H., Katsumata, Y. and Ozawa, T., "The Effect of Phosphine on Respiration of Rat Liver Mitochondria." Journal of Biochemistry, Vol. 69 1971), p. 589.

Nakakita, H., "The Mode of Action of Phosphine." Nippon Noyaku Gakkaishi, (abstract) Vol. 12, No.2 (1987), pp.299-309.

National Cancer Institute (NCI), 1989a. Letter from Dr. T. Cameron, Chairman, Chemical Selection Working Group, National Cancer Institute, to Dr. D. Canter, NTP.

National Cancer Institute (NCI), 1989b. Summary of Data for Chemical Selection. Phosphine. Prepared for National Cancer Institute by Technical Resources, Inc., Tracor Technical Resources under Contract No. N01-CP-71082.

National Fire Protection Association, Fire Protection Guide on Hazardous Materials, Ninth Edition. Quincy, Massachusetts: National Fire Protection Association, 1986, p. 325M-80.

National Institute of Occupational Safety and Health (NIOSH). NIOSH Pocket Guide to Chemical Hazards, DHEW (NIOSH) Publication No. 85-114. National Institute for Occupational Safety and Health. Washington, D.C., February 1987.

National Institute of Occupational Safety and Health (NIOSH). National Occupational Exposure Survey (NOES), data communicated by Joseph A. Seta, Acting Section Chief, Division of Surveillance, Hazard Evaluations and Field Studies. April, 1990.

Occupational Safety and Health Administration. Air Contaminants, (29 CFR Part 1910). Federal Register, Vol. 54, No. 12, January 12, 1989, pp. 2335-2568.

Plunkett, E.R., Handbook of Industrial Toxicology, Third Edition. New York: Chemical Publishing Company, Inc., 1987, pp. 430-433.

Proctor, N.H. and Hughes, J.P., Chemical Hazards of the Workplace. Lippincott Company, 1978, pp. 415-416.

Reynolds, J.E.F., ed., Martindale: The Extra Pharmacopeia, Twenty-ninth Edition. London: The Pharmaceutical Press, 1989, p. 1345.

Rodenberg, H.D., Chang, C.C. and Watson, W.A., "Zinc Phosphide Ingestion:A Case Report and Review." Veterinary and Human Toxicology, Vol 31, No. 6. (1989), pp.559-562.

Roytech Publications, Suspect Chemicals Sourcebook. California: Roytech Publications, 1989, p. 133.

Sax, N.I. and Lewis, R.J. Sr., Hawley's Condensed Chemical Dictionary, Eleventh Edition. New York: Van Nostrand Reinhold, 1987, p. 909.

Sax, N.I. and Lewis, R.J. Sr., Dangerous Properties of Industrial Materials, Volume III. Seventh Edition. New York: Van Nostrand Reinhold, 1989, pp. 2768-2769.

Sax, N.I., "Toxicological Effects of Nonnuclear Pollutants." Atmospheric Science and Power Production, Technical Information Center, Office of Scientific and Technical Information, United States Department of Energy, 1984, pp. 746-766.

Shusterman, D., Balmes, J. and Cone, J., "Behavioral Sensitization to Irritants/Odorants After Acute Overexposures." Journal of Occupational Medicine, Vol. 30, No.7 (July, 1988), pp. 565-567.

Sittig, M., Handbook of Toxic and Hazardous Chemicals, Second Edition. Park Ridge, New Jersey: Noyes Publications, 1985, pp. 717-718.

Society for Occupational and Environmental Health (SOEH), New Technologies: Issues in Occupational and Environmental Health. 1990 Annual Conference. (Miller, G.A., "Hazard Assessment of Tertiarybutylarsine (TBA) and Tertiarybutylphosphine (TBP). Liquid Replacements for Arsine and Phosphine." April 23-25, 1990.

SRI International, 1989 Directory of Chemical Producers, United States of America, pp.247,307,853, Menlo Park, California.

SRI International, 1989 Directory of Chemical Producers, Western Europe, pp. 61, 95, 316, 322, 766, 1689, Menlo Park, California.

Taylor, R.C., Kolodny, R., and Walters, D.B., "An Improved Method for the Preparation of Phenylphosphine and a Procedure for the Removal of the Toxic Vapors Produced." Synthesis in Inorganic and Metal Organic Chemistry, Vol. 3, No. 2 (1973), pp. 175-179.

Taylor, R.C. and Walters, D.B., "1,2-Bis(phosphino)ethane." Inorganic Synthesis, Vol. 14 (1973), pp. 10-14.

Tazhibaev, S.H., Mamyrbaev, A.A., and Takhtaev, F., "Phospholipid Composition of the Lipids of Subcellular Structure Membranes in the Liver of Rats Given Various Diets and Exposed to the Action of Phosphorus and Fluorine Compounds." Vopr. Pitan. (abstract of article printed in Russian), Vol.1 (1986), pp. 51-55.

United States Environmental Protection Agency, 1990a. Personal Communication from Mr. Jeff Davidson, OTS, U.S Environmental Protection Agency to Dr. Victor Fung, NTP, April 1990.

United States Environmental Protection Agency, 1990b. U.S. Environmental Protection Agency, Computer Printout (TSCAPP): 1977 Production Statistics for Chemicals in the Nonconfidential Initial TSCA Chemical Substances Inventory. Washington, DC: Office of Pesticides and Toxic Substances.

Wald, P.H. and Becker, C.E., "Toxic Gases Used In The Microelectronics Industry." Occupational Medicine, Vol. 1, No. 1 (1986), pp.105-117.

Waritz, R.S. and Brown, R.M., "Acute and Subacute Inhalation Toxicities of Phosphine, Phenylphosphine and Triphenylphosphine." American Industrial Hygiene Association Journal, Vol. 36, (1975), pp. 452-458.

Weast, R.C., ed., CRC Handbook of Chemistry and Physics, Seventieth Edition. Boca Raton, Florida: CRC Press, Inc., 1989, p. B-113.

Wilson, R., Lovejoy, F.H., Jaeger, R.J., and Landrigan, P.L., "Acute Phosphine Poisoning Aboard a Grain Freighter." Journal of the American Medical Association, Vol. 244, No. 2 (1980), pp. 148-150.

World Health Organization, Environmental Health Criteria 73, Phosphine and Selected Metal Phosphides. World Health Organization, Geneva, 1988.

WHO Pesticide Residues Series, No. 1 (1972), Switzerland, pp. 289-295.

Younis, S.A., Al-Hakkak, Z.S., Al-Rawi, F.I., and Hagop, E.G., "Physiological and Cytogenic Effects of Phosphine Gas In *Allium Cepa* (L)." Journal of Stored Products Research, Vol. 25, No.1 (1989), pp. 25-30.

Zaebst, D.D., Blade, L.M., Burroughs, G.E., Morrelli-Schroth, P. and Woodfin, W.J., "Phosphine Exposures in Grain Elevators During Fumigation With Aluminum Phosphide." Applied Industrial Hygiene, Vol. 3, No. 5 (1988), pp. 146-154.

APPENDIX I. ON-LINE DATABASES SEARCHED

	DATE OF SEARCH	TIME PERIOD
BRS:		
HZDB	February, 1990	
DIALOG:		
Agricola	February, 1990	1970-1990
Agris International	February, 1990	1974-1990
Biosis Previews	February, 1990	1969-1990
CAB Abstracts	February, 1990	1972-1990
Chem Bus Newsbase	March, 1990	1984-1990
Chemical Exposure	April 1990	1981-1990
Compendex Plus	February, 1990	1970-1990
CRIS USDA	February, 1990	
Embase	February, 1990	1974-1990
Enviroline	February, 1990	1970-1990
Environmental Bibliography	February, 1990	1974-1990
Federal Register	February, 1990	1977-1990
Foods Adlibra	February, 1990	1974-1990
FSTA	February, 1990	1969-1990
Life Sciences Collection	February, 1990	1978-1990
Medline	February, 1990	1966-1990
NTIS	February, 1990	1964-1990
Occupational Safety and Health	February, 1990	1973-1990
PTS Newsletter	February, 1990	1987-1990
PTS Prompt	February, 1990	1972-1990
Pollution Abstracts	February, 1990	1970-1990
Trade and Industry ASAP	February, 1990	1983-1990
MEAD:		
Nexis/Lexis-BNA ENV	April, 1990	
NLM:		
Chemid	February, 1990	
Chemline	February, 1990	
HSDB	February, 1990	
RTECS	February, 1990	
Toxline 65	February, 1990	1965-1980
Toxline	February, 1990	1981-1980
Toxlit	February, 1990	1981-1990
Toxlit 65	February, 1990	1965-1980
STN:		
CA	February, 1990	1967-1990
Chemlist	April, 1990	
CIN	February, 1990	1974-1990

APPENDIX II. SAFETY INFORMATION

- ### HANDLING AND STORAGE

  Store in a cool place away from moist air. Do not store phosphine with cylinders containing oxygen or other highly oxidizing or flammable materials. Cylinders containing phosphine must be stored away from sources of heat to avoid the development of pressure within the cylinder. Ground all lines and equipment used with phosphine [DPIMR, 1986]. Reserve stocks of phosphine are not to be stored with cylinders containing oxygen or other highly oxidizing or flammable materials. Phosphine must be used in hoods vented to the outside with scrubbing devices for treatment and removal of noxious and toxic odors and vapors [Taylor, et al., 1973; Taylor and Walters, 1973].

- ### EMERGENCY FIRST AID PROCEDURES

  Inhalation: IMMEDIATELY leave the contaminated area and take deep breaths of fresh air. Administer pure oxygen. If breathing is weak and has stopped, give artificial respiration with simultaneous administration of oxygen. IMMEDIATELY call a physician and be prepared to transport the victim to a hospital even if no symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop.

  Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) must be used.

  Skin: Exposure of skin to compressed gasses may result in freezing of the skin. Treatment for frostbite may be necessary. Remove the victim from the source of the contamination. IMMEDIATELY wash affected areas gently with cold water (and soap, if necessary) while removing and isolating all

contaminated clothing. Dry carefully with clean, soft towels. If symptoms such as inflammation or irritation develop, IMMEDIATELY call a physician or go to a hospital for treatment.

Eye: First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control center. Do not put any ointments, oils, or medication in the victim's eyes without specific instructions from a physician. If symptoms such as redness or irritation develop, immediately transport the victim to a hospital.

- PROTECTIVE EQUIPMENT

Eye: Non-vented safety goggles

Gloves: Disposable gloves

Clothing: Minimally, a disposable laboratory suit (e.g. Tyvek®) shall be worn, as specified in the most current NTP Statement of Work).

Respiratory Protection: Supplied air respirator or self-contained breathing apparatus. However, if the ambient sampling port indicates that the air in the study room is not contaminated, personnel entering the study room need not wear respirators.

- EXTINGUISHANT

Water Spray. Shut off the flow of gas. Use water to keep fire-exposed containers cool and to protect personnel who are involved in the shut-off.

- MONITORING PROCEDURES

There is no NIOSH analytical method reputed in the NIOSH Manual of Analytical Methods for phosphine. However this chemical can be monitored by collection on silver nitrate impregnated cellulose yielding free silver. The silver is converted to the nitrate, then to the sulfide which is analyzed colorimetrically [Braker and Mossman, 1980].

- SPILLS AND LEAKAGE

Persons not wearing the appropriate protective equipment and clothing shall be restricted from areas of spills until cleanup has been completed. If phosphine is spilled the following steps shall be taken:

1. Remove all sources of ignition.

2. Ventilate the area of the leak to disperse the gas.

3. Stop the flow of gas. If the source of the leak is a cylinder and cannot be stopped, remove the cylinder to a safe place in a well-ventilated, isolated area. Repair the leak or allow the cylinder to empty.

4. Do not use a flame to detect phosphine leaks. Soapy water, painted over the suspected area, will indicate leaks by the formation of bubbles [Braker and Mossman, 1980].

- DECONTAMINATION OF LABORATORY EQUIPMENT

TDMS Terminal: Whenever feasible, a protective covering (e.g.,plastic wrap) shall be placed over the keyboard when in use.

General Equipment: Before removing general laboratory equipment (i.e.lab carts, portable hoods and balances) from animal dosing rooms and/or chemical preparation areas, a decontamination process shall be conducted in addition to routine housekeeping procedures.

- WASTE MANAGEMENT AND DISPOSAL PROCEDURES

Waste Management: If an inhalation study is to be conducted, all exhaust air from the inhalation chamber must be cleaned with appropriate air cleaning devices unless the laboratory has informed local and state air pollution regulatory agencies of both the laboratory's operating practices and the potential hazards and noxious odors of the chemicals in use. Compliance with all federal, state and local air pollution laws and regulations is required. A specific air cleaning system design must consider the specific conditions of the laboratory (eg., air flow rates and volumes, mixing of exhaust streams, size of inhalation chamber, etc,) and the dosing regimen selected. Consideration of the use of bromine/water or undiluted chlorox as a scrubber or gas dispersion bubble tower is recommended [Taylor, et al., 1973; Taylor and Walters, 1973]. Air cleaning systems designs must be described by

the laboratory and approved by the NTP Office of Laboratory Health and Safety.

Waste Disposal: Securely package and label, in double bags, all waste material. All potentially contaminated material (i.e.,carcasses, bedding, disposable cages, labware) shall be disposed of as hazardous waste by incineration in a manner consistent with federal (EPA), state, and local regulations in a licensed hazardous waste landfill.