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Summary Review of Health Effects Associated with Elemental and Inorganic Phosphorus Compounds:

Health Issue Assessment

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
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Preface

The Office of Health and Environmental Assessment has prepared this health assessment to serve as a source document for EPA use. The summary health assessment was developed for use by the Office of Air Quality Planning and Standards to support decision making regarding possible regulation of phosphorus as a hazardous air pollutants.

In the development of the assessment document, the scientific literature has been inventoried through January 1989, key studies have been evaluated, and summary/conclusions have been prepared so that the chemicals' toxicity and related characteristics are qualitatively identified. Observed effect levels and other measures of dose-response relationships are discussed, where appropriate, so that the nature of the adverse health responses is placed in perspective with observed environmental levels.

Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risk to public health.

If a review of the health information indicates that the Agency should consider regulatory action for this substance, considerable effort will be undertaken to obtain appropriate information regarding sources, emissions, and ambient air concentrations. Such data will provide additional information for drawing regulatory conclusions regarding the extent and significance of public exposure to this substance.

ABSTRACT

Phosphorus is a nonmetallic essential element. Although phosphorus occurs naturally in the environment, most of the phosphorus in the environment occurs during its manufacture into one of the three allotropic forms (white, red, or black) or into phosphorus compounds and during the transport and use of these compounds.

White phosphorus/felt and red phosphorus/butyl rubber are irritating to the skin and eyes. Phosphoric acid, phosphorus pentoxide, and the phosphorus chlorides are irritating, in some cases corrosive, to the skin, eyes, and mucous membranes. Inhalation of these compounds has produced respiratory tract irritation in mammals. The phosphorus chlorides have also produced effects on the kidney, liver, and nervous system of experimental animals. Phosphine is highly toxic by the inhalation route of exposure and has reportedly produced gastrointestinal, cardiorespiratory, and central nervous system effects in humans. A definite conclusion regarding the possible reproductive/ teratogenic, mutagenic, or carcinogenic potential of these compounds cannot be drawn because of the lack of adequate studies.

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1. Summary and Conclusions

1.1 ELEMENTAL PHOSPHORUS

Phosphorus, a nonmetallic essential element, occurs in three allotropic modifications: white (or yellow), red, and black. White phosphorus, the best known form, is a highly reactive tetrahedral molecule that occurs almost exclusively as salts of phosphoric acid. Red phosphorus is less reactive and is produced by heating white phosphorus in an inert atmosphere. Black phosphorus is produced from white phosphorus under pressure.

Phosphorus can be released into the atmosphere during its manufacture, transport, or conversion to products such as detergents, phosphoric acid, munitions, fireworks, insecticides, and rat poison. Volatilization from soil and water and remobilization from sinks (i.e., soil and aquatic sediments) may also occur.

The only study found in the published literature on the levels of elemental phosphorus in air reported levels of up to 2.46 mg/m^3 in the form of particulate matter in the vicinity of St. Louis, Missouri. However, estimates have been made of the amount of phosphorus released in the air as a result of mining and the manufacture, use, and disposal of phosphorus containing products.

According to the U. S. Environmental Protection Agency, the largest single source of phosphorus air emissions is the combustion of coal, accounting for 23 percent of the total ambient air concentration of phosphorus. Estimates of white phosphorus releases from white phosphorus/felt munitions manufacture place the emission of elemental phosphorus at 0.5 mg/m^3 as a worst-case upper limit and a 1-hour exposure of 0.5 g/m^3 in resting humans, but exposure to concentrations as low as 185 mg/m^3 for 5 minutes may produce sore throat, coughing, nasal discharge, tightness in the chest, and congestion. In one study, inhalation of an unknown amount of white phosphorus for 15 to 20 minutes also caused laryngitis, which persisted for several months. Toxic symptoms observed in some workers accidentally exposed to 35 mg/m^3 of phosphorus and 22 mg/m^3 of phosphorus pentoxide for 2 to 6 hours at 7-hour intervals (total exposure time not given) included weakness, malaise, headache, vertigo, tracheobronchitis, and tenderness and enlargement of the liver.

Elemental white phosphorus can be absorbed by ingestion, inhalation, and dermal contact. The major tissues accumulating white phosphorus and liver, kidney, lung, bone, and skeletal muscle. One inhalation study with radiolabelled red phosphorus in mice showed the chemical to be distributed in the digestive and respiratory tracts. After two days, only the lungs showed some radioactivity which was retained there for at least 10 days. White phosphorus is eliminated from the body through urine and feces.

Available studies on health effects of elemental phosporus deal primarily with white phosphorus, and to a lesser extent with red phosphorus. Additionally, much of the research examines the effects of exposure to phosphorus smoke compounds, specifically white phosphorus/felt and red phosphorus/butyl rubber and their combustion products. Table 1-1

Table 1-1. Summary of Significant Toxic Effects of Elemental Phosphorus Compounds

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
White phosphorus (WP) *White phosphorus/ felt smoke* (WP/F)				
LCt_{50} = 94,126 mg·min/m^3, rat LCt_{50} = 5,321 mg·min/m^3, guinea pig	WP and WP/F not mutagenic in *Salmonella*; WP/F not mutagenic in *Drosophila* and rats; no carcinogenicity data found	WP/F not teratogenic in rats. Repeated oral doses of 0.75 mg/kg WP caused high mortality in pregnant rats. NOAEL[a] = 0.015 mg/kg	Humans and animals: WP causes severe skin burns; 0.1 percent WP in oil not irritating to rabbit skin and eyes; WP/F severly irritating to skin and eyes of rabbits; WP/F not sensitizing	*Inhalation exposure* Humans: 700 mg/m^3 is minimm harassing concentration in working humans, 1,000 mg/m^3 in resting humans; 185 mg/m^3 for 5 min produces respiratory distress; chronic exposure may cause necrosis of the jaw, other bone abnormalties, and liver.
LD_{LO} = 50-100 mg, humans				Animals: LOAEL[b] = 193 mg/m^3 damage (rats) based on effects noted in the respiratory tract, changes in body and organ weights, and blood chemisrty and hematology after subchronic exposure; subchronic exposure to lower levels (160 mg/m^3) have reportedly produced bone changes in rats.

Table 1-1. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
				Oral exposure Humans: 15 mg may cause toxic symptoms; major target organs are the gastrointestinal tract, liver, kidneys, brain, and cardiovascular system; fatty degeneration of the liver is a characteristic lesion of phosphorus poisoning. Animals: toxic effects similar to effects seen in humans; major organs affected are the liver, kidneys, gstrointestinal tract, and heart; levels of 1.48 g/kg produced lethargy, gastric distress, prostration, and death in mice, rats, and rabbits; severe hypoglycemia, suggestive of liver damage, reported in dogs given 0.5 mg for several days. *Dermal exposure* Humans: severe burns are associated with massive hemolysis, changes in blood chemistry, oliguria, and renal failure.

Table 1-1. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation Sensitization	Other Effects/ Target Organ
Red phosphorus/butyl rubber smoke LCt_{50} = 222,715 mg·min/m^3, rat	Nonmutagenic in *Salmonella*; no carcinogenicity data found	No data found	Severe skin and eye irritation and corneal ulceration in rabbits; not sensitizing in guinea pigs	*Inhalation exposure* Humans: no data found Animals: respiratory distress, abnormalities of larynx and trachea, alveolitis, bronchopneumonia, decreased liver, kidney and body weight, and decreased pulmonary bactericidal activity.
LCt_{50} = 4,040 mg mg-min/m^3,guinea pig				
LDt_{50} = >451,680 mg·min/m^3, dog				

a NOAEL = No-observed-adverse-effect level.
b LOAEL = Lowest-observed-adverse-effect level.

summarizes significant toxic effects of elemental phosporus compounds, emphasizing those effects produced by inhalation and indicating significant data gaps.

The effects of acute exposure by inhalation to white and red phosphorus and smoke compounds are similar in laboratory animals and humans and are usually limited to the upper respiratory tract. Overt effects are nasal discharge, coughing, sore throat, difficult breathing, laryngitis, and bronchitis. Sensitivity to white phosphorus/felt or red phosphorus/butyl rubber smoke via inhalation appears to be greatest in guinea pigs. Acute phosphorus intoxication in humans from inhalation has not often been reported. However, the estimated minimum harassing exposure concentration is 700 mg/m^3 in working humans and 1,000 µg/m^3 in resting humans, but exposure to concentrations as low as 185 mg/m^3 for 5 minutes may produce sore throat, coughing, nasal discharge, tightness in the chest, and congestion. In one study, inhalation of an unknown amount of white phosphorus for 15 to 20 minutes also caused laryngitis, which persisted for several months. Toxic symptoms observed in some workers accidentally exposed to 35 mg/m^3 of phosphorus and 22 mg/m^3 of phosphorus pentoxide for 2 to 6 hours at 7-hour intervals (total exposure time not given) included weakness, malaise, headache, vertigo, tracheobronchitis, and tenderness and enlargement of the liver.

The minimum lethal oral dose of white phosphorus in humans is estimated to be 100 mg (1.4 mg/kg), but could be as low as 50 mg (0.7 mg/kg) for a 70-kg individual. An oral dose of 15 mg (0.2 mg/kg) may cause toxic effects. After acute oral intake, the major target organs damaged by white phosphorus in laboratory animals and humans are the gastrointestinal tract, liver, kidney, brain, and cardiovascular system. The effects on the gastrointestinal tract are due to local irritation, whereas the effects on the other organs are due to systemic absorption. A characteristic lesion due to white phosphorus intoxication is fatty degeneration of the liver in both laboratory animals and humans.

Unlike acute exposure, which causes similar effects in laboratory animals and humans, different effects have been observed in animals and humans following subchronic/chronic exposure to white phosphorus. In laboratory animals, oral or subcutaneous administration causes reduced growth, reduced survival at high doses, and increased survival at low doses. Liver damage is usually moderate. Characteristic bone pathology, observed at doses as low as 0.05 mg/kg/day in rats and guinea pigs, involves a thickening of the epiphyseal line and extension of trabeculae into the shaft. Rats exposed via inhalation to a vapor concentration of 150 to 160 mg/m^3 of yellow phosphorus 30 minutes daily for 60 days also develop the typically widened epiphyseal line, pronounced trabeculation with insufficient ossification, and abnormal development of long bones. These abnormalities are different from the necrosis of the jaw produced in humans by chronic occupational exposure to white phosphorus.

Subchronic inhalation exposure of laboratory animals to white phosphorus/ felt smoke causes lesions in the respiratory tract similar to those in humans after acute inhalation exposure. The mortality rate in rats exposed to 1,161 mg/m^3 15 minutes/day for 13 weeks was 40 percent. Histopathological examination revealed laryngitis, tracheitis, congestion, and bronchitis. A lowest-observed-adverse-effect-level (LOAEL), based on effects on the respiratory tract, changes in body and organ weights, and blood chemistry and hematology, was 193 mg/m^3.

Phosphorus toxicity was mostly seen in factory workers in the early 1900's who were exposed to phosphorus vapor for a considerable length of

time. Humans occupationally exposed to white phosphorus may develop necrosis of the jawbone, a specific suppurative lesion that can result in the loss of some or all of the upper or lower jawbone. Necrosis of the jawbone may appear as early as 3 months or as late as 23 years after initial exposure. The airborne levels of phosphorus were not known in the case histories of phosphorus necrosis presented in the literature; therefore the disease process cannot be correlated with concentrations of phosphorus in air.

A study of healthy workers in a phosphorus plant, with exposure times ranging from 1 to 17 years, revealed no statistical differences in hematology and plasma levels of inorganic phosphorus, alkaline phosphatase, calcium, or magnesium; nor were there differences in bone density. In contrast, a recent Russian study reported liver damage and possible bone abnormalities in industrial workers engaged in the production of yellow phosphorus. Exposure reportedly ranged from 3 to 5 years at the maximal permissible air concentration and occasional elevated levels of phosphorus. The maximum allowable level established in the Soviet Union is 0.03 mg/m^3.

White phosphorus/felt smoke at a concentration of 1,000 mg/m^3 induced a few major malformations consisting of brachygnathia, thin-walled heart, and reversed ductus arteriosus in rats. These malformations have not been confirmed; however, exposure to white phosphorus/felt smoke does cause reduce survival, viability, and lactation indices in pups at 1,000 mg/m^3.

In one report, female rats administered 0.75 mg/kg of yellow phosphorus orally for 80 days prior to mating, and through two gestation periods, experienced a high mortality rate. A total of 13 females (43 percent) died within two days of parturition and the deaths were attributed to difficulty in parturition. Doses of 0.015 and 0.005 mg/kg had no adverse effects. A no-observed-adverse-effect level (NOAEL) of 0.015 mg/kg was established.

There is no evidence that elemental phosphorus induces teratogenic or reproductive effects in humans. There were also no available studies regarding carcinogenicity and therefore, elemental phosphorus is classified in Group D according to the U. S. Environmental Protection Agency guidelines on carcinogenicity.

1.2 Inorganic Phosphorus Compounds

Only limited information was found in the published literature on the effects of the selected inorganic phosphorus compounds in humans and experimental animals. A summary of the reported effects appears in Table 1-2.

Phosphine (PH_3), a toxic gas with an unpleasant odor of decaying fish, may be emitted from processes such as metal shaving, sulfuric acid tank cleaning, generation of acetylene from impure calcium carbide, and the handling of phosphorus explosives. Phosphine evolves when acid or water come in contact with metallic phosphides. It is used for fumigation of grain and is generated by reacting aluminum or calcium phosphide with water. It is released in small quantities from combustion of white and red phosphorus screening smokes. An estimated half-life of 2 to 8 hours in the atmosphere indicates that it would not persist in the environment.

The 4-hour LC_{50} of 15.4 mg/m^3 in rats indicates that phosphine is highly toxic by the inhalation route of exposure. Little species variation has been observed in laboratory animals exposed to this chemical. The effects of acute exposure preceding death are mainly secondary to respiratory tract damages. Pathological changes in animals exposed to high concentrations of phosphine (about 560 mg/m^3) include pulmonary edema, liver and kidney effects, and degenerative changes in the brain. Low concentrations (3.75 mg/m^3) have

Table 1-2. Summary of Significiant Toxic Effects of Inorganic Phosphorus Compounds

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
Phosphine (PH_3)				
LC_{50} = 15.4 mg/m^3(4hr), rat	No data found	No data found	Not irritating	*Inhalation exposure* Humans: inhalation of 14.0 mg/m^3 for several hours produces gastrointestianl, cardiac/respiratory, and central nervous system symptoms; long-term exposure to 0.04 mg/m^3 or less causes headaches. Animals: exposure to nonlethal levels of phosphine produce mild irritation, major target organs are the respiratory tract, liver, kidneys, heart, and brain.
IDLH* = 280 mg/m^3				*Oral exposure* Humans: no data found Animals: ingestion of phosphine treated diets containing 0 996 mg/kg phosphine for 2 years produced no treatment-related effects in rats.

Table 1-2. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
Phosphorus pentoxide (P_2O_5) LC_{50} = 61 mg/m^3 (1hr), guinea pig	No data found	No data found	Humans: skin, eye, and mucous membrane irritation; corrosive	*Inhalation exposure* Humans: 0.8-5.4 mg/m^3 tolerated level, 3.6-11.^{3} mg/m^3 tolerated with cough; 100 mg/m^3 not tolerated by unacclimated individuals.
LC_{50} = 271 mg/m^3 (1hr), mouse				
LC_{50} = 1,212 mg/m^3 (1hr), rat				Animals: no data found on the effects on target organs.
LC_{50} = 1,689 mg/m^3 (1hr), rabbit				*Oral exposure* No data found on the effects of ingestion of phosphorus pentoxide in humans or animals.

Table 1-2. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation Sensitization	Other Effects/ Target Organ
Phosphoric acid (H_3P0_4) LD_{50} = 1,530 mg/kg (oral), rat LD_{50} = 2,740 mg/kg (dermal), rabbits	No data found	No data found	Humans: skin and eye irritation	*Inhalation exposure* Humans: upper respiratory tract irritation; 1 mg/m³ irritating to un-acclimated individuals Animals: no data found. *Oral exposure* Humans: metabolic disorders and burning sensation in the throat and gastrointestinal tract Animals: no data found.
Phosphorus trichloride ($PC1_3$) LC_{50} = 590 mg/m³ (4 hr), rat LC_{50} = 283 mg/m³ (4hr), guinea pig IDLH* = 283 mg/m³	Nonmutagenic in *Salmonella;* no carcinogenicity data found	No data found	Humans: severe skin, eye, and mucous membrane irritation, corrosive	*Inhalation exposure* Humans: 10-20 mg/m³ causes respiratory irritation within 2-6 hours; exposure for 1 to 2 years, pulmonary emphysema. Animals: upper respiratory tract irritation; dystrophic changes in the kidneys, liver, and nervous system.

Table 1-2. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
				Oral exposure Humans: no data found Animals: produces effects on organs similar to that seen in inhalation experiments.
Phosphorus pentachloride ($PC1_5$) LC_{50} = 295 mg/m³, rat LD_{50} = 1,031 mg/m³ (10 min), mouse IDLH* = 200 mg/m³	No data found	No data found	Humans: skin, eye, and mucous membrane irritation, corrosive	*Inhalation exposure* Humans: respiratory tract irritation, possible kidney damage. Animals: respiratory tract irritation, kidney, liver, and nervous system dystrophy. *Oral exposure* Humans: no data found Animals: produces effects similar to those seen during inhalation exposure.

Table 1-2. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
Phosphorus oxychloride ($POC1_3$)				
LC_{50} = 303 mg/m^3 (4 hr), rat LC_{50} = 335 mg/m^3 (4hr), guinea pig	Chromosomal aberrations in rats; no carcinogenicity data found	Effects on sperm motility in rats	Humans: skin, eye, and mucous membrane irritation, corrosive	*Inhalation exposure* Humans: threshold exposure concentration for irritation reported to be 1 mg/m^3. Animals: respiratory tract irritation, kidney, liver, and nervous system dystrophy; 1.34 mg/m^3 for 4 months causes respiratory irritation, degenerative changes of brain and bone tissue, liver and kidney dystrophy *Oral exposure* Humans: no data found Animals: dystrophic changes in the kidneys, liver, and nervous system

Table 1-2. (continued)

Lethality	Mutagenicity/Carcinogenicity	Teratogenicity/Reproductive Effects	Skin and Eye Irritation, Sensitization	Other Effects/ Target Organ
Phosphorus sesquisulfide (P_3S_4) LD_{50} = 100 mg/kg (oral), dog	No data found	No data found	Humans: allergic contact dermatitis and sensitization	*Inhalation exposure* Humans: prostration, vertigo, gastrointestinal effects, and lpos-ening of teeth from long-term use of matches. Animals: no data found. *Oral exposure* No data found on the ingestion of this compound by either man or experimental animals.

*IDLH = Immediately dangerous to life and health

been tolerated for 34 days without clinical injury. Long-term ingestion of a phosphine-fumigated diet containing 0.99 mg/kg reportedly produced no adverse effects in rats.

Poisoning via inhalation in humans, usually an accidental occurrence, has resulted from grain fumigation, releases from ferrous alloys stored on ships, the generation of acetylene from portable generators used by welders, and exposure in submarines carrying sodium phosphide warning lights. Phosphine is readily absorbed by the lungs and gastrointestinal tract; some of the absorbed phosphine is also eliminated through the lungs. The poisoning symptoms reported in grain fumigators, intermittently exposed to about 14 mg/m^3 for several hours, fall into three main categories; gastrointestinal (diarrhea, nausea, epigastric pain, and vomiting), cardiac/respiratory (tightness of chest, breathlessness, chest pain, palpitations, and severe retrosternal pain), and central nervous system (headache, dizziness, and staggering gait). The only symptom in subjects exposed to 0.04 mg/m^3 was headache. Postmortem examination of a child who died because of leakage of phosphine on a grain freighter revealed myocardial injury, pulmonary edema, and widespread small-vessel injury. The exposure level was not determined.

Phosphorus pentoxide or phosphoric acid anhydride (P_2O_5) avidly absorbs moisture from the air, forming phosphoric acid. Because of its great affinity for water, it is used as a drying agent. Phosphorus pentoxide is the primary combustion product when white or red phosphorus is burned in air. The major environmental transformation is by hydrolysis to phosphoric acid.

Phosphorus pentoxide is locally corrosive and irritating to mucous membranes, eyes, and skin because of its strong dehydrating action and exothermic formation of phosphoric acid. Workers noticed but were not uncomfortable at levels of 0.8 to 5.4 mg/m^3, and they tolerated 3.6 to 11.3 mg/m^3, with coughing. Only acclimated workers tolerated levels as high as 100 mg/m^3. Phosphorus pentoxide particles in contact with the eyes cause burns of the eyelids and cornea.

A leading inorganic acid in the U. S. economy, phosphoric acid (H_3PO_4) had an estimated production volume of 11,717 tons in 1988. Its major use is in the manufacture of superphosphate fertilizers and detergents. Because of its high production volume and many applications, potential exposure is expected to be high. In the production of phosphorus munitions, hourly air emissions of 255 Lb/hour were estimated. Washout is the primary fate of phosphoric acid released to the atmosphere. Phosphoric acid reacts with most environmental media to yield ubiquitous salts such as calcium, iron, and aluminum phosphates.

The only information found regarding the acute toxicity of phosphoric acid in laboratory animal was an oral LD_{50} in rats of 1,530 mg/kg and a diurnal LD_{50} of 2,740 mg/kg for rabbits.

Phosphoric acid also is a skin and eye irritant; it may produce skin burns and dermatitis. At a concentration of 1 mg/m^3, the U. S. Threshold Limit Value-Time Weighted Average, irritation may occur in unacclimated individuals. Only one study was found in the published literature on the effects of ingestion of phosphoric acid and the amount of the acid ingested was not given. However, the individual experienced some metabolic disorders and a mild burning sensation in the throat and gastrointestinal tract.

Chlorinated phosphorus compounds are industrially important chemicals used as intermediates in the manufacture of pesticides, surfactants, gasoline additives, pharmaceuticals, and other compounds. Exposure may occur during their manufacture and their varied applications. Phosphorus trichloride (PCl_3) is a very corrosive liquid, which reacts exothermically with water, releasing

hydrochloric and phosphoric acid. Acute as well as chronic health effects have been reported in workers exposed to 11 to 23 mg/m^3 and occasionally higher levels of phosphorus trichloride. The acute effects included a burning sensation of the eyes and throat, photophobia, chest oppression, cough, and bronchitis. Chronic exposure for 1 to 2 years produced pulmonary emphysema.

Phosphorus pentachloride (PCl_5) is very irritating to all mucous surfaces, including the lungs. The chemical can cause serious skin burns by an exothermic reaction with moisture, forming hydrochloric and phosphoric acid. One report indicated that phosphorus pentachloride may produce kidney damage.

Phosphorus oxychloride ($POCl_3$) presents similar hazards as phosphorus trichloride and phosphorus pentachloride. The vapors of this readily volatilizing chemical are very irritating to the eyes, skin, and mucous membranes of animals and humans. Inhalation may cause pulmonary edema. The chemical produces slowly healing corneal burns in humans. Subchronic exposure of rats to about 1.34 mg/m^3 for 4 months produced a number of effects including respiratory symptoms, degenerative changes of the brain, mild liver and kidney dystrophy, and bone abnormalities. The chemical also affected sperm motility and produced chromosomal aberrations.

Phosphorus sesquisulfide (P_3S4) is used in making matches and friction strips for match boxes. In addition to causing eye and respiratory tract irritation, it causes contact dermatitis, with both immediate and delayed hypersensitivity reactions in humans. A number of cases of allergic contact dermatitis, traced to phosphorus sesquisulfide contained in safety matches, have been recorded in the literature. In one study, repeated and long-term use of matches produced recurring episodes of edematous dermatitis, accompanied by prostration, vertigo, gastrointestinal disturbances, and loosening of teeth.

No information was found in the published literature on the teratogenic or reproductive effects of the inorganic phosphorus compounds in animals or humans or on the carcinogenic potential of these compounds in humans. In the only studies found on the carcinogenic potential of the inorganic phosphorus compounds in animals, phosphine did not demonstrate any carcinogenic effects in rats consuming phosphine-fumigated diets. According to the U. S. Environmental Protection Agency guidelines on carcinogenicity, the inorganic phosphorus compounds (phosphine, phosphoric acid, phosphorus pentoxide, phosphorus pentachloride, phosphorus oxychloride, and phosphorus sesquisulfide) are classified in Group D, not classifiable as to human carcinogenicity because adequate animal studies or epidemiological data are lacking.

2. BACKGROUND INFORMATION

This review provides a brief summary of the available information concerning the potential health effects associated with exposure to elemental phosphorus and phosphorus compounds. Acute and chronic health effects are addressed, including systemic toxicity, genotoxicity, and reproductive and developmental effects. This report also briefly reviews physical and chemical properties, sources, environmental fate, and concentrations found in air, as a background for placing the health effects discussion in perspective. Because of the large number of phosphorus compounds, this report will focus on only elemental phosphorus and a group of inorganic phosphorus compounds selected because of the potential for exposure from their manufacture and use and/or their known toxicity to humans and other mammals.

2.1 Chemical Characterization and Measurement

2.1.1 *Elemental Phosphorus*

Phosphorus (CAS No. 7723-14-0), a nonmetallic essential element, has the empirical and molecular formula P. About 60 years ago, three major allotropic modifications of elemental phosphorus were recognized; white (or yellow when impure), red, and black. White phosphorus is the best known form and of greatest commercial importance. It is the most volatile and reactive form of the solid, igniting spontaneously in air. It is soluble in organic solvents but shows only limited solubility in water. At room temperature, white phosphorus exists as the alpha form, consisting of cubic crystals containing P_4 molecules. At -79.6 °C it converts to hexagonal crystals (Windholz et al., 1983). Red phosphorus is very insoluble and is more stable, although on exposure to air it reacts slowly with oxygen and water vapor. It exists in a number of different polymeric modifications which often coexist in a given preparation (Van Wazer, 1982). Black phosphorus, a crystalline amorphous solid resembling graphite, is the least known form of phosphorus. It is insoluble in most solvents and thermodynamically the most stable of the phosphorus allotropes.

Analytical methods for the detection of white phosphorus in air include: neutron activation analysis (Carlton and Lehman, 1971), flame emission photometry (Prager and Seitz, 1975), and colorimetry (Rushing, 1962). Analytical techniques which are not specific for elemental phosphorus or other phosphorus compounds but determine the total amount of phosphorus in a sample include X-ray spectroscopy, emission spectroscopy, and spark source mass spectrometry (Wasti et al., 1978).

In water, suitable analytical techniques include neutron activation (Lai and Rosenblatt, 1977a), flame emission photometry (Prager and Seitz, 1975), and gas-liquid chromatography (Addison and Ackman, 1970). 2.1.2 Inorganic Phosphorus Compounds.

2.1.2 Inorganic Phosphorus Compounds

Phosphine (PH_3) (CAS No. 7803-51-2), a toxic gas with an odor of decaying fish, ignites spontaneously in air in the presence of traces of diphosphane (P_2H_4) and other impurities (Sax, 1986). It is only slightly soluble in water but will combine violently with oxygen and the halogens (Windholz et al., 1983).

Analytical methods for the detection of phosphine in air include gas chromatography (Berck et al., 1970; Bond and Dumas, 1982), gas chromatography-mass spectrometry and electrochemical/coulometric methods (Verstuyft, 1978), colorimetry/spectrophotometry (Dechant et al., 1966), and column/paper chromatographic methods (Muthu et al., 1973).

Phosphorus pentoxide, also known as phosphoric anhydride (P_2O_5) (CAS No. 1314-056-3), is a stable white solid which exists in several crystalline or amorphous modifications. It readily absorbs moisture from the air, forming phosphoric acid by exothermic hydrolysis (Windholz et al., 1983; Beliles, 1981; Boenig et al., 1982). The analytical method used for the determination of phosphorus pentoxide in air is colorimetry (Wasti et al., 1978).

Phosphoric acid or orthophosphoric acid (H_3PO_4) (CAS No. 7664-38-2) exists as a clear syrupy liquid or as deliquescent crystals (Heimann, 1983). It is a tribasic acid, stronger than acetic, oxalic, or silicic acid, but weaker than sulfuric, nitric, hydrochloric, or chromic acid. The most concentrated commercial form of this compound contains 85 percent phosphoric acid (Beliles, 1981). Analytical methodology for the determination of phosphoric acid in air are colorimetry (National Institute of Occupational Safety and Health, 1977) and colorimetry/spectrophotometry (Wasti et al., 1978).

Phosphorus trichloride (PCl_3) (CAS No. 7719-12-2), a colorless fuming liquid, reacts exothermically with water, releasing hydrochloric and phosphoric acid. It volatilizes at room temperature (Beliles, 1981). Phosphorus trichloride is an extremely corrosive liquid, forming phosphine upon heating (Heimann, 1983). Colorimetry is the analytical technique used for the quantitation of phosphorus trichloride in air (National Institute for Occupational Safety and Health, 1979).

Phosphorus pentachloride (PCl_5) (CAS No. 10026-13-8) is a yellow, fuming, crystalline mass with a pungent unpleasant odor. It reacts with water, hydrolyzing to phosphoric acid and hydrochloric acid (Windholz et al., 1983). When heated, it produces phosphorus trichloride and chlorine (Beliles, 1981). The analytical method used for the determination of phosphorus pentachloride in air is colorimetry (National Institute for Occupational Safety and Health, 1979).

Phosphorus oxychloride or phosphoryl chloride ($POCl_3$) (CAS No. 10025-87-3) is a clear, fuming liquid with a pungent odor. It is stable below 300 °C and yields phosphoric acid upon hydrolysis (Boenig et al., 1985). When heated to decomposition it emits fumes of Cl^-, PO_x, and NO_x (Sax, 1984).

Phosphorus sesquisulfide (P_4S_3) (CAS No. 1314-85-8) is a crystalline yellow solid. It is insoluble in cold water but will decompose in hot water (Heimann, 1983).

2.2 Production and Uses

2.2.1 *Elemental Phosphorus*

Domestic production capacity of elemental phosphorus as of 1988 was approximately 376,000 metric tons (SRI International, 1988). As of 1988,

elemental phosphorus was produced domestically by 5 companies. Table 2-1 shows the producers and their annual production capacities.

White phosphorus is produced by several methods. The most important means of production is by the electric-arc process. Phosphate rock is ground, formed into pellets, and smelted with coke and silica in an electric furnace to produce elemental phosphorus vapors (U. S. Environmental Protection Agency, 1982; Van Wazer, 1982). The white phosphorus vapors are then cleaned and collected by passing through an electrostatic precipitator and condenser (Van Wazer, 1982). White phosphorus is also produced as an intermediate in the thermal process for phosphoric acid production (Lowenheim and Moran, 1975).

Red phosphorus is produced by heating white phosphorus to approximately 400°C in the absence of air or in an inert atmosphere (Lowenheim and Moran, 1975). Black phosphorus is produced from white phosphorus under pressure (Hawley, 1981).

Most of the white phosphorus produced is ultimately utilized in the production of phosphoric acid and phosphates (Lowenheim and Moran, 1975). It is also used in the production of phosphorus sulfides, phosphorus halides, phosphorus pentoxide, and red phosphorus. It is used in ferrous metallurgy, in insect and rodent poisons, and in the manufacture of artificial fertilizers, semiconductors, and electroluminescent coatings (Sittig, 1985). The military uses include the production of mortar and artillery shells and hand and rifle grenades. While white phosphorus is a commercially important chemical, red phosphorus is a specialty item. It is a component of the box coatings of safety matches and is used in the manufacture of fireworks (Van Wazer, 1982). There are no current uses for black phosphorus (Hawley, 1981).

2.2.2 Inorganic Phosphorus Compounds

Phosphine is not considered an important industrial chemical (Beliles, 1981). Commercially, phosphine is produced by the reaction of aluminum phosphide with water or by an electrolytic process whereby nascent hydrogen reacts with elemental phosphorus (Boenig et al., 1982). It is used as a grain fumigant, as a doping agent for electronic components, in chemical synthesis (American Conference of Governmental Industrial Hygienists, 1980), and in the control of rodents and moles by placing the compound in outdoor burrows and closing the openings (Hayes, 1982).

Phosphorus pentoxide is made commercially by burning phosphorus in a stream of air. Estimated U. S. production of phosphorus pentoxide in 1985 was 6,300 thousand tons (Toxnet, 1989). Phosphorus pentoxide has a great af-

Table 2-1. United States Producers of Elemental Phophorus (1988)

Company	*Location*	*Annual Capacity (thousands of metric tons)*
FMC Corporation	*Pocatello, ID*	*137*
Monsanto Company	*Soda Springs, ID*	*95*
Occidental Petroleum Corporation	*Columbia, TN*	*57*
Stauffer Chemical Company	*Mount Pleasant, TN*	*45*
	Silver Bow, MN	*42*

Capacity data are on a P_4 basis.
Source: SRI International (1988).

finity for water and is used in this capacity as a drying agent (Beliles, 1981). It is also used in the manufacture of phosphorus oxychloride, acrylate esters and surfactants, as a catalyst in air blowing of asphalt, and in other applications (Boenig et al., 1982).

Phosphoric acid is manufactured by the wet process or the furnace (thermal) process. The wet process acid, produced directly from phosphate ores, has a high production volume, low cost, and low purity. It is used mostly for the production of fertilizers. Phosphoric acid manufactured by the furnace or thermal process is produced from elemental phosphorus. It is produced in much smaller quantities for uses other than fertilizer applications, such as metal treatment, refractories, catalysts, and food and beverages (Hudson and Dolan, 1982). Estimated production of phosphoric acid in the United States for 1987 was 10,473 thousand tons. Estimated production in 1988 was 11,717 thousand tons, an increase of 11.9 percent from 1987 (Reisch, 1989).

The single greatest use of phosphoric acid is in the manufacture of phosphate salts, with superphosphate fertilizers representing the single largest market (Hudson and Dolan, 1982). Phosphoric acid is used in the manufacture of detergents, activated carbon, animal feed, ceramics, dental cement, pharmaceuticals, soft drinks, gelatin, rust inhibitors, wax, and rubber latex. It is used for electropolishing, engraving, photoengraving, lithograving, metal cleaning, sugar refining, and water treating (Sittig, 1985).

Phosphorus trichloride is manufactured by the direct union of phosphorus and chlorine. Phosphorus trichloride is one of the largest volume primary products of phosphorus, second only to phosphoric acid and its salts. The estimated production capacity for phosphorus trichloride produced in the United States as of January 1988 was 169 thousand tons (SRI International, 1988). Phosphorus trichloride, reacting readily with oxygen, sulfur, chlorine, and water, serves as an intermediate in the manufacture of phosphorus oxychloride, phosphorus sulfochloride, phosphorus pentachloride, and phosphorous acid (H_3PO_3) (Boenig et al., 1982). It is used as an intermediate in the preparation of pesticides, surfactants, gasoline and lubricating oil additives, plasticizers, and dyes, as a catalyst, and as an ingredient in textile finishing agents (American Conference of Governmental Industrial Hygienists, 1980; Chemical Economics Handbook, 1983; Windholz et al., 1983).

Phosphorus pentachloride is made from phosphorus trichloride and chlorine or by burning elemental phosphorus in the presence of excess chlorine (Boenig et al., 1982). It is used for replacing hydroxyl groups by chlorine, particularly for converting acids into acid chlorides (Windholz et al., 1983).

Phosphorus pentachloride is also used in the manufacture of agricultural chemicals, chlorinated compounds, gasoline additives, plasticizers and surfactants, and pharmaceuticals (Sittig, 1985).

Phosphorus oxychloride is manufactured by oxidizing phosphorus trichloride or by reacting pentachloride with pentoxide. The estimated production capacity for phosphorus oxychloride produced in the United States as of January 1988 was 66 thousand tons (SRI International, 1988). Phosphorus oxychloride is used in the manufacture of many pesticides and pharmaceuticals, as well as plasticizers, gasoline additives, and hydraulic fluid (Sittig, 1985). In the manufacture of pesticides, it is extensively used as an intermediate for alkyl and aryl orthophosphate triesters (Windholz et al., 1983).

Phosphorus sesquisulfide is produced by direct union of the elements. The temperature of the sulfur and the quantity of phosphorus determine whether phosphorus sesquisulfide or the pentasulfide are formed.

Sesquisulfide is purified by vacuum distillation or washing with water or sodium bicarbonate solution (Boenig et al., 1982).

2.3 Environmental Release and Exposure

Although phosphorus is the twelfth most abundant element in nature it does not occur in the free state but instead is found in the form of phosphates in the minerals fluorapatite, vivianite, chlorapatite, and wavelite, and in phosphate rock. It occurs in all fertile soils and in small quantities in granite rocks (U. S. Environmental Protection Agency, 1982). Although natural discharge of phosphorus in the environment may occur (weathering and leaching of phosphate rock, pollen, plant residue, and wild animal and bird waste), phosphorus is found in the environment almost exclusively as the result of anthropogenic sources (mining, processing, and the manufacture, use, and disposal of phosphorus and phosphorus-containing products, coal combustion, and forest fires) (U. S. Environmental Protection Agency, 1982; Mishra and Shukla, 1986; Raison et al., 1985).

2.3.1 Elemental Phosphorus

Only limited information was found in the published literature on the actual ambient levels of elemental phosphorus. However, estimates of phosphorus releases as the result of mining, processing, and the manufacture, use, and disposal of phosphorus-containing products have been made by several researchers.

Lum et al. (1982) reported elemental phosphorus levels ranging from 370 to 2,460 µg/g in the form of particulate matter in the vicinity of St. Louis, Missouri. Berkowitz et al. (1981) estimated that emissions of elemental phosphorus from the manufacture of phosphorus munitions could be as great as 0.5 mg/m^3/hour (worst-case upper limit), with a more likely upper limit of 0.5 µg/m^3/hour.

These authors also estimated community exposure as a result of deployment of white phoshorus/felt and red phosphorus/butyl rubber screening smokes in training or testing field activities. Estimated exposures ranged for 146 mg/m^3 (as P_2O_5) 100 m downwind from deployment to 0.963 mg/m^3, 5,000 m downwind. Community exposures are not expected to be severe at a distance greater than 300 m. However, particularly sensitive individuals may encounter respiratory irritation at distances of about 5,000 m.

In 1979, the U. S. Environmental Protection Agency estimated coal combustion to be the largest single source of phosphorus air emissions, accounting for about 23 percent of the total national air emissions of phosphorus. The second largest source (about 20 percent) was phosphate rock mining and beneficiation activities. The third was iron manufacture (about 11 percent). Fuel oil combustion ranked fourth (7 percent), followed by the manufacture of animal feed-grade calcium phosphates (6 percent). All other estimated source quantities of phosphorus in air emissions were less than 5 percent. Refer to Table 2-2 for emission factors.

White phosphorus may enter the aquatic environment as phossy water which contains dissolved and colloidal phosphorus as well as larger suspended particles and oxides of phosphorus. Phossy water is generated wherever white phosphorus is manufactured or stored underwater (Sullivan et al., 1979).

Following the opening of a plant producing elemental phosphorus in Long Harbour, Placentia Bay, Newfoundland, phossy water was discharged to adjacent waters. Although the levels of phosphorus released were not given,

Table 2-2. Estimated Emission Factors for Point Source Emission of Phosphorus to the Environment

Industry or Activity Description	Air Emission (kg P/MT product)	Discharged Waste Water (kg P/MT product)
Phosphate rock mining and beneficiation:		
Eastern operations	0.094	0.005
Western operations	0.180	–
Industrial Manufacturing:		
Elemental phosphorus	0.64	0.15
Dry process phospheric acid	0.57	0.044
Phosphorus pentoxides	8.50	0.024
Phosphorus trichloride	10.8	0.05
Phosphorus oxychloride	4.74	0.05
Phosphorus pentasulfide	15.14	0.034
Sodium phosphate	2.0	0.004
Feed-grade calcium phosphates	2.4	0.17
Phosphorus based detergents	0.007	0.029
Direct acid treatment of metal surfaces	0.12	0.044
Agricultural consumption of phosphate rock:		
Wet-process phosphoric acid	0.166	0.0006
Superphosphoric acid	0.007	0
Normal superphosphate	0.47	0.0003
Triple superphosphate	0.35	0.00002
Ammonium phosphate	0.149	0.002
Defluorinated phosphate rock (livestock and poultry feeds)	2.2	0.33
Animal feed-grade calcium phoshates	2.6	0.026

Source: U. S. Environmental Protection Agency (1979).

concentrations of approximately 5,000 parts per million (ppm) were found in the sediments in many areas of the bay, except for one location approximately 1.5 miles from the phosphorus outfall that had a concentration of approximately 1 ppm.

Before water recycling measures were implemented, concentrations of 16.0 to 53.4 mg/L of white phosphorus have been reported in effluents at the Pine Bluff Arsenal, Arkansas, from the manufacture of white phosphorus munitions employing the wet-fill method (Pearson et al., 1976). Lai et al. (1979) reported concentrations of white phosphorus in Yellow Lake, Pine Bluff Arsenal, ranging from 0.005 to 0.010 µg/L, while the Arkansas River contained 0.003 to 0.004 µg/L.

2.3.2 Inorganic Phosphorus Compounds

Exposures to phosphine may occur when acid or water comes in contact with metallic phosphides such as aluminum phosphide or calcium phosphide. These two phosphides, pesticides used on grain, release phosphine during fumigation. It may also evolve during the generation of acetylene from impure calcium carbide, metal shaving, sulfuric acid tank cleaning, rust proofing, and ferrosilicon, phosphoric acid, and elemental phosphorus explosive handling (Sittig, 1985). Phosphine is also produced from incomplete combustion of white phosphorus/felt and from the solid phase oxidation of red phosphorus/butyl rubber as a function of relative humidity (Spanggord et al., 1985). Accidental release of phosphine was reported by Gould et al. (1986) when a 20-foot shipping container containing aluminum phosphide aboard a ship exploded. A survey of the ship found 40 to 60 ppm of phosphine in one hold. Devai et al. (1988) showed that phosphine is released from sewage treatment plants and from sediments of shallow waters. They estimated that about 5 g of phosphorus/day is released as phosphine from a tank settling 2,000 m^3/day of raw sewage.

Carpenter et al. (1978) list phosphorus pentoxide as a secondary air pollutant which may result from the open burning of waste munitions. They also cite a study that attempted to derive typical daily emissions for large-scale open burning of several explosives by extrapolation from laboratory tests. Open burning of 3.8 tons of the waste munition PBX-9494 was estimated to result in the daily release of 49 pounds of phosphorus pentoxide. Trace quantities of phosphorus pentoxide have also been identified in atmospheric emissions from electric arc alloy and steel melting operations (Bates and Scheel, 1974).

The principal atmospheric emission from the manufacture of phosphoric acid by the thermal process is particulate phosphoric acid mist (U. S. Environmental Protection Agency, 1980a,b). The two major components of this process include combustion of elemental phosphorus to produce phosphorus pentoxide and hydration of the pentoxide to produce the acid. Estimated particulate emissions from a typical thermal process phosphoric acid plant (as 100 percent phosphorus pentoxide) are 1.04 kg/hour (2.3 Lb/hour) or 8.2 Mg/year (9.1 tons/year) (U. S. Environmental Protection Agency, 1980a).

Phosphoric acid is the major phosphorus compound released in stack emissions during the production of phosphorus munitions (Berkowitz et al., 1981). At Pine Bluff Arsenal, Arkansas, air emissions of 255 pounds of phosphoric acid/hour occurred under normal operations of Ventura scrubbers, and emissions as great as 5,100 Lb/hour could occur during improper scrubbing operations.

Emissions from a British plant manufacturing sulfuric acid, phosphoric acid, and sodium tripolyphosphate, measured as deposited phosphates ranged from 636 mg/L in the immediate vicinity of the plant to 1.8 mg/L at a sampling site 2.5 km distant (Harrison, 1983).

No information was located in the published literature on the environmental release of or exposure to phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, or phosphorus sesquisulfide.

2.4 Environmental Fate

2.4.1 *Elemental Phosphorus*

In air, elemental phosphorus in the vapor phase reacts rapidly with atmospheric oxygen to produce phosphorus oxides (Spanggord et al., 1985). According to the findings of Dainton and Bevington (1946), white phosphorus inflames at most environmental pressures and temperatures greater than 5°C; hence, it is not likely that white phosphorus will persist in air. White phosphorus/felt was found to react rapidly with air (t1/2 = about 5 minutes), while red phosphorus/butyl rubber was more persistent in air (t1/2 = 1.8 years) (Spanggord et al., 1985).

The majority of phosphorus compounds released and dispersed in the air from the production and use of military screening smokes will be rained out as phosphoric acid or phosphates and deposited on land and in aquatic systems (Berkowitz et al., 1981). Anaerobic sediments and soil can serve as sinks of white phosphorus that, in turn, can serve as long-term sources of mobilization into the environment (Lai, 1981; Spanggord et al., 1985).

After release into waterways, white phosphorus rapidly oxidizes and hydrolyzes. Volatilization is also a potential route of loss. White phosphorus appears to be resistant to anaerobic degradation (Spanggord et al., 1985). Dissolved oxygen concentration, temperature, pH, metals, and sediment particles will affect the transformation of phosphorus in water (Spanggord et al., 1985; Zitko et al., 1970). Oxidation is the primary route of loss from sediments.

In soils, oxidation is also the predominant route of degradation of white phosphorus. Biotransformation does not appear to be significant. Some loss from soil to aquatic systems can occur through leaching, but is probably not significant. Because of the limited availability of oxygen in soils and the formation of oxides, which impede further oxidation, white phosphorus is likely to persist when buried in soil (Spanggord et al., 1985).

2.4.2 Inorganic Phosphorus Compounds

Phosphine is not expected to persist in the environment (Spanggord et al., 1985). Because of its high vapor pressure (1×10^4 torr) and low water solubility, it will rapidly volatilize into the atmosphere. In the atmosphere, oxidative reactions with ozone and hydroxyl radical will limit its persistence to half-lives of 8 and 5 hours, respectively. In the presence of sunlight, incompletely understood interactions with tropospheric agents will yield a half-life of 2 to 3 hours (Spanggord et al., 1985).

Phosphorus pentoxide in the atmosphere is readily hydrolyzed to yield phosphoric acid (Spanggord et al., 1983; Berkowitz et al., 1981). Phosphoric acid in the atmosphere will be rained out and deposited on land and in aquatic systems (Berkowitz et al., 1981).

No information was found on the environmental fate of phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, or phosphorus sesquisulfide.

2.5 Environmental Effects

2.5.1 Elemental Phosphorus

Abiotic effects resulting from release of white phosphorus to aquatic systems include increased acidity, decreased dissolved oxygen, and

increased sedimentation. Increased acidity and decreased dissolved oxygen could result from the oxidation of phosphorus to hypophosphorous, phosphorous, and phosphoric acids (Lai and Rosenblatt, 1977b). Peer (1972) noted local changes in sediment characteristics consisting of substantially increased deposition of fine particulates from the area of effluent discharge of a phosphorus production plant.

Field and laboratory studies indicate that white phosphorus is toxic to waterfowl and fish. Wild mallard ducks feeding in areas of phossy water discharge have ingested lethal quantities of elemental phosphorus (Coburn et al., 1950). In a series of experiments conducted with black and mallard ducks there was a marked individual variation in tolerance, but a single dose of 3 mg/kg of body weight resulted in death in 6 to 33 hours in all ducks studied. Acute poisoning caused depression, followed by leg weakness, violent convulsions, and death. Birds suffering from chronic poisoning steadily lost weight and showed signs of paralysis. All poisoned birds displayed fatty degeneration of muscle tissue, liver, and kidneys.

Much of the available information concerning the toxicity of white phosphorus to aquatic species derives from studies initiated in response to a massive fish kill caused by wastewater discharged from the ERCO phosphorus production plant in Long Harbour, Placentia Bay, Newfoundland. Hodder et al. (1972) reported an 80 percent decline in the abundance of *Clupea harengus* (herring) in Placentia Bay over a 1-month period. Mortalities resulted also in a decreased yield in nearby St. Mary's Bay, where herring migrate to reproduce. Massive herring mortalities were observed up to 60 miles from the localized pollution site in Placentia Bay (Zitko et al., 1970).

In static tests with fish, *Lepomis macrochirus* (bluegill sunfish) was the most sensitive species with a 96-hour LC_{50} of 6 µg/L, and *Ictalurus punctatus* (channel catfish) was the least sensitive with a 96-hour LC_{50} of 73 µg/L. In dynamic bioassays, fish were even more sensitive to white phosphorus. The LC_{50} for bluegill was 2.4 µg/L and that for channel catfish 19 µg/L (Bentley et al., 1978). The LT_{50} for *Salvelinus fontinalis* (brook trout) exposed to 0.5 µg/L was 121 hours (Fletcher et al., 1970) and that for *Salmo salar* (Atlantic salmon) exposed to 0.79 µg/L was 195 hours (Fletcher and Hoyle, 1972). Incipient levels (lethal concentration for 50 percent mortality from long exposure) ranged from 0.6 µg/L for bluegill (Bentley et al., 1978) to 18 µg/L for Atlantic salmon (Zitko et al., 1970). Maddock and Taylor (1976) measured the acute toxicity of dissolved elemental phosphorus to cod (*Gadus morhua*). The 48-hour LC_{50} was 14.4 µg/L and the incipient lethal level was approximately 1.0 to 2.0 µg/L. The toxic effect of phosphorus in herring, salmon, and lobster was irreversible and probably cumulative (Zitko et al., 1970). In flow-through studies of critical life stage, Bentley et al. (1978) found that the most sensitive life stages for *Pimephales promelas* (fathead minnow) are 30-day-old and 60-day-old fry.

Chronic exposure of fathead minnow to a white phosphorus concentration of 1.5 µg/L reduced survival in all fish. By day 150, the growth of all fish surviving exposures to 1.5 or 3.4 µg/L was so stunted that internal and external evidence of sexual maturity was absent. Even at 0.4 µg/L, the lowest concentration tested, hatchability was significantly reduced (Bentley et al., 1978).

Several investigators reported cardiovascular changes in fishes associated with phosphorus exposure (Pippy et al., 1972; Zitko et al., 1970; Fletcher et al., 1970; Fletcher and Hoyle, 1972). The symptoms included externally visible redness, hemolysis, low hematocrits, and pale internal organs and blood. The lowest hematocrits were associated with long, low-level exposure. Hemolysis

was observed in fish as well as in *Homerus americanus* (lobster). Substantial variation of response existed among species. Herring was the most severely affected aquatic species in the natural environment. Histological changes included damage to the gill, kidney, liver, and spleen. In lobster, exposure to white phosphorus caused degeneration of the hepatopancreas and antennal gland and coagulation of the blood.

Bioaccumulation of phosphorus is rapid, with the greatest uptake in the liver and muscle of fish and the hepatopancreas of the lobster; however,depuration occurs within seven days after exposure. Uptake appears to be positively correlated with lipid content. Reported bioconcentration factors range from 10 to 15,000 in fish, 10 to 1,267 in invertebrates, and is 22 in seaweed (Bentley et al., 1978; Dyer et al.; 1970; Maddock and Taylor, 1976; Fletcher, 1971). Fletcher (1974) reported the biologic half-life of yellow phosphorus in tissues of Atlantic cod (*Gadus morhua*) exposed in seawater. They were 4.71, 6.16, and 5.27 hours for blood, muscle, and liver, respectively. Shorter half-lifes were observed in Atlantic Salmon (*Salmo salar*), ranging from 0.9 hours in the liver to 1.3 hours in gills.

In contrast to the relatively rapid half-life of phosphorus in tissue of living cod, Dyer et al. (1972) found a slow rate of phosphorus degradation in muscle tissue of processed dead cod. Using white muscle of Atlantic cod (*Gadus morhua*) which had been exposed *in vivo* to elementary phosphorus, the authors found that phosphorus was remarkably stable during processing of the fish by commercial procedures. Icing of both round fish and fillets, freezing and thawing, salting, and cooking did not produce a product that was sufficiently safe for human consumption. The various methods produced some decrease in the initial phosphorus content, but in almost all of the samples, about 40 percent or more remained.

In chronic studies with macroinvertebrates, exposure of water fleas (*Daphnia magna*) to 8.7 µg/L of phosphorus significantly reduced survival. Concentration of <6.9 µg/L did not affect survival or the number of young produced by first and second generations (Bentley et al., 1978).

Limited studies on the toxicity of white phosphorus to algae reveal variable results and no exposure-response relationship (Bentley et al., 1978; Poston et al., 1986). The growth of two species of blue-green algae, *Anabaena flos-aquae* and *Microcystis aeruginosa,* was stimulated, but the growth of *Navicula pelliculosa,* a diatom, and *Selenastrum capricornutum*, a green alga was inhibited.

Field studies indicate that effluents containing white phosphorus adversely affect the receiving aquatic systems. Releases have altered the structure of benthic communities by decreasing diversity and by selective mortality. Pearson et al. (1976) reported that phosphorus and phosphate species were significant factors governing the distribution of benthic organisms in Yellow Lake, Pine Bluff Arsenal, Arkansas. Surveys of Placentia Bay, Newfoundland, showed that the only live benthic species collected in the vicinity of the outfall was *Modiolus modiolus* (sea mussel). A more distant location showed reduced biomass and diversity. Scallop mortalities were observed 1,000 m from the pipe. Fve percent of a population of sand dollars (*Echinarachnius parma*) were surviving in an area where 90 percent would normally be alive (Peer, 1972).

2.5.2 Inorganic Phosphorus Compounds

The only study found in the available literature on the environmental effects of the inorganic phosphorus compounds was a study designed to determine the effect of acidity on bluegill sunfish. In that study Ellgaard and Gilmore (1984) exposed bluegill sunfish to various concentrations of

phosphoric acid. No mortality was observed from pH 5.0 to 3.5. When the pH reached 3.25 and 3.0, the mortality was 13 and 100 percent, respectively. At sublethal concentrations, the bluegill became hypoactive.

3. HEALTH EFFECTS

3.1 Pharmacokinetics and Metabolism

There are only limited quantitative data on the pharmacokinetics and metabolism of elemental and inorganic phosphorus compounds. There are, however, studies which indicate that these compounds are absorbed. Most of these studies deal with the toxicological properties of elemental phosphorus and inorganic phosphorus compounds and are discussed elsewhere in this document.

3.1.1 Elemental Phosphorus

Only one study was found on the absorption of inhaled elemental phosphorus. High levels of radioactivity were detected in the lungs and digestive tract of mice immediately after exposure for 1 hour to an aerosol containing 5 mg/m^3 ^{32}P-red phosphorus. Radioactivity was retained in the lungs for at least 10 days, but the digestive tract was free from phosphorus within 48 hours. Radioactivity was not detected in systemic organs and it was therefore difficult to determine whether the phosphorus was actually absorbed (Dalhamn and Holma, 1959).

After administering rats 0.75 mg of radiolabelled phosphorus by gastric intubation, Ghoshal et al. (1971) reported that within 2 to 3 hours following administration approximately 65 to 70 percent of the administered dose was recovered in liver, and approximately 40 percent remained after 24 hours. The recovery from other organs 2 hours after exposure was as follows: blood, 12 percent; kidneys, 4 percent; and spleen, pancreas, and brain, 0.4 percent each. Approximately 82 percent of the administered dose was absorbed within 2 hours. Lee et al. (1975), after administering rats 0.1 percent ^{32}P-white phosphorus in peanut oil by gastric intubation, reported that about 60 to 65 percent of the oral dose was absorbed within 24 hours. A large amount of radioactivity was recovered in the liver, with significant amounts also recovered from blood and skeletal muscle.

Cameron and Patrick (1966) demonstrated that phosphorus is absorbed after administering 0.5, 3.5, and 20.0 mg of ^{32}P-white phosphorus to mice, rats, and rabbits, respectively, by gastric intubation. After 48 hours, the distribution of radiolabelled phosphorus was fairly uniform across species. The relative distribution was blood > feces > bowel > liver > kidney ≥ spleen > lung ≥ heart. No quantitative data on the amounts of absorbed phosphorus were given.

Subramanian et al. (1985) determined the phosphorus content in some autopsy samples of human liver, kidney cortex, and kidney medulla from residents of Kingston and Ottawa, Ontario. There were no significant differences between the two communities and the values were considered to be within the normal range. Liver and kidney (cortex and medulla) samples contained 1,800 to 2,800 and 1,300 to 2,200 mg/kg wet weight of phosphorus, respectively.

Phosphorus appeared to accumulate preferentially in the liver. The median phosphorus content in kidney was about 66 percent of that in liver.

Though white phosphorus is readily absorbed from the gastrointestinal tract, red phosphorus is considered nontoxic by the oral route because of poor absorption (Berkowitz et al., 1981). No information was found indicating the actual extent of red phosphorus absorption.

In a study on dermal absorption, Walker et al. (1969) burned white phosphorus pellets (25 mg) on the skin of a young pig. The residue on the skin was 24 percent acids of phosphorus, 93 percent of which was orthophosphoric acid. Approximately 2.71 mg of phosphorus penetrated the skin as orthophosphoric acid. However, phosphorus did not penetrate the skin beyond 2 mm of the surface.

Whiteley et al. (1953) studied the uptake of radioactive phosphorus by rabbit skin. Rabbits were injected intravenously with 75 μCi/kg of ^{32}P and killed at various intervals between 5 minutes and 72 hours after injection. Within 5 minutes after injection, radioactivity was taken up by the skin, with more taken up by the areas of active hair growth than by quiescent areas. This difference, which was maintained throughout the observation period, was attributed to the greater incorporation of ^{32}P in nucleic acids in the areas of active hair growth.

In humans, no convincing evidence was found by Walker et al. (1947) and Summerlin et al. (1967) that phosphorus is absorbed dermally in sufficient quantities to cause systemic effects. These studies are discussed in more detail in Section 3.8.1. Hughes et al. (1962) did not find significant differences in mean hematological and blood chemistry values between phosphorus-exposed workers and control subjects, although systemic changes were observed in some cases of chronic exposure to white phosphorus fumes.

Increases in serum inorganic phosphate levels are not always demonstrated immediately after acute ingestion of elemental phosphorus. In most cases normal inorganic phosphate levels and sometimes hypophosphatemia are observed rather than hyperphosphatemia. McCarron et al. (1981) reported that serum inorganic phosphate levels dropped to 1.5 and 1.8 mg/mL on the day of and the fourth day after ingestion of elemental phosphorus, respectively. Normal values range from 3.0 to 4.5 mg/mL (Berkow, 1982). In similar cases an increase in inorganic phosphate levels was not observed until 15 days and 4 or 5 days after intoxication (Diaz-Rivera et al., 1950). The authors suggested that the delayed hyperphosphatemia may be due to accumulation of phosphorus in tissues, especially in bone, and that it is later mobilized by a change in the acid-base balance. Winek et al. (1973) reported that the phosphorus content in liver was 0.049 mg percent and 0.78 mg percent in patients who died 8 and 22 hours, respectively, after ingestion of elemental phosphorus. In another patient who died within 3.5 hours, the phosphorus content in the kidney was 0.095 mg percent.

Phosphorus is eliminated through urine and feces (Cameron and Patrick, 1966; Lee et al., 1975). Forty-eight hours after dosing mice, rats, and rabbits by gastric intubation with ^{32}P-white phosphorus, radioactivity appeared in urine of rabbits but not in mice and rats. Radioactivity was also found in feces of all three species (Cameron and Patrick, 1966). Lee et al. (1975), however, found that 17.1 percent of an orally administered dose of ^{32}P-white phosphorus appeared in urine of rats 4 hours after dosing (Table 3- 1). At 1 and 5 days, 34.5 percent and 46.7 percent, respectively, appeared in urine. The fecal content of ^{32}P-white phosphorus was 2.0 percent, 16.6 percent, and 33.0 percent at 4 hours, 1 day, and 5 days, respectively. The authors did not determine whether the radioactivity in fecal material was due to direct elimination from the gastrointestinal tract or was the result of biliary excretion.

Table 3-1. Distribution and Excretion of Radioactivity in Rats Receiving ^{32}P-White Phosphorus

	Percent of Administered Dose		
	4 Hours	1 Day	5 Days
Gastrointestinal tract plus contents	57.0 ± 3.4[c]	15.3 ± 4.0	1.7 ± 0.2
Feces	2.0 ± 1.0	16.6 ± 3.8	33.0[d]
Whole blood[a]	6.1 ± 1.1	4.1 ± 0.5	1.7 ± 0.0
Urine	17.1 ± 2.2	34.5 ± 6.1	46.7[d]
Liver	16.1 ± 4.6	16.9 ± 0.7	6.3 ± 0.3
Kidneys	0.7 ± 0.2	0.8 ± 0.1	0.4 ± 0.0
Spleen	0.1 ± 0.0	0.1 ± 0.0	0.1
Brain	0.1 ± 0.0	0.1	0.1
Lungs	0.4 ± 0.0	0.3 ± 0.1	0.2 ± 0.0
Skeletal muscle[b]	4.0 ± 0.0	5.5 ± 0.2	6.0 ± 0.6
Recovery	98.6 ± 5.0	94.0 ± 3.3	6.0

[a]Based on 7.0 percent of the body weight.
[b]Based on 40 percent of the body weight.
[c]Mean ± S.E. of three rats.
[d]Pooled samples from three rats.

Source: Lee et al. (1975).

Thin layer chromatography of the urine from rats administered ^{32}P-white phosphorus separated two major radioactive components: one was inorganic phosphate and the other was a more nonpolar component suggestive of organic phosphate. Analysis of liver extracts also demonstrated two classes of metabolites with properties similar to those found in the urine (Lee et al., 1975).

3.1.2 Inorganic Phosphorus Compounds

The effects of phosphine on numerous organs suggest a wide tissue distribution (Hayes, 1982). Nevertheless, the chemical was not detected in tissues of fatal cases of phosphine poisoning (Harger and Spolyar, 1958). Harger and Spolyar (1958) cite other investigators who suggested that phosphine is readily metabolized to phosphates, thereby simply adding to the pool of existing phosphates. The tissues from two fatal cases of phosphine poisoning reportedly contained lower oxides of phosphorus (Reinl, 1956).

The only other study found in the published literature on the absorption and distribution of either of the other inorganic phosphorus compounds was that of Pena Payero et al. (1985). In that study an intense taste of matches was experienced by a patient several minutes after a patch test of phosphorus sesquisulfide was applied. Based on that finding, the authors suggested that the chemical is rapidly absorbed through the skin.

Regardless of the route of absorption, some phosphine is excreted by the lungs and may be recognized by its characteristic disagreeable odor (Hayes, 1982). This odor was noticed until the 11th day in the breath of a man who swallowed aluminum phosphide tablets (Zipf et al., 1967), indicating that the chemical may remain in the body for an extended period of time. Information

on the elimination of the other inorganic phosphorus compounds was not found.

3.2 BIOCHEMICAL EFFECTS

3.2.1 Elemental Phosphorus

Because white phosphorus intoxication produces a characteristic lesion, fatty degeneration of the liver, several studies have been conducted to analyze various biochemical changes that may contribute to this effect. Seakins and Robinson (1964) observed the following changes 24 hours after oral administration of 1.5 mg of white phosphorus to rats: increased liver weight, increased total amount and concentration of esterified fatty acids and cholesterol, elevated total amount of phospholipids but decreased concentration, and marked reduction of mean plasma concentrations of esterified fatty acids, cholesterol, and phospholipids.

A small increase in hepatic triglycerides was observed in rats as early as 2 hours following administration of 10 mg/kg of white phosphorus by gastric intubation. After 12 hours, hepatic triglycerides were significantly elevated. Administration of the antioxidants glutathione or propyl gallate prior to white phosphorus treatment prevented the elevation of hepatic triglycerides induced by oral doses of phosphorus, indicating that antioxidants may prevent phosphorus-induced fatty degeneration of the liver (Pani et al., 1972).

Jacqueson et al. (1979) demonstrated that total hepatic lipids and triglycerides were elevated in rats after subcutaneous administration of 10 mg/kg of white phosphorus. Chromatographic analysis of hepatic triglycerides showed increases in the relative amounts of oleic, palmitoleic, and stearic acids, and a decrease in linoleic acid.

Ghoshal et al. (1969) showed that hepatic triglycerides in rats were significantly elevated 6, 12, and 24 hours after administering 7.5 mg/kg of yellow (white) phosphorus by gastric intubation. According to Ghoshal et al. (1969, 1972), an observed increase in lipid peroxidation of hepatic microsomes (measured by absorption of conjugated dienes), which precedes the elevation in hepatic triglycerides, may be the cause of abnormal fat accumulation in the liver of rats treated orally with 7.5 mg/kg of phosphorus. In contrast, Pani et al. (1972) failed to find an increase in lipid peroxidation (conjugated dienes) in rats given 10 mg/kg of white phosphorus orally.

The secretion of enzymes from hepatocytes, as reflected by their increased appearance in the blood, serves as an indicator of hepatotoxicity (Kulkarni and Hodgson, 1980). Plasma levels of glutamic-oxalacetic transaminase (GOT) were significantly elevated 24 hours after administering 7.5 mg/kg of yellow (white) phosphorus to rats by gastric intubation; the levels of glutamic-pyruvic transaminase (GPT) were not altered (Ghoshal et al., 1969). Serum GPT levels in mice also remained unaltered one and four days after administering 5 mg/kg of white phosphorus by gastric intubation (Hurwitz, 1972).

Pulmonary free cells collected by lavage from rats exposed by inhalation to combustion products of red phosphorus/butyl rubber aerosols displayed increased ATP levels and decreased ectoenzyme activity for 5'-nucleotidase in alveolar macrophages (Aranyi et al., 1988). These biochemical alterations were observed following single (1 g/m^3 for 3.5 hours) or multiple exposures (0.3 to 1.2 g/m^3 for 2.25 hours/day, 4 consecutive days/week for 4 or 13 weeks), with the exception of a medium exposure level in the 13-week study. Both changes were reversible.

3.2.2 Inorganic Phosphorus Compounds

The mechanism of action of phosphine has been studied biochemically in isolated mitochondria. Nakakita et al. (1971) showed that phosphine inhibits the respiratory chain in rat liver mitochondria using succinate or pyruvate plus malate as a substrate. Phosphine has a direct effect on electron transport in mouse liver mitochondria and is thought to be a competitive inhibitor of cytochrome oxidase (Chefurka et al., 1976). *In vivo*, acute inhalation exposure of rats has been correlated with decreased mitochondrial respiration, affecting particularly the oxidation of ∝-ketoglutarate. The coenzyme A levels in liver mitochondria were slightly lower than in controls and the oxidative phosphorylation of heart, but not of liver mitochondria, was reduced (Neubert and Hoffmeister, 1960).

No information was found in the published literature on the biochemical effects of phosphorus pentoxide, phosphoric acid, phosphorus trichloride, phosphorus pentachloride, phosphorus oxychloride, or phosphorus sesquisulfide.

3.3 Acute Toxicity

3.3.1 Elemental Phosphorus

A comprehensive study on the effects of white phosphorus smoke in rats and guinea pigs was carried out by Brown et al. (1980). White phosphorus felt cubes weighing 2.5 to 60 g were ignited in a chamber containing the test animals. The major combustion component was phosphorus pentoxide in addition to phosphorus trioxide and phosphorus dioxide. Rats were exposed for 60 or 90 minutes to concentrations ranging from 505 to 2,018 mg/m^3, with concentration x time (CxT) values ranging from 30,300 to 181,620 mg·min/m^3. Guinea pigs were exposed for 5 to 60 minutes to concentrations ranging from 88 to 810 mg/m^3, with CxT values ranging from 545 to 48,060 mg·min/m^3. Although occasional changes were observed in both species, concentration-dependent or agent-related changes in the hematology and blood chemistry were not observed.

In rats, the acute signs of toxicity were gasping and ataxia at exposures of 797 mg/m^3 for 90 minutes (71,753 mg·min/m^3); nevertheless, the animals recovered. Respiratory distress was observed in animals surviving higher exposures, but they recovered within 24 hours. The mortality ranged from 0 percent at 505 to 797 mg/m^3 to 90 percent at 2,018 mg/m^3. An LCt_{50} of 94,126 mg·min/m^3 was determined by statistical analysis of the concentration-response data. Histopathological examination of selected animals from the high exposure group showed fibrin thrombi in heart and lungs, acute diffuse congestion, and focal perivascular edema and hemorrhage in the lungs. A definite relationship between the induction of the lesions and exposure was not established (Brown et al., 1980).

One guinea pig exposed to 176 mg/m^3 died during the 30 minute exposure period. However, no other deaths or adverse effects were observed in guinea pigs at CxT values ranging from 545 to 3,840 mg·min/m^3. Respiratory distress was a common problem in animals exposed to CxT values higher than 5,410 mg·min/m^3. Almost all the animals that survived the immediate effects of exposure subsequently recovered. All animals exposed to CxT values of 14,310 and 48,060 mg·min/m^3 corresponding to 477 mg/m3 for 30 minutes and 801 mg/m^3 for 60 minutes, respectively, died during exposure or within 15 minutes after exposure, except one animal which

survived for 3 days. An LCt_{50} of 5,321 mg·min/m^3 was established from the concentration-response data. Studies on pulmonary resistance in guinea pigs exposed to 3,840 and 5,280 mg·min/m^3 did not reveal a significant difference between exposed and control animals (Brown et al., 1980).

In a series of tests, White and Armstrong (1935) exposed mice, rats, and goats to white phosphorus for 1 hour at levels ranging from 110 to 1,690, 380 to 4,810, and 540 to 11,470 mg/m^3, respectively. Mortality ranged from 5 percent at 110 mg/m^3 to 95 percent at 1,690 mg/m^3 in mice. Rats appeared to be much more tolerant of the phosphorus smoke than mice. The mortality ranged from 0 at 380 mg/m^3 to 100 percent at 4,810 mg/m^3. In goats, mortality ranged from 0 at up to 4,810 mg/m^3 to 100 percent at 8,010 mg/m^3. Signs of toxicity were noted in exposed animals at the lowest exposure levels. The toxic manifestations included pulmonary congestion and hemorrhage and cloudy swelling of the liver and kidneys. Cloudy swelling of the heart was also noted in mice and rats. In goats, inflammatory reactions in the trachea with pus and pneumonia were noted. Deaths were attributed to the toxic effects of the phosphorus in rats, the irritative and toxic effects of the phosphorus in goats, and the irritative effects of the phosphorus in mice.

Death occurred within four days in eight dogs given oral doses of 0.5 to 1.0 mg/day of phosphorus (Williamson and Mann, 1923). Three animals developed severe hypoglycemia, which became apparent only a few hours prior to death. The blood sugar level was normal in the remaining animals. Blood urea was increased in seven animals, significantly in six. The severe hypoglycemia suggested that the liver was damaged.

Cutler (1931) obtained similar results with respect to the induction of hypoglycemia. Dogs were administered phosphorus orally in doses of 2 mg/kg on day 1, 1 mg/kg on day 3, and 1 mg/kg on day 5, but only if intoxication was not observed earlier. Overt symptoms of phosphorus poisoning included sluggishness, tremors, vomiting, convulsions, and coma. There was a decrease in blood sugar in all animals in addition to increases in guanidine, nonprotein nitrogen, amino nitrogen, urea, and creatine.

Lee et al. (1975) administered a 0.1 percent solution of white phosphorus by gastric intubation to rats, mice, and rabbits. Animals surviving treatment were observed daily for mortality and signs of toxicity. Both mice and rats suffered from depression and anorexia. The livers were enlarged and yellowish in color.

Brown et al. (1980) administered to rats 1.48, 1.86, 2,43, or 2.96 g/kg of white phosphorus/felt smoke condensate by gastric intubation. The acute signs of toxicity were lethargy, gastric distress, and prostration. Death occurred within 24 hours.

O'Donoghue (1985) reported that acute poisoning following large doses of yellow phosphorus results in fatty degeneration in the parenchymal cells of major organs, especially the liver, kidneys, and heart. Neurological effects included vascular endothelial damage, hemorrhage, and enlargement or swelling of the glia. Diffuse cortical and focal perivascular neuron degeneration may also occur.

Urine, blood, and liver of rabbits injected subcutaneously with 5 mg/kg of yellow (white) phosphorus were subjected to chemical analysis, and liver and kidney specimens were analyzed microscopically (Huruya, 1928). Fatty deposits appeared in the interstitium and parenchyma of the liver. Damage to the kidney was found in the renal tubules but rarely in the glomeruli. Liver weight, nonprotein nitrogen, polypeptide nitrogen, total fatty acid, and cholesterol increased with severity of fatty degeneration of the liver. Chemical analysis of blood revealed that total nitrogen, nonprotein nitrogen, and

polypeptide nitrogen also increased. The volume of urine and the urine absolute total nitrogen and percentage urea nitrogen decreased, whereas the alkalinity and ammonia nitrogen increased.

Buchanan et al. (1954) injected three dogs subcutaneously with 0.4 and one dog with 0.2 mg/kg/day of phosphorus. Two of three animals given 0.4 mg/kg/day died on day 6, and the third animal stopped eating on day 7 and was killed on day 14. On day 3 the dogs began to vomit mucous material which became bloody prior to death. All organs were hemorrhagic; fatty degeneration of the liver was observed in a narrow zone around the central vein. The kidney tubules were necrotic and fatty degeneration was observed in those less severely damaged. The one dog given 0.2 mg/kg/day had hemorrhagic liver, intestines, and kidneys. Fatty vacuolization was observed in the peripheral areas of the lobules in the liver. Kidney tubules had granular plugs and the epithelium began to slough off. Clinical studies showed a significant increase in urine creatine and a decrease in creatinine levels indicating an impairment in kidney function. In addition, urine choline levels showed a slight increase immediately preceding death.

Experimental white phosphorus burns produced in New Zealand white rabbits caused postburn electrolyte changes consisting of depression of serum calcium and elevation of serum phosphorus. In addition, electrocardiographic abnormalities (prolongation of the QT interval, bradycardia, and ST-T wave changes) were observed. Mortality rates were 65 to 85 percent (Bowen et al., 1971).

Appelbaum et al. (1975) evaluated the subcellular changes resulting from experimental phosphorus burns in rats. Pathological changes were observed 72 hours postburn, primarily in the kidneys. The changes included ischemic glomeruli, capillary collapse, proliferation of mesangial areas, basement membrane thickening, and necrosis in proximal tubules. Effects included oliguria, polyuria, and anuria. Serum urea, serum glutamic pyruvate transaminase (SGPT), and phosphate were elevated.

Marrs (1984) exposed rats and rabbits for 30 minutes to single exposures of smoke from two pyrotechnic mixtures. Composition I contained 95 percent red phosphorus and 5 percent butyl rubber (0.68 g/m^3 as phosphorus) and composition II contained 97 percent phosphorus and 3 percent butadiene styrene (0.67 g/m^3 as phosphorus). Both mixtures produced histological changes in the respiratory tract that included abnormalities of the larynx and trachea, and alveolitis; a few cases of bronchopneumonia were observed.

Rats exposed to red phosphorus/butyl rubber aerosols at concentrations ranging from 0.5 to 3 g/m^3 for 1 to 4 hours showed highly significant decreases in pulmonary bactericidal activity to inhaled radiolabelled *Klebsiella pneumoniae* after single or multiple exposures. Pulmonary free cells obtained by tracheobronchial lavage from rats exposed to the higher concentrations were significantly decreased (Aranyi, 1983). In a later experiment Aranyi et al. (1988) exposed rats to combustion products of red phosphorus/butyl rubber aerosols at a concentration of 1 g/m^3 for a 3.5 hour single exposure. Exposed rats showed a decreased ability to kill inhaled *Klebsiella.* As in the earlier study, pulmonary free cells collected by lavage were decreased.

Subsequent mortality studies with red phosphorus/butyl rubber aerosols suggest that exposure concentration is the determining factor in mortality rather than length of exposure. Rats were given single 1-hour exposures of 2.0, 2.22, 2.62, 3.09, or 3.15 g/m3 and observed for 14 days. Maximum mortality (20 to 25 percent) occurred after a 1-hour exposure to 3 g/m^3, while 2.62 g/m^3 resulted in 6 percent deaths. A single 4-hour exposure to 0.88 g/m^3

with a CxT value similar to those in the 3.09 to 3.15 g/m^3 1-hour exposures was not fatal (Aranyi, 1983).

In a range-finding study, Burton et al. (1982) exposed rats to 3.1, 4.3, 5.3, or 8.5 g/m^3 red phosphorus/butyl rubber smoke aerosols for 1 hour or to 1.5 g/m^3 for 4 hours. Chemical analysis of the aerosols suggested that the principal product of red phosphorus/butyl rubber combustion is phosphorus pentoxide, which then hydrolyzes to form a series of polyphosphoric and cyclopolyphosphoric acids. Also detected were low concentrations of phosphine. Lesions common to all exposed groups involved the larynx and epiglottis. Pulmonary congestion, edema, and hemorrhage were pronounced only in the two highest exposure groups. Deaths occurred on days 1 through 11 postexposure, suggesting both acute and delayed effects. Of the 10 animals exposed to 3.1 g/m^3 for 1 hour, one animal died on day 6 and 10 postexposure. Exposure to 1.5 g/m^3 for 4 hours resulted in 4 deaths.

Weimer et al. (1977) exposed rats, guinea pigs, and dogs to red phosphorus/butyl rubber screening smoke. Airborne concentrations were based on phosphoric acid content. Rats were exposed to from concentrations 1,128 to 1,882 mg/m^3 for 60 to 240 minutes; guinea pigs from 120 to 2,277 mg/m^3 for 5 to 150 minutes; and dogs from 1,212 to 1,882 mg/m^3 for 30 to 240 minutes. Based on mortality data, red phosphorus/butyl rubber smoke appeared to be only slightly toxic in rats and dogs but highly toxic in guinea pigs. The mortality in rats ranged from 0 percent at 1,128 mg/m^3 for 60 minutes to 100 percent at 1,882 mg/m^3 for 240 minutes. In guinea pigs, the mortality ranged from 0 percent at 120 mg/m^3 for 5 minutes to 100 percent at 1,483 mg/m^3. All but one of the dogs survived the smoke exposures. Following exposure, all animals showed signs of respiratory distress that was more marked with increasing exposure levels and time. Animals usually displayed hyperactivity which persisted up to 2 days postexposure. Conjunctivitis was noted in rats and dogs at the higher exposure levels. Exposed male rats had significantly lower liver weights than control animals. Kidney and body weights were also less than those in controls at the higher exposure levels.

3.3.2 Inorganic Phosphorus Compounds

Symptoms observed in rats, resulting from single acute inhalation expo sures to phosphine, were typical of mild irritation, such as red ears, salivation, lacrimation, face pawing, and dyspnea. Histologic examination of tissues did not show any pathologic changes. The 4-hour LC_{50} was 15.4 mg/m^3. Repeated 4-hour inhalation exposures to about 5.6 mg/m^3 for 10 days produced mild respiratory irritation and in addition a slightly reduced body weight gain, which returned to normal after 12 days. Piloerection was noted during the fourth and subsequent exposures (Waritz and Brown, 1975).

Little species variation was observed in rats, rabbits, guinea pigs, and cats exposed by inhalation to phosphine at concentrations ranging from 7.5 to 564.0 mg/m^3 (Klimmer, 1969). At high phosphine concentrations, the animals quickly developed lassitude, immobility, restlessness, ataxia, pallor, convulsions, and death within 30 minutes or less, with apnea preceding cardiac arrest. Similar symptoms with slower onset and progression were noted at the intermediate concentrations. The first several 6-hour exposures to the lowest fatal concentration (7.5 mg/m^3) did not produce detectable adverse effects; however, further exposure led to pulmonary edema and respiratory failure.

Exposure-response studies in rats indicated that at concentrations of 7.5 mg/m^3 phosphine and above, the effects were cumulative, while concentra-

tions of 3.75 mg/m^3 and below produced no clinical evidence of cumulative effects (rats tolerated 3.75 mg/m^3 for 820 hours without clinical injury) (Klimmer, 1969).

The only pathological change in rats, rabbits, guinea pigs, and cats killed rapidly by high exposures to phosphine may be pulmonary edema. Those killed more slowly may show pulmonary edema, hemorrhages of the mucosa, slight diffuse fatty infiltration of the liver, and isolated necrosis of the tubular epithelium of the kidneys. Pathological changes in the brain may include pronounced dilatation of the perivascular spaces, changes in the nuclei of ganglion cells with glial reaction, disintegrating Purkinje cells with multiplication of the Bergmann glia, edema of the white matter of the cerebellum, and occasional damage to the capillary epithelium. The glial reactions were not found in cats and guinea pigs (Klimmer, 1969). Table 3-2 summarizes some lethality data in laboratory animals due to phosphine inhalation.

Acute toxicity data for phosphorus pentoxide in laboratory animals indi cate a wide interspecies difference. The acute 1-hour inhalation toxicity of phosphorus pentoxide in terms of LC_{50} values is 61, 271, 1,212, and 1,689 mg/m^3 for guinea pigs, mice, rats, and rabbits, respectively (Ballantyne, 1981).

The only information regarding the acute toxicity in laboratory animals was an oral LD_{50} value of 1,530 mg/kg for rats and a dermal LD_{50} value of 2,740 mg/kg for rabbits (RTECS, 1989).

A slight transient epithelial edema and conjunctival hyperemia was noted in a rabbit's eye irrigated for 5 minutes with a 0.16 M solution of orthophosphoric acid (H_3PO_4) buffered to pH 3.4. The eye was normal by the next day. However, injection into the rabbit corneal stroma or application of metaphosphoric acid (HPO_3) to the cornea after removal of the epithelium, caused detectable injury below pH 5.5 (Grant, 1974).

Grant (1974), citing Flury and Zernik (1931), report that cats exposed to phosphorus trichloride concentrations of 11 to 23 mg/m^3 for 6 hours developed respiratory difficulties and conjunctivitis; exposure to 130 to 510 mg/m^3 for the same time period caused clouding of corneas and severe systemic effects.

Weeks et al. (1964) studied the acute vapor toxicity from single 4-hour exposures of rodents to the vapors of phosphorus trichloride and the effects on its toxicity when the vapor was neutralized with ammonia in air. The 4-hour LC_{50} for phosphorus trichloride in rats and guinea pigs was 590 mg/m^3 and 283 mg/m^3, respectively. During exposure to phosphorus trichloride, rats and guinea pigs were restless and agitated and exhibited porphyrin secretion

Table 3-2. Lethality of Phosphine in Animals

Species	Route	Concentration/Effect
Rat	Inhalation	16.5 mg/m^3 4 hr, LC_{50}
Mouse	Inhalation	412.5 mg/m^3 2 hr, LC_{LO}
Guinea pig	Inhalation	150.0 mg/m^3 2 hr, LC_{LO}
Rabbit	Inhalation	3,750.0 mg/m^3 20 min, LC_{LO}
Cat	Inhalation	75.0 mg/m^3 2 hr, LC_{LO}

Source: RTECS 1989

around the eyes and reddish-brown discoloration of the pelt. The chemical was severely corrosive, producing necrosis of paws and nostrils. Areas of necrosis appeared in kidney tubules; pulmonary damage was only slight. When ammonia was added to the atmosphere, the symptoms of irritation were markedly reduced. The toxicity of phosphorus trichloride (which hydrolyzed about 40 percent) was only slightly reduced in rats, but significantly reduced in guinea pigs.

Russian investigators (Roshchin and Molodkina, 1977) carried out acute toxicity studies with phosphorus trichloride in rats, guinea pigs, mice, and rabbits. Acute inhalation as well as oral administration by gavage produced pronounced irritation and systemic effects in all species tested. The irritating effects, characterized by corneal turbidity, skin ulcers around mouth and nose, and respiratory irritation, were attributed to the hydrolysis of phosphorus trichloride to hydrochloric and phosphoric acid. Dystrophic changes were found in kidneys, liver, and nervous system. Roshchin and Molodkina (1977) classified the chemical as extremely toxic when inhaled (LC_{50} = 226 mg/m^3 or about 40 ppm) and less toxic by the oral route (LD_{50} = 550 mg/kg).

Acute exposure of laboratory animals by inhalation or gastric intubation to phosphorus pentachloride (levels not reported) produced respiratory irritation, and dystrophy in the kidneys, liver, and nervous system (Roshchin and Molodkina, 1977). The irritant effects were less severe than those observed with exposure to phosphorus trichloride. The compound was less toxic when taken orally than by inhalation. The inhalation LC_{50} for rats is 295 mg/m^3. The oral LD_{50} is 660 mg/kg (Sax, 1984).

Weeks et al. (1964) studied the acute inhalation toxicity of phosphorus oxychloride in rats and guinea pigs. During exposure to the chemical, the animals showed signs of irritation and developed porphyrin secretions around the eyes. The 4-hour LC_{50} values were 303 mg/m^3 and 335 mg/m3 for rats and guinea pigs, respectively. All deaths occurred within 48 hours of exposure, preceded by gasping and convulsions. In surviving animals, the toxic symptoms abated during the 14-day observation period. The lungs of animals that died were dark red. Tissue examination showed desquamation of tracheal and bronchial epithelium, resulting in plugging of the lumen of the bronchi and bronchioles. The toxicity of phosphorus oxychloride, which hydrolyzed about 15 percent in the vapor phase, was not significantly affected by neutralization with ammonia.

Roshchin and Molodkina (1977) carried out acute, subacute, and chronic toxicity studies of phosphorus oxychloride on specified numbers of rats, guinea pigs, mice, and rabbits. However, in describing the effects, the number and species tested generally were not specified, except for a few instances which mentioned rats. Acute effects of phosphorus oxychloride resulting from a single inhalation or oral exposure were respiratory tract irritation and dystrophic changes in internal organs, particularly in kidneys, liver, and nervous system. The inhalation LC_{50} was 71 mg/m^3 (exposure time not given).

An oral LD_{LO} value of 100 mg/kg in dogs was the only information found for effects of phosphorus sesquisulfide in experimentla animals (Sax, 1984).

3.4 SUBCHRONIC AND CHRONIC TOXICITY

3.4.1 Elemental Phosphorus

Inuzuka (1956) reported that rats exposed to 150 to 160 mg/m^3 yellow phosphorus 30 minutes/day for 60 days developed bone changes consisting

of a widened epiphyseal line, irregular cell configuration, trabeculation with insufficient ossification, and developmental changes of long bones. Young animals were more severely affected than older ones. There were, however, no significant changes in the Ca/P ratio or phosphorus content of long bones.

Brown et al. (1981) carried out a systematic study to examine the effects of subchronic exposure to white phosphorus smoke on rats. The four concentrations were 1,161 mg/m^3 (high), 589 mg/m^3 (intermediate), 193 mg/m^3 (low), and 0 (control). The animals were exposed to smoke, generated by burning white phosphorus/felt, for 15 minutes/day, 5 days/week for 13 weeks. The mortality rate was high in the high-exposed group, but no animals in the intermediate and low exposure groups died prior to scheduled sacrifice. Of the 72 rats exposed to the highest concentration of phosphorus, 23 died within 6 weeks, and by the end of the experiment, a total of 29 had died. Immediate effects of the high levels of phosphorus were dyspnea and wheezing, which cleared up within 2 hours.

There were no agent-related changes in body and organ weights during the course of this experiment. Blood chemistry and hematology as well showed no agent-related changes, suggesting that inhalation of white phosphorus/felt smoke does not produce systemic effects under the conditions of this study. Pulmonary rales were noted in 3 of 12 rats exposed to the high level of phosphorus, but did not occur in the intermediate, low, or control groups. There were also indications that the tidal volume was reduced and breathing rate was increased in males in the high exposure group for the duration of the study (Brown et al., 1981).

Histopathological evaluations showed that >70 percent of the animals that died spontaneously after exposure to the white phosphorus smoke developed laryngitis, tracheitis, and congestion. Bronchitis was observed in 20 percent and interstitial pneumonia in 53 percent. With the exception of interstitial pneumonia, these lesions were agent-related. Laryngitis was moderate in the high-exposure group; tracheitis was moderate to slight in the high-exposure group and slight to minimal in the intermediate-exposure group. No cases of laryngitis and only one case of tracheitis were observed in the low-exposure group; congestion and bronchitis were absent. Under the conditions of this study, the lowest-observed-adverse-effect level (LOAEL) was 193 mg/m^3 (Brown et al., 1981).

A recent Russian study investigated the morphology of the oral mucosa in rats after long-term exposure to the atmosphere of a phosphorus factory (Ruzuddinov and Rys-Uly, 1986). Rats were kept in the furnace room of a phosphorus factory 4 hours daily, 5 days/week for up to 4 months (exposure levels not given). After 1 month, the structural integrity of the epithelium of the oral mucosa was normal in most animals. In the second month, hyperkeratosis of the mucosa of the gum, cheek, hard palate, and tongue and vascular disturbances in the form of increased permeability of the capillary walls were observed. Progressive pathological changes were found in the third and fourth month of exposure. Toward the end of the experiment, dystrophic and atrophic changes were observed in the epithelium, leading in some cases to a decrease in thickness of the epithelial layer. The maximum allowable level in the Soviet Union is 0.03 mg/m^3 (International Labour Office, 1980).

Strelyukhina (1984) reported hepatic changes in rats in the form of congestion, fatty degeneration of the hepatocytes, and toxic hepatitis after orally ingesting 1.0 mg/kg of white phosphorus for 15 days to 4 months. Fibrosis and internodular cirrhosis was evident in some animals exposed to phosphorus for 3 to 4 months. Similar results were reported by Mallory (1933)

after orally administering rabbits and guinea pigs 0.25 to 1.0 mg/kg phosphorus/day until the animals were sacrificed.

Phosphorus-induced cirrhosis of the liver was observed at 8 weeks in animals administered 1 mg/kg, while animals given lower doses required over 4 months to develop cirrhosis of the liver. Phosphorus caused damage to fibroblasts of the stroma and to hepatic cells throughout the liver. Damage to fibroblasts was followed by regeneration as evidenced by mitotic activity and periportal fibrosis which extended irregularly into the lobule. Damage to hepatic cells, which was extensive after administering 1 mg/kg/day, was also followed by regeneration.

Ashburn et al. (1948) were not able to induce clear-cut cirrhosis in guinea pigs administered phosphorus for 35 weeks. However, other extensive liver changes were observed. The animals were given 0.75 mg/kg for 4 days each week or 1.5 mg/kg twice weekly in a 0.1 percent solution of olive oil, per os. The lesions appearing after dosing 4 times per week were identical in incidence and type to those appearing after dosing twice weekly. Nine weeks after initiating treatment, hepatic lesions appeared in the hilar portion of most lobes and extended toward the surface of the liver. As treatment progressed, the lesions increased in size and frequency. Extreme atrophy was observed in lobes containing lesions, whereas hypertrophy was observed in uninvolved lobes. Early lesions were characterized by destruction of parenchyma cells and hydropic, fatty, or other degenerative changes in surviving cells. Other changes included bile duct proliferation and an inflammatory response with infiltration of lymphocytes and large mononuclear cells. In late lesions, few parenchyma cells, fibrous tissue, a few normal bile ducts, and collapsed sinusoids were observed. Necrosis was limited to a few isolated cells distributed throughout the liver. A slight increase in the amount of periportal collagen was observed after 16 weeks.

Sollmann (1925) found that rats maintained on a diet containing phosphorus experience weight loss. Young female rats were placed on a diet containing phosphorus at daily doses of 0.072 mg/kg, 0.018 mg/kg, or 0.0033 mg/kg for 22 weeks. A pronounced depression of growth and weight loss was observed in rats administered 0.072 mg/day. Animals removed from the diet at 10 weeks did not gain but ceased to lose weight. Similar, but less severe effects were noted in animals exposed to 0.018 mg/kg. Removal from the diet containing phosphorus at 16 weeks caused normal growth to resume. Growth of rats placed on 0.0033 mg/kg was unaffected by phosphorus up to the 15th week, at which time growth ceased. Removal from the diet caused a rapid increase in weight gain such that at 22 weeks treated animals weighed more than controls. Older male rats on a dose regimen of 0.0027 mg/kg/day of phosphorus for 25 weeks showed considerable fluctuations in growth prior to the 15th week. Thereafter growth was rapid and was 13 percent that of controls by the 25th week of treatment. A recent study by Monsanto (1985) did not confirm the extreme weight loss in rats given 0.075 mg/kg/day of white phosphorus prior to and through two gestation periods.

Adams and Sarnat (1940) reported that phosphorus has an effect on bones. These researchers administered 0.6 mg/day of yellow phosphorus orally to rabbits for 13 to 117 days and phosphorized cod liver oil (0.01 percent phosphorus) to rats for 22 to 57 days. General growth and longitudinal bone growth in both rabbits and rats were adversely affected by yellow phosphorus. The average daily increase in tibial diaphysis was 0.36 mm in control rabbits and only 0.27 mm in phosphorus-treated litter mates. Histological evaluation showed dense "phosphorus" bands in the metaphysis of long bones during the period of exposure and increased numbers of

trabeculae due to reduced resorption of the intercellular calcified cartilage matrix. Zones of abnormally calcified dentin were also found in molars and incisors during the period of ingestion. Thickening and increased radiographic density of the metaphyseal bone were observed by Whalen et al. (1973) after feeding rats a diet containing approximately 0.065 mg phosphorus/kg/day for 16 days. Histologically, the trabeculae were found to be abnormally thickened, accounting for the increased density.

Fleming et al. (1942) administered white phosphorus mixed with stock diet at equivalent doses of 0.2 to 1.6 mg/kg/day to rats for their entire lifetime, (up to 512 days in some animals). Except for the group receiving 0.8 mg/kg/day, mortality decreased with decreasing dosage; the average survival of all treated animals, however, was greater than or equal to that of controls (Table 3-3). Histopathological evaluation revealed changes in the bones consisting of thickening of the epiphyseal line and extension of the trabeculae into the shaft in all phosphorus exposed animals.

As part of the same experiment Fleming et al. (1942) also administered white phosphorus to rats and guinea pigs by subcutaneous injection. Rats were injected twice weekly with doses ranging from 0.05 to 3.2 mg/kg/day up to 720 days and guinea pigs with doses ranging from 0.05 to 0.4 mg/kg/day up to 1,160 days. The mortality rate in treated rats decreased with decreasing doses of phosphorus (Table 3-3). At the lowest doses (0.05 or 0.1 mg/kg/day), the mortality rate was lower than that in controls. Thus, as in the oral study, low doses of phosphorus were associated with improved survival in rats. Almost all the rats exposed to phosphorus at all dose levels developed bone changes consisting of thickening of the epiphyseal line and extension of trabeculae into the shaft. These changes were more pronounced than those observed in rats administered phosphorus in their diets. The livers of a few animals showed mild fatty degeneration and those of two animals, periportal fibrosis. Liver damage, therefore, was insignificant considering the long period of treatment. Guinea pigs, given twice weekly subcutaneous injections of phosphorus, showed similar skeletal changes, though less severe than those observed in rats. The relationship between bone pathology in laboratory animals and the effects of chronic occupational exposure to elemental phosphorus in humans (see Section 3.8.1, necrosis of the jaw bone) is unknown.

One-year-old dogs weighing 10 kg were injected subcutaneously with 0.1 mg/kg/day of phosphorus for 55 to 115 days (Buchanan et al., 1954). All animals lost 2.5 to 3.0 kg of weight between day 25 and 51 of treatment, then gained 1.85 to 2.85 kg prior to sacrifice. All animals became ill prior to sacrifice. Some dogs developed fatty degeneration of the liver, hydropic degeneration of the kidney, and accumulated large amounts of hemosiderin in the spleen.

Because phosphorus causes changes indicating that fat metabolism may be disturbed, such as fatty degeneration of liver and other organs, Fleming and Collings (1951) carried out studies to determine if the fat content in the blood as measured by the chylomicron count, may also be altered by phosphorus. Rats received 1.1 mg/kg/day of yellow (white) phosphorus three times a week by subcutaneous injection for 45 days. Throughout the experiment, there was a slightly elevated base count in phosphorus treated animals. The chylomicron count of control animals peaked at 4 hours, while the 4-hour chylomicron counts of treated animals were markedly reduced until the 12th day. Thereafter, they increased until near normal values were reached by the end of the experiment.

Table 3-3 Oral and Subcutaneous Toxicity of White Phosphorus in Rats

Dose (mg/kg/day)	Total Dose (mg)	Average Survival (days)	Deaths/100 Animal-Days
Oral			
1.6	718	449	0.25
0.8	265	332	0.30
0.4	181	454	0.22
0.2	96	479	0.21
Controls	0	348	0.33
Subcutaneous			
3.2	10	3.2	31.6
1.6	15	0.3	10.7
1.2	13	11	9.1
0.8	112	140	0.72
0.4	136	340	0.30
0.2	89	442	0.23
0.1	53	530	0.19
0.05	31	610	0.17
Controls	0	480	0.24

Source: Fleming et al. (1942).

Lhota and Hannon (1979) observed that rats injected subcutaneously with 0.5, 1.0, or 2.0 mg/kg/day of yellow (white) phosphorus for 30 days or less lost weight. Young adult rats injected with 0.5 mg/kg/day lost less weight than fully mature or young rapidly growing rats. Whatever the age or weight at the beginning of treatment, the period of weight loss was followed by a period of cyclic weight loss and gain with an overall net weight gain. Exposure to 1.0 or 2.0 mg/kg led to a dose-dependent progressive weight loss and eventual death in young rapidly growing rats.

In the only study found evaluating the effects of subchronic exposure to red phosphorous in experimental animals, Aranyi et al. (1988) exposed rats to combustion products of red phosphorus/butyl rubber aerosols at concentrations ranging from 0.3 to 1.2 g/m^3 for 2.25 hours/day, 4 consecutive days/week for 4 and 13 weeks. Exposed rats showed a decreased ability to kill inhaled *Klebsiella*. Pulmonary free cells collected by lavage were decreased. Concentrations of 0.75 g/m^3 or more produced terminal bronchiolar fibrosis in all rats after the 4- and 13-week exposures. The severity of the lesions increased with increasing concentrations and duration of exposure.

3.4.2 Inorganic Phosphorus Compounds

Several studies on the effects of long-term exposure of laboratory animals to phosphine have been identified in the published literature; however, these studies mainly address the health effects associated with the ingestion of phosphine-treated food or feed items. The only other study found which addresses the effects associated with long-term exposure to the inorganic phosphorus compounds addresses the effects of inhaled phosphorus oxychloride. The effects of long-term exposure to phosphorus pentoxide, phosphoric acid, phosphorus pentachloride, phosphorus chloride, and phosphorus sesquisulfide in laboratory animals are unknown.

Mueller (1940) found that rabbits tolerated phosphine concentrations of 7 mg/m^3, 4 hours/day, for 2 months, but died after seven similar exposures to 14 mg/m^3. After repeated exposures to 14 mg/m^3, some of the animals still appeared well, but experienced breathing difficulty and paralysis shortly before death. A concentration of 35 mg/m^3 was fatal after a few hours. Histologic examination of tissues revealed a pronounced hyperemia in all organs, particularly in lungs, liver, kidneys, and brain. Other pathologic changes included heart enlargement, lung edema, and mucous accumulation in trachea and bronchi. The author indicated that the toxic effects may be cumulative.

Several investigators addressed the potential health hazards associated with the consumption of phosphine-fumigated foods. Kadkol and Jayaraj (1968) showed that ingestion of a phosphine-fumigated rice diet by rats for 12 weeks did not modify weight gain or food intake, nor was there a change in hemoglobin levels or histopathology. Determination of liver and kidney weights showed a slight exposure-related increase in male rats. The authors did not indicate the levels of residual phosphine in the treated diet. (McGregor, 1980).

Hackenberg (1972) fed rats for two years a diet treated with high concentrations of phosphine-releasing Phostoxin® tablets, using an equivalent of 10 times the recommended concentration of Phostoxin® The average residual phosphine level in 3 of 16 batches of treated diet was 0.996 mg/kg. Behavior, general appearance, survival, body weight, food consumption, hematology, blood chemistry, urinalysis, and bone smear data, as well as microscopic findings and tumor analysis did not reveal any toxic effects from consumption of the Phostoxin®-treated diet.

A recent study also indicated that long-term ingestion of a phosphine-fumigated feed does not produces adverse health effects in rats. Cabrol Telle et al. (1985) exposed rats to about 0.005 mg/kg (5 ppb) of phosphine in the diet for two years. There were no marked changes in growth, food intake, nitrogen balance, functional behavior, or incidence or type of tumor.

Subchronic exposure of rats to 1.34 mg/m^3 (0.2 ppm) of phosphorus oxychloride affected body weight gain and caused changes in respiration rate and oxygen consumption. Urinary hippuric acid excretion was decreased, indicating a disturbance in the detoxifying function of the liver. After an exposure of four months, the experimental animals exhibited pronounced morphological changes of the respiratory system, characterized by catarrhal desquamative rhinitis, tracheitis, and bronchitis. Other pathological changes were degenerative changes of the brain and mild liver and kidney distrophy. The animals showed signs of enterocolitis. Changes were also noted in calcium, phosphorus, and chlorine metabolism. Changes in bone tissue were indicative of osteoporosis (Roshchin and Molodkina, 1977).

3.5 TERATOGENICITY AND REPRODUCTIVE EFFECTS

3.5.1 Elemental Phosphorus

Starke et al. (1982) reported the effects of exposure to airborne white phosphorus/felt smoke on development and reproduction in rats. Pregnant rats were exposed daily for 15 minutes (starting on day 6 of pregnancy and continuing to day 15) to concentrations of 0, 500, or 1,000 mg/m^3 phosphorus/felt smoke. The results are shown in Table 3-4. Major variations were unilateral anophthalmia, narrow atria, short tongue, brachygnathia, and thin-walled heart. Minor variations were ectopic kidneys, ectopic testicles, and reversed ductus arteriosus. This study suggested the possibility of developmental toxicity from inhalation of white phosphorus/felt smoke.

As part of the same investigation (Starke et al., 1982), male rats were exposed for 15 minutes/day, 5 days/week for 10 weeks and female rats were exposed similarly for 3 weeks to 0, 500, or 1,000 mg/m^3 white phosphorus/felt smoke to evaluate the effect of varying concentrations of phosphorus on the reproductive potential of these animals. Exposure of the females continued through mating, gestation, and lactation. Litters were exposed for up to 21 days of age. There were no gross abnormalities in any of the pups delivered nor significant differences in the litter sizes. The mean body weights of the pups in the high-exposure group were lower at all ages than those in the low-exposure and control groups. The survival, viability, and lactation indices of pups in the highest exposed animals were significantly lower than the other groups. Because the mothers did not resume nursing for 2 to 3 hours after exposure, this difference was attributed to the weakened condition of the mothers exposed to 1,000 mg/m^3.

A high mortality rate in female rats exposed to phosphorus was observed in a one-generation reproduction study conducted by Monsanto (1985). The increased mortality was attributed to difficulty in parturition. Yellow (white) phosphorus was administered by gavage at levels of 0.005, 0.015, or 0.075 mg/kg/day for 80 days prior to and through two gestation periods. Sixteen of the thirty females in the high exposure group died during treatment, 13 of which died during the last 2 days of gestation. The mortality rates were low in the other exposure groups and in males. No other clinical signs of toxicity were observed except for hair loss in the high-exposure group. Histopathological evaluation, including that of bone and liver, did not reveal significant effects of yellow phosphorus in exposed males, females, or pups. A "no-observed-adverse-effect level" (NOAEL) of 0.015 mg/kg/day was established.

3.5.2 Inorganic Phosphorus Compounds

No information was found in the published literature on the teratogenicity of reproductive effects of the inorganic phosphorus compounds.

3.6 Mutagenicity

3.6.1 Elemental Phosphorus

The mutagenicity of phosphorus has been evaluated in microbial, insecticidal, and mammalian test systems. White and red phosphorus were tested for mutagenicity in the Ames test. White phosphorus in water ("phossy water") at a concentration of 100 µL/plate produced no mutagenic activity in *Salmonella typhimurium* strains TA100, TA1535, TA98, TA1537, and TA1538 either in the presence or absence of metabolic activation (Ellis et al., 1978). A

Table 3-4 ***White Phosphorus/Felt Smoke Induced Visceral and Skeletal Variations and Abnormalities***

Variations and Abnormalities	Air Control	Low Dose 500 mg/m^3	High Dose 1,000 mg/m^3
Visceral			
Prominent renal pelvis	4	3	5
Ectopic kidney(s)	1	4	
Narrow atrium	1	1	1
Thin-walled heart			1
Reversed ductus arterious			9
Underdeveloped testicles	3	1	
Ectopic testicles			3
Hemorrhagic eyes		1	
Anophthalmia unilateral*			
Short tongue*	1	1	
Brachygnathia*			1
Skeletal			
Fourteenth rib extra (rudimentary)	16	39	25
Cleft sternebrai	2	0	2
Dumbbell-shaped sternebrae	16	7	6
General hypoplasia of the sternebrae	35	46	38
Dumbbell-shaped vertebrae-thoracic	9	11	2
Hypoplasia of xyphoid process	2	11	19

*Abnormalities.

Source: Starke et al. (1982).

concentration of 10 µL/plate was cytotoxic to all five strains and 1.0 µL/plate was cytotoxic to strain TA1535. The same *Salmonella* strains exposed to red phosphorus at levels up to 10 mg/plate with or without metabolic activation did not display any mutagenic activity (McGregor, 1980).

Escherichia coli was used in tests for lethality due to DNA damage. No toxic effects were found at exposure levels of 10 mg/plate of red phosphorus. Negative results were obtained in mitotic recombination tests in the yeast *Saccharomyces cerevisiae* exposed to red phosphorus (McGregor, 1980).

White phosphorus/felt smoke condensate was tested for its ability to induce mutations in fruit flies. Exposure to concentrations of 0.01 to 10 percent in food for 42 hours did not induce sex-linked recessive mutations on the X-chromosome of *Drosophila melanogaster.* Nevertheless, an exposure-dependent increase in toxicity was observed; concentrations of 10 percent produced 100 percent mortality within 72 hours, 1 percent concentration produced 11 percent mortality, 0.1 percent concentration produced 2 percent mortality, and 0.01 percent caused no mortality (Brown et al., 1980).

Starke et al. , (1982) conducted studies to determine if white phosphorus/-felt smoke produced dominant lethal mutations in rats. Fertile male rats were exposed for 15 minutes/day, 5 days/ week for 10 weeks to smoke concentrations of 0, 500, or 1,000 mg/m^3. The rats were mated during exposure to the highest concentration. For the most part, there were no significant differences between controls and animals exposed to smoke. More resorptions were observed in females mated with males exposed to the lowest concentration than in females mated wtih control or high-exposed animals. Since this parameter was not concentration-dependent, it was not significantly related to exposure. Therefore, white phosphorus smoke at concentrations of 500 or 1,000 mg/m^3 did not induce dominant mutations in rats.

3.6.2 Inorganic Phosphorus Compounds

Only limited information was found in the published literature on the mutagenic activity of the inorganic phosphorus compounds. Using a modified Ames test, phosphorus trichloride was found not to be mutagenic in *Salmonella typhimurium* (McMahon et al., 1979). In a study by Roshchin and Molodkina (1977) exposure to 1.34 mg/m^3 (0.2 ppm) phosphorus oxychloride produced increased numbers of chromosomal aberrations and cytostatic activity in rats. However, at a lower exposure level (0.48 mg/m3; 0.08 ppm), the chromosomal aberrations did not differ significantly from those observed in controls.

3.7 Carcinogenicity

3.7.1 Elemental Phosphorus

No studies were found specifically addressing the carcinogenic potential of the elemental phosphorus compounds in animals. However, neoplastic lesions were not observed in rats administered white phosphorus orally (0.2 to 1.6 mg/kg/day) or subcutaneously (0.05 to 3.5 mg/kg/day) or in guinea pigs administered white phosphorus subcutaneously (0.05 to 0.4 mg/kg/day) over their entire lifetime (Fleming et al., 1942).

3.7.2 Inorganic Phosphorus Compounds

The only studies on the carcinogenic potential of the inorganic phosphorus compounds found in the published literature were two studies on the oral administration of phosphine via feed. Phosphine was found not to be carcinogenic in rats under the conditions of the studies. Refer to Section 3.4.2 for details of the studies.

3.8 Effects on humans

3.8.1 Elemental Phosphorus

No information was found in the published literature regarding the effects of inhalation or ingestion of red phosphorus and only limited information on the effects of inhalation of white phosphorus in humans. Exposing 108 men to 87 to 1,770 mg/m^3 of white phosphorus smoke (length of exposure not given) caused throat irritation and coughing. This experiment led Cullumbine (1944, as reported in Wasti et al., 1978) to establish 700 mg/m^3 as a minimum harassing exposure level in working men and 1,000 mg/m^3 in resting men.

White and Armstrong (1935) carried out a very limited experiment in which male human subjects were exposed to white phosphorus smoke in a chamber. The concentrations ranged from 185 mg/m^3 to 592 mg/m^3 and the exposure times ranged from 5 to 15 minutes. Irritation of the throat, especially while talking was the most common effect. Coughing was frequently reported, in addition to congestion, tightness in the chest, and nasal discharge. The authors suggested that exposure to 514 mg/m^3 approached the maximum concentration at which humans may be exposed for 15 minutes without encountering serious effects.

Walker et al. (1947) reported the effects of inhalation of white phosphorus smoke on four women exposed during an accident in a plant processing white phosphorus munitions. Other components in the smoke, in addition to those produced by the burning of white phosphorus, may have been present, although no information on these components was available. The women were exposed for 15 to 20 minutes in a closed room that rapidly filled with dense smoke. All of the women developed respiratory symptoms: choking sensations, feelings of suffocation, sense of tightness in the chest, coughing, tenacious sputum production, rales, sore throat, and hoarseness. The women who became hoarse also showed erythema and edema of the larynx and vocal cords. Injury apparently extended well into the bronchi since these patients expectorated bronchial casts containing necrotic superficial layers of bronchial epithelium. Chest X-rays revealed patchy areas of infiltration that cleared within 5 to 10 days. Coughing and expectoration subsided within several days but hoarseness persisted long after other evidence of respiratory tract irritation disappeared.

Five males were exposed to white phosphorus vapors composed of 35 mg/m^3 of phosphorus and 22 mg/m^3 of phosphorus pentoxide at an industrial site (Aizenshtadt et al., 1971). They were exposed for 2 to 6 hours at 7-hour intervals (total exposure time not given) while cleaning a tank of "Cottrell Milk" (an aqueous suspension of phosphorite, quartzite, and coke dust) by hand without protective equipment. Within 6 to 20 hours, all developed symptoms of malaise, weakness, dry cough, and slight hyperthermia. The next day, dyspnea, cough with thick discharge, high fever (5/5), headache, vertigo, chest pains(2/5), rhinitis, and epistaxis (1/5) were noted. Further examination revealed hyperemia of the face and pharynx (2/5), multiple diffuse rales (5/5), bubbling rales (3/5), tender liver upon palpation (4/5), and hepatomegaly (1/5). Laboratory tests showed evidence of leukocytosis with relative lymphocytopenia, increased erythrocyte sedimentation rate, normal bilirubin and residual nitrogen, reduced cholesterol, and dysproteinemia. Erythrocyte acetylcholinesterase was reduced by 17 percent and plasma acetylcholinesterase by 35 percent.

According to Sollmann (1957) the estimated minimal lethal dose of elemental (yellow or white) phosphorus to humans is 50 mg (0.7 mg/kg), most often 100 mg (1.4 mg/kg), but 15 mg (0.2 mg/kg) may cause serious toxic effects. These doses were estimated from patients who did not receive medical treatment after intoxication. Because treatment changes both the prognosis and the lethality of a particular dose of elemental phosphorus (Polson et al., 1983), humans have recovered from larger doses. Information on the acute oral effects of phosphorus has come primarily from analyzing cases of accidental or intentional ingestion of yellow phosphorus contained in preparations such as pesticide paste, fireworks, and match tips. The major targets of elemental phosphorus poisoning are the gastrointestinal tract, brain, liver, kidney, and cardiovascular system (McCarron et al., 1981).

The classical description of acute oral phosphorus poisoning divides the symptoms into three stages: initial (stage 1), latent (stage 2), and systemic (stage 3) (McCarron et al., 1981; Hayes, 1982). Stage 1 symptoms, attributed to local irritation of the gastrointestinal tract, include nausea, vomiting, abdominal pain, thirst, garlic breath, hematemesis, and slight diarrhea. Stage 2 symptoms are described as a period of well being, during which there is an abatement of symptoms. Stage 3 symptoms include the reappearance of more severe nausea, vomiting, and abdominal pain, and the appearance of hepatomegaly, jaundice, CNS injury, hemorrhage, oliguria, peripheral vascular collapse, coma, and death (Cameron and Rentoul, 1963; McCarron et al., 1981; Hayes, 1982). Death in the third stage usually results from liver failure, but also may be due to cardiovascular collapse or kidney failure (Diaz-Rivera et al., 1950). The length of each stage is variable: stage 1 lasts from 24 to 48 hours, stage 2 from a few hours to as long as 10 days, and stage 3 may begin within the first 4 to 5 days and last for a variable length of time depending upon the degree of intoxication (Cameron and Rentoul, 1963; Hayes, 1982). Table 3-5summarizes the gross symptoms in several case studies of patients who died or recovered after ingesting elemental phosphorus.

The relationship between dose of phosphorus and mortality rates in the 56 cases studied by Diaz-Rivera et al. (1950) is presented in Table 3-6. For the most part, doses of 1.57 g or more were fatal with only 2 out of 21 patients surviving ingestion of 1.57 g of phosphorus. Doses of 0.78 g or less were associated with a high survival rate, with 27 of 33 patients surviving.

Hepatomegaly is one of the characteristic symptoms of phosphorus poisoning. Of the 56 cases reported by Diaz-Rivera et al. (1950), 41 developed hepatomegaly. Impending death was associated with patients who developed this symptom within the first 48 hours (52 percent mortality), whereas all of those who developed the symptom after 48 hours survived. The livers of patients who ingested phosphorus were yellow, with areas of necrosis. They also had slight to moderate leukocytic infiltration, fibrosis, and extensive fatty degeneration with vacuolization. The pathological changes may cause loss of the lobular structure of the liver (Dwyer and Helwig, 1925; LaDue et al., 1944; Wechsler and Wechsler, 1951; Cameron and Rentoul, 1963).

Myocardial damage induced by acute phosphorus poisoning consisted of abnormalities in the electrocardiograms (EKG), prolongation of QT interval, ST and T wave changes, abnormalities in rhythm, and low voltage of QRS complexes (Diaz-Rivera et al., 1961). Pietras et al. , (1968) observed that EKG abnormalities were reversible. Microscopic examination of the heart showed fatty degeneration, interstitial edema without cellular infiltrates, and cells with vacuolated cytoplasm (Diaz-Rivera et al., 1961; Cameron and Rentoul, 1963). Wechsler and Wechsler (1951) also found evidence of myocardial necrosis.

Table 3-5 Gross Symptoms of Patients Who Ingested Elemental Phosphorus

Age	Sex	Approximate Dose of P (g)	Vomiting and/or Hematemesis	Abdominal Pain	CNS Toxicity	Shock or Low BP	Liver Toxicity	Renal Toxicity	Cardiac Damage	Other Effects	Time of Death or Recovery	References
Died												
19 yr 65 yr	F	0.10[a]	-	+	+	+	-	+	-	-	52 hr	Ladue et al., 1944
19 yr	F	0.156	+	+	+	-	+	+	-	-	3½ days	Hann and Veale, 1910
31 yr[b]	F	0.19	+	+	+	+	+	+	-	-	8 days	Diaz-Rivera et al., 1950
19 yr	F	0.23	+	-	+	+	-	-	+	-	8 hr	Rubitsky and Myerson, 1949
69 yr	F	0.70	+	-	+	+	+	+	+	-	5 days	McCarron et al., 1981
16 yr	F	1.10	-	-	-	+	-	+	+	Vascular Damage	22 hr	Talley et al., 1972
43 yr	M	1.134	+	+	+	-	+	+	+	-	Day 5	Cameron and Rentoul, 1963
28 yr	M	1.57	+	+	+	-	+	-	+	Hyperphosphatemia	Day 5	Diaz-Rivera et al., 1950
Recovered												
10 mos	F	0.12	-	-	+	+	+	-	-	-	Day 5	McCarron et al., 1981
23 yr	F	0.13	+	+	+	-	+	+	-	Leukocytosis	Day 29	McCarron et al., 1981
71 yr	F	0.5	+	-	+	+	+	-	-	Anemia	Day 42	Caley and Kellock, 1955
22 yr	M	0.78	-	+	+	-	+	+	+	Hyperphosphatemia	Day 30	Diaz-Rivera et al., 1950
30 yr	M	0.78[a]	+	+	+	+	+	+	+	Anemia	Day 30	Pietras et al., 1968
61 yr	M	1.20[a]	+	+	-	-	+	+	-	-	Day 56	LaDue et al., 1944
24 yr	M	1.57	+	+	+	-	+	+	-	-	Day 21	Diaz-Rivera et al., 1950

[a]Dose estimated by McCarron et al., (1981).
[b]Patient refused medical treatment.

Table 3-6 Oral Toxicity of Elemental Phophorus in Humans

Dose (g)	No. Cases	Mortality (%)
6.30	1	100
4.62	1	100
1.57	21	90
0.78	18	16.3
0.39	14	14.3
0.19*	1	100

*Patient refused medical treatment.

Source: Diaz-Rivera et al., (1950).

The prevalence of abnormalities in EKG's in relation to the dose of phosphorus was 33 percent of 6 patients ingesting less than 0.38 g, 45 percent of 11 patients ingesting 0.39 to 0.74 g, 56 percent of 23 patients ingesting 0.75 to 1.49 g, and 67 percent of 10 patients ingesting 1.57 g or more (Diaz-Rivera et al., 1961). Myocardial damage was also observed in a 16-year-old female who ingested 1.11 g of phosphorus and died within 33 hours (Talley et al., 1972), in a 30-year-old male who ingested approximately 1.18 g and recovered (Pietras et al., 1968), and in a 21-year-old male who ingested 1.5 g and recovered (Newburger et al., 1948).

Cushman and Alexander (1966) reported a case of acute phosphorus poisoning with hypocalcemia and hypophosphatemia. Increased urinary excretion of calcium and phosphate in relation to the measured oral intake suggested a disturbance of the proximal tubular function. Neuropathology characterized by lipid accumulation within neurons may occur in humans within hours of yellow phosphorus ingestion (O'Donoghue, 1985).

Because white phosphorus ignites spontaneously in air, it causes severe burns if it comes in contact with the skin. Phosphorus burns have been sustained in industrial accidents and in the battlefield (Walker et al., 1947; Summerlin et al., 1967; Berkowitz et al., 1981). Walker et al. (1947) evaluated 27 casualties resulting from four accidents in plants processing white phosphorus munitions at Edgewood Arsenal, MD. Of the 27 casualties, 9 with third degree burns over 90 percent or more of the body surface died almost immediately, 3 with third degree burns over 35 to 65 percent of the body surface died within 19 hours, and 15 with third degree burns over up to 19 percent and different amounts of second degree burns survived. Both second and third degree burns were similar to thermal burns. Systemic effects due to white phosphorus burns were not noted; liver damage, as indicated by serum bilirubin levels and bromosulfalein retention studies, was not observed; blood sugar and serum calcium were normal; phosphorus excretion was reduced rather than elevated.

During a 17-year period (1969 through 1985), 49 patients were admitted to the U. S. Army Institute of Surgical Research for chemical burns resulting from exposure to white phosphorus (Mozingo et al., 1988). Most of the injuries occurred in Vietnam. Systemic toxicity was noted in two cases resulting from cutaneous absorption of copper sulfate used to neutralize white phosphorus burns. Compared with other chemical burns, white phosphorus had more associated injuries and required longer hospital stays.

Summerlin et al. (1967) described three cases of white phosphorus burns accompanied by massive hemolysis. Case 1 was a 25-year-old male who had sustained burns over 29 percent of his body surface; case 2, a 46-year-old male who had burns over 12.5 percent of his body surface; and case 3, a 24-year-old male who had burns over 7.5 percent of his body surface. In each case hemoglobinemia, hemoglobinuria, hematuria, bilirubinemia, mild (case 2 and 3) to severe (case 1) hypocalcemia, oliguria, and renal failure were observed. Case 2 showed evidence of hyperphosphatemia. Case 1 also showed evidence of myocardial ischemia, which disappeared on the fifth hospital day. Massive hemolysis could not definitely be attributed to systemic effects of white phosphorus burns.

Chronic exposure of humans to white phosphorus causes a characteristic lesion, necrosis of the jaw, sometimes referred to as phosphorus necrosis or "phossy jaw" (Miles, 1972). Because white phosphorus was used in the lucifer match industry, numerous cases of this occupational disease appeared during the 19th and the early part of the 20th century. It was the phosphorus-related necrosis of the jaw which lead to international legislation prohibiting the manufacture, sale, and transport of phosphorus matches in several European countries in 1906. Phosphorus necrosis of the jaw was also associated with the manufacture of fireworks and the production of phosphorus (Ward, 1926). Although Ward (1926) and Oliver (1938) considered phosphorus necrosis due to industrial sources as a disease of the past, subsequent cases were reported by Kennon and Hallam (1944), Heimann (1946), and Hughes et al. (1962). A very recent case, although not of industrial origin, was described by Jakhi et al. (1983).

In a survey of 15 matchmaking factories in the United States from 1908 to 1909, 65 percent (2,334) of 3,591 workers were exposed to phosphorus. More than 150 cases (four were fatal) of phosphorus necrosis were discovered; the majority were women and children less than 16 years old. In three fireworks factories employing 71 workers, 14 cases (two fatal) were discovered (Ward, 1926).

According to Sollmann (1957), the incidence of phosphorus necrosis was less than 5 percent of those exposed to phosphorus. While the disease affected relatively few people, it was the most disfiguring of all occupational diseases in the 19th and early 20th century (Ward, 1926). The estimated mortality rate from phosphorus necrosis was 20 percent (Hunter, 1969). The clinical symptoms usually begin with a tooth ache, more often in the lower jaw, followed by suppurative ulceration of the gums around a diseased tooth or a root abscess which does not heal after extraction, with suppurating fistula, and progressive necrosis of the maxilla (Sollmann, 1957). The progress of the disease, in earlier cases, resulted in the loss of large portions of the jawbone during the formation of large sequestrae; consequently, the facial structures became grossly disfigured. Sequestrae are pieces of dead bone that become separated from healthy bone during the process of necrosis. The more recent cases of phosphorus necrosis were very mild compared to the disease in the last century (Hughes et al., 1962).

The cause of phosphorus necrosis is still questionable; phosphorus itself (Oliver, 1938; Hughes et al., 1962), combustion products (fumes, vapors, or smoke) made up of oxides of phosphorus (Hughes et al., 1962; Miles, 1972), phosphoric acid, and phosphorous acid (Oliver, 1938) each have been implicated as the causative agent. Some individuals are more susceptible to phosphorus necrosis than others, particularly those with poor oral hygiene, caries, a tooth extracted during exposure to phosphorus, or other dental diseases (Ward, 1926; Kennon and Hallam, 1944; Miles, 1972). In recent

years, strict medical and dental surveillance, early diagnosis, and treatment have caused reductions in both the incidence and the severity of this occupational disease.

Fragility of long bones which led to bone fractures in lucifer match workers under relatively so-called "trifling" circumstances suggest that phosphorus may act by a systemic route (Oliver, 1938). Also, the delayed onset of phosphorus necrosis after workers are removed from the source of exposure, is suggestive of a systemic action (Hughes et al., 1962).

The airborne levels of phosphorus were not known in the case histories of phosphorus necrosis presented in the literature; therefore, the disease process could not be correlated with concentrations of phosphorus in the air. The duration of exposure prior to onset of necrosis of the jaw was known in most cases but varied considerably. Ward (1926) observed that exposure ranged from less than 3 months to 12 years prior to the onset of the disease. In two fatal cases, one was exposed for 6 years and the other for 2 years. The duration of the illness ranged from about 5 months, in one worker employed for 10 years, to 6 years in another worker employed for 12 years. In the 11 cases reported by Legge (1920) the duration of exposure ranged from 5 months to 23 years. The duration of the illness ranged from 2 months to 5 years. The duration of exposure in the cases described by Kennon and Hallam (1944) ranged from 13 months to 10 years. In three cases the disease did not reveal itself until after the worker had left the phosphorus process.

Hughes et al. (1962) studied 48 healthy men working in a phosphorus plant to evaluate the systemic effects of phosphorus exposure. The duration of exposure ranged from 1 to 17 years. The 28 control subjects were not perfectly age matched. Statistical differences were not found in the hematological evaluation or in plasma levels of inorganic phosphorus, alkaline phosphatase, calcium, and magnesium; radiographs did not reveal differences in density of bones.

Evidence of functional liver damage and possible bone abnormalities are reported in a more recent Russian study of 337 workers engaged in the production of yellow phosphorus (Ozerova et al., 1971, as reported in Idler et al., 1981). Exposure ranged from 3 to 5 years at maximal permissible air concentrations and occasional elevated levels of phosphorus. The maximum allowable level in the Soviet Union is 0.03 mg/m^3 (International Labour Office, 1980).

No information was found in the published literature on the carcinogenic potential of elemental phosphorus. Therefore, according to the U. S. Environmental Protection Agency's proposed guidelines for carcinogenicity, elemental phosphorus is classified under Group D, not classifiable as to human carcinogenicity.

3.8.2 Inorganic Phosphorus Compounds

Harger and Spolyar (1958) reported that 59 cases of phosphine poisoning, including 26 deaths, have been recorded between 1900 and 1958. Phosphine poisonings have been reported in people exposed to releases from ferrous alloys stored on freight boats, in occupants of apartments near fumigated grain elevators, in welders breathing acetylene from portable generators, and in submarine crews carrying sodium phosphide for the production of warning lights formines (Harger and Spolyar, 1958).

The inhalation of phosphine is usually an accidental occurrence and its disagreeable odor is quickly apparent. However, the odor threshold of 2.0 to 3.0 mg/m^3 (Sax, 1986) does not necessarily provide an adequate warning of

the presence of dangerous amounts (Heimann, 1983). The acute hazard levels of phosphine in humans are summarized in Table 3-7.

Wilson et al. (1980) describe the acute phosphine poisoning of two children and 29 of 30 crew members caused by the leakage of phosphine fumigant from an inadequately sealed hold aboard a grain freighter. One child died. The prevailing symptoms which occurred about four days after fumigation were headache, fatigue, nausea, vomiting, cough, and shortness of breath. Others included jaundice, paresthesias, ataxia, intention tremor, and diplopia. Postmortem examination of the child revealed focal myocardial infiltration with necrosis, pulmonary edema, and widespread small-vessel injury. Indications of myocardial injury were also noted in the surviving child. Urinalysis and liver function tests of the crew members showed the following abnormalities; occult blood in the urinary tract, bilirubinuria, and elevated serum transaminase and lactic dehydrogenase levels. Abnormal clinical and laboratory findings in the affected individuals returned to normal six days after hospitalization. The severity and duration of the illness was positively correlated with having lived or worked in areas of the ship with high phosphine concentrations. In some areas of the ship the concentration of phosphine greatly exceeded the TLV value of 0.42 mg/m^3 or the odor threshold of 2.0 to 4.0 mg/m^3. Phosphine levels in representative areas of the ship were: 28.0 to 42.0 mg/m^3 in a void space on the main deck, 11.0 to 14.0 mg/m^3 near a hatch, and 0.7 mg/m^3 in some living quarters.

Jones et al. (1964) reported that most of 67 grain fumigators, intermittently exposed to phosphine during fumigation with aluminum phosphide and shipping of bulk wheat, exhibited symptoms of phosphine poisoning in varying degrees. The symptoms fell into three main categories: gastrointestinal (diarrhea, nausea, epigastric pain, and vomiting), cardiac/respiratory (tightness of chest, breathlessness, chest pain, palpitations, and severe retrosternal pain), and central nervous system (headache, dizziness, and staggering gait). In half of those affected, the symptoms appeared immediately, while others experienced a delay of several hours to two days. There was no evidence of chronic effects and no tendency to develop adaption. Concentrations of 0.4 mg/m^3 or less sometimes produced headache but no other symptoms during intermittent exposures over several months. The measured phosphine concentrations in the breathing zone of workers ranged from 0 to 49.0 mg/m^3, but averaged below 14.0 mg/m^3 in most cases. Employees in shipping areas experienced the highest measured concentrations of phosphine, with exposure duration greater than 8 hours/day for several days.

The pattern of illness in the two studies discussed above resembled that found in crew members of a British submarine which carried sodium phosphide for the production of mine warning lights (Glass, 1957). The symptoms included greyish pallor, dizziness, shortness of breath, vomiting, tightness of the chest and palpitations, spasmodic attacks of dyspnea, blurred vision, and collapse. Liver function tests were normal. The symptoms were considered mild and were attributed to short exposure times and low phosphine levels (phosphine levels on the submarine were not determined).

Misra et al. (1988a) evaluated the health effects of occupational exposure to phosphine resulting from grain fumigation in India. Twenty-two workers (mean age 48 years, mean duration of exposure 11.1 years) were examined. The phosphine concentration in the work environment ranged from 0.23 to 2.81 mg/m^3. Exposure to the chemical caused mild to moderate respiratory, neurological, and gastrointestinal symptoms which were transient. They

Table 3-7 Acute Hazard Levels of Phosphine in Humans

Concentration	Exposure Period	Data
1.4 mg/m^3	7 hr 1x/week	Maximum safe exposure
35 mg/m^3	1 hr 1x/week	Maximum safe exposure
70 mg/m^3	0.1 hr 1x/week	Maximum safe exposure
9.8 mg/m^3	Several hr	Maximum tolerated concentration
280 mg/m^3	--	Immediately dangerous to life and health (IDLH)
2,800 mg/m^3	Few min	Lethal

Source: Sax (1986).

included cough, dyspnea, tightness of the chest, headache, giddiness, numbness, lethargy, anorexia, and epigastric pain.

Phosphine may be released during the generation of acetylene from impure calcium carbide (Sittig, 1985). Harger and Spolyar (1958) described the death of an acetylene operator from pulmonary edema. The probable cause of death was exposure to phosphine at levels of about 11.0 mg/m^3 for 1 to 2 hours/day for 5 to 6 weeks.

A case of human oral poisoning by phosphine, with suicidal intent, has been reported by Zipf et al. (1967). It involved a 25-year-old man who swallowed six aluminum phosphide tablets dissolved in water. If all the material had been retained, about 6,000 mg of phosphine could have been released. The immediate effects were severe substernal and upper abdominal pain, intolerable burning sensation of the whole body, severe vomiting, and loss of consciousness. On the day after ingestion there was hematuria, leukocyturia, and proteinuria. From the fourth day on, uremia and pulmonary edema were observed. Other major complications included damage to the heart, brain, and liver (scleral icterus and hepatomegaly).

Another study by Misra et al. (1988b) examined eight cases of phosphine poisoning in India following ingestion of aluminum phosphide tablets with suicidal intent. The mean age of the patients was 23 years. Six patients died shortly after ingestion of aluminum phosphide with peripheral vascular failure as the major course of death. Phosphine poisoning was characterized by vomiting, restrosternal and abdominal pain, peripheral vascular failure, cardiac arrhythmia, and altered consciousness. One patient developed jaundice and another developed acute renal failure. Postmortem examination of two patients revealed pulmonary edema; desquamation of the lining of bronchioles; gastrointestinal mucosal congestion; petechial hemorrhages of the liver and brain; vacuolar degeneration of hepatocytes; dilatation and engorgement of hepatic central veins, sinusoids, and areas showing nuclear fragmentation.

The possibility of chronic phosphine poisoning as a result of extended exposure has been mentioned by some authorities (Beliles, 1981; Torkelson et al., 1966), but no such cases have been documented in the available literature.

Phosphoric acid may cause irritation of the upper respiratory tract, eyes, and skin; it also may produce skin burns and dermatitis (Sittig, 1985). At a concentration of 1.0 mg/m^3, the Federal standard, phosphoric acid mist is irritating to unacclimated workers but is easily tolerated by acclimated workers

(Sittig, 1985). The World Health Organization (1986) indicates that about 0.5 mg/m^3 of phosphoric acid is irritating to unacclimatized individuals.

A single drop of orthophosphoric acid (0.16 M, buffered to pH 2.5) caused a moderate brief stinging but no injury in the human eye. The same solution adjusted to a pH of 3.4 elicited no discomfort (Grant, 1974).

In a human experiment, 50 percent phosphoric acid was applied to the gingival tissue and teeth of 26 orthodontic patients (ages 12 to 16 years). The acid was in contact with the gingiva and teeth for 90 seconds and then rinsed off. After a period ranging from one to seven days, examination of the treated tissues did not show any demonstrable effect resulting from contact with phosphoric acid (Forsberg, 1982).

In a related study, Johnson et al. (1970) tested the effects of phosphoric acid, a component of silica cement for dental fillings, on dental pulp. Sound teeth, exposed to 6 M phosphoric acid buffered to a pH of 3.5 or 5.0 or to distilled water, revealed the same extent of inflammatory changes in dental pulp. Exposure to the acids, however, produced an increasing number of inflammatory responses as the thickness of dentine protecting the pulp decreased.

A case report indicates that phosphoric acid ingestion may produce metabolic abnormalities in addition to local caustic effects (Caravati, 1987). A 64-year-old man intentionally ingested 3 to 4 ounces of a porcelain and metal cleaner containing phosphoric acid. He developed hyperphosphatemia, hypocalcemia, and systemic metabolic acidosis. The caustic effects were mild and consisted of burning sensation in the throat and mild mucosal burns of the gastrointestinal tract.

Phosphorus trichloride in liquid as well as vapor form is highly irritating to the skin and mucous membranes, respiratory tract, and eyes. Severe acid burns can occur (Grant, 1974; Beliles, 1981).

Occupational exposure to phosphorus trichloride during its manufacture resulted in acute and subacute adverse health effects in workers who had been exposed to the chemical from 1951 to 1952 (Sassi, 1953). Under normal working conditions, workroom levels were 10 to 20 mg/m^3 but reached levels as high as 80 to 150 mg/m^3 at times when the plant was out of order. The acute effects, beginning after 2 to 6 hours of exposure, were characterized by a burning sensation in the eyes and throat, photophobia, feeling of chest oppression, dry cough with mucous membrane irritation, and slight bronchitis. The symptoms disappeared after 3 to 6 days. After exposure for 1 to 8 weeks, the workers developed slight pharyngeal irritation, coughing, catarrh, nocturnal dyspnea, and pronounced bronchial asthma. The symptoms lasted for 10 to 15 days, and had a tendency to recur and develop into chronic asthmatic bronchitis with emphysema. Slight rises in temperature accompanied by moderate leukocytosis with neutrophilia were frequently found. Chronic exposure for 1 to 2 years produced pulmonary emphysema.

Wason et al. (1984) studied 17 patients who were exposed to phosphorus trichloride spilled in a railroad accident. Cleanup attempts with water led to the release of phosphorus trichloride, phosphoric acid, hydrochloric acid, and phosphorus oxides. At the time of the accident the patients experienced the following symptoms: burning and watery eyes, blurred vision, skin and throat irritation, cough, shortness of breath, and headache. The study could not distinguish the effects of exposure to phosphorus trichloride from the additional irritating reaction products. Screening tests of liver function showed a transient elevation of lactic dehydrogenase in six patients. Pulmonary function tests revealed statistically significant decreases in vital capacity, maximal breathing capacity, forced expiratory volume in one second, and

maximal expiratory flow rate at 25 percent vital capacity in those closest to the accident site. The pulmonary effects were directly correlated with the distance from the accident and duration of exposure. Follow-up tests of seven patients one month later showed improved pulmonary function.

Because of its fuming and deliquescent properties, phosphorus pentachloride is very irritating and corrosive to the skin, eyes, and all mucous membranes, including the lungs (Boenig et al., 1982; Beliles, 1981). The chemical can cause serious skin burns by reacting with moisture with the liberation of heat and formation of hydrochloric and phosphoric acids (Boenig et al., 1982).

Eleven workers accidentally inhaled a gaseous mixture of hydrogen chloride, phosphorus pentachloride, phosphorus oxychloride, oxalyl chloride, and oxalic acid as a result of an explosion in a factory where the chemicals had been manufactured (Rosenthal et al., 1978). Mucosal irritation was reported during the time period required for escape from the enclosed area (1.5 to 2 minutes). The major symptoms were hoarseness, wheezing, cough, and shortness of breath. Evidence of obstruction of the airways consisted of mild interstitial and alveolar edema, diffusion defects, and hypoxemia. A few patients had moderately severe conjunctivitis. Leukocytosis was found in four patients, slightly elevated lactic dehydrogenase levels in three, traces of albumin in urine in one, and erythrocytes in the urine in two others. In most cases, the pulmonary disorders cleared within a few days. In one most severely affected patient, abnormal pulmonary function persisted for two years. Each of the components of the gaseous mixture inhaled (4/5 compounds contained chlorine) is irritating to the mucous membranes and may produce respiratory effects; thus, the toxic effects could not be attributed simply to the two phosphorus compounds.

One report indicates that inhalation of phosphorus pentachloride may cause damage to the kidneys (Von Oettinger, 1958). The compound reportedly produced acute nephritis with oliguria (no details of exposure conditions were provided).

Roshchin and Molodkina (1977) found that the threshold limit for the irritating effects of phosphorus pentachloride in humans and laboratory animals are similar, namely about 10.0 mg/m^3. Based on these findings, they suggested a highest permissible concentration in the work place of 0.2 mg/m^3, which is identical to that proposed for phosphorus trichloride.

Phosphorus oxychloride presents similar hazards as phosphorus trichloride and phosphorus pentachloride. The vapors of this readily volatilizing chemical are very irritating to the eyes, skin, and mucous membranes. Severe burns result from direct contact with the liquid. Inhalation can cause pulmonary edema (Boenig et al., 1982).

A survey conducted by NIOSH at a manufacturing plant indicates that workers exposed to phosphorus trichloride and phosphorus oxychloride may experience intermittent respiratory distress (wheezing, chest tightness, and breathlessness). In a follow-up study covering a two-year period, half of the exposed workers of the original study reported a higher incidence of intermittent respiratory distress, but there was no significant impairment of pulmonary function when compared with unexposed individuals (Moody, 1981).

McLaughlin (1946) reported two cases of slow healing burns of the cornea in humans produced by exposure to phosphorus oxychloride. As with exposure to phosphorus trichloride and pentachloride, Roshchin and Molodkina (1977) found that the threshold for the irritant effects of phosphorus

oxychloride are similar in humans and rats. However, phosphorus oxychloride is more irritating, with a threshold exposure concentration of 1 mg/m^3.

The dust or fume of phosphorus sesquisulfide may be irritating to the eyes, respiratory tract, and skin (Beliles, 1981). Several cases of allergic contact dermatitis caused by phosphorus sesquisulfide contained in safety matches have been reported in the literature (Burgess, 1951; Chiarenza and Gallone, 1981; Steele and Ive, 1982; White and Rycroft, 1983; Burge and Powell, 1983; Ayala et al., 1987; Pena Payero et al., 1985). Burgess (1951) described primary dermatitis of the face and area around the eyes in two women due to contact with matches or hypersensitivity to fumes of match tips containing phosphorus sesquisulfide. Daily lighting of matches resulted in recurring episodes of edematous dermatitis over a period of several years. In one case, the episodes were accompanied by prostration, vertigo, loss of appetite, nausea, and vomiting. In both cases, a marked loosening of the teeth was observed. The author suggested that the dental changes are similar to those seen in individuals exposed to elemental phosphorus. Both local and systemic symptoms disappeared on discontinuing the use of matches.

Burge and Powell (1983) described a patient with dermatitis, traced to matches, who developed both immediate and delayed hypersensitivity reactions to phosphorus sesquisulfide. Symptoms included generalized pruritus, hand eczema, conjunctivitis, and eyelid swelling. The skin lesions cleared when the patients avoided matches.

Recurrent facial eczema (extending over a period of 9 months to 5 years) in three women exposed to phosphorus sesquisulfide matches is described by Steele and Ive (1982). Two of the patients were smokers and match users, the third was a nonsmoker but exposed to the allergen in her work environment.

An allergic eczematous reaction and immediate hypersensitivity to phosphorus sesquisulfide matches occurred in a 34-year-old male and affected the face, thigh, penis, and fingers. Facial irritation and wheezing episodes were sometimes noticed after periods of about 1 hour when the patient was in areas where others had been smoking (White and Rycroft, 1983).

Intense itching with scaly patches in areas on leg and chest where matches come in contact with skin were described by Chiarenza and Gallone (1981) in a patient who carried matches in his pockets over an extended period of time. Lymphomatoid contact dermatitis (characterized by infiltrated plaque-like lesions with some similarities to lymphoma or mycosis fungoides) resulting from exposure to phosphorus sesquisulfide as an allergen is reported by Ayala et al. (1987). A 62-year-old farmer had a 2-year history of recurring pruritic eruptions of the face and plaque-like lesions on both outer thighs. The condition was attributed to matches (containing phosphorus sesquisulfide) in trouser pockets and use of fertilizers and fungicides, probably containing phosphorus as a component.

Pena Payero et al. (1985) reported a case of eczematous dermatitis of the thighs in a 32-year-old male from contact with matches in trouser pockets. Also present were scaly erythematous lesions on the eyelids and back of the hands. A patch test with 0.5 percent phosphorus sesquisulfide produced an immediate severe urticarial response and an eczematous reaction at 48 hours which lasted for several days. The patient noted an intense taste of matches several minutes after the patch test was applied.

No information was found in the published literature on the carcinogenic potential of the inorganic phosphorus compounds (phosphine, phosphoric acid, phosphorus trichloride, phosphorus pentachloride, phosphorus

oxychloride, and phosphorus sesquisulfide). Therefore, these compounds are classified as Group D carcinogens, not classified as to human carcinogenicity.

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