TOXICOLOGICAL PROFILE FOR WHITE PHOSPHORUS

Prepared by:

Sciences International, Inc.
Under Subcontract to:

Research Triangle Institute
Under Contract No. 205-93-0606

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 1997

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UPDATE STATEMENT

A Toxicological Profile for White Phosphorus was released in August 1989. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

PEER REVIEW

A peer review panel was assembled for White Phosphorus. The panel consisted of the following members:

1. Dr. Dominic Cataldo, Staff Scientist, 908 South Nelson Street, Kennewick, WA
2. Dr. Vincent Garry, Director and Associate Professor, Environmental Medicine, University of Minnesota, Minneapolis, MN
3. C. Steven Godin, Ph.D., D.A.B.T., Manager, Drug Metabolism, Cephalon, Inc., West Chester, PA

These experts collectively have knowledge of white phosphorus's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

This statement was prepared to give you information about white phosphorus and white phosphorus smoke and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites as in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. White phosphorus has been found in at least 77 of 1,430 current or former NPL sites. However, the total number of NPL sites evaluated is not known. As more sites are evaluated, the number of sites at which white phosphorus is found may increase. This is important because exposure to white phosphorus may harm you and because these sites are sources of human exposure to white phosphorus.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as white phosphorus, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, lifestyle, and state of health.

1.1 WHAT ARE WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE?

Pure white phosphorus is a colorless-to-white waxy solid, but commercial white phosphorus is usually yellow. Therefore, it is also known as yellow phosphorus. White phosphorus is also called phosphorus tetramer and has a garlic-like smell. In air, it catches fire at temperatures

1. PUBLIC HEALTH STATEMENT

l0-15 degrees above room temperature. Because of its high reactivity with oxygen in air, white phosphorus is generally stored under water. White phosphorus does not occur naturally. Industries produce it from naturally occurring phosphate rocks.

White phosphorus is used mainly for producing phosphoric acid and other chemicals. These chemicals are used to make fertilizers, additives in foods and drinks, cleaning compounds, and other products. Small amounts of white phosphorus have been used as rat and roach poisons and in fireworks. In the past, white phosphorus was used to make matches, but another chemical with fewer harmful health effects has since replaced it.

In the military, white phosphorus is used in ammunitions such as mortar and artillery shells, and grenades. When ammunitions containing white phosphorus are fired in the field, they burn and produce smoke. The smoke contains some unburnt phosphorus, but it mainly has various burned phosphorus products. In military operations, such smoke is used to conceal troop movements and to identify targets or the locations of friendly forces. White phosphorus munitions are intended to burn or firebomb the opponents, in other words, to effectively produce widespread damage but not kill the enemy.

You will find more information on the physical properties and uses of white phosphorus and white phosphorus smoke in Chapters 3 and 4 of this profile.

1.2 WHAT HAPPENS TO WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE WHEN IT ENTERS THE ENVIRONMENT?

White phosphorus enters the environment when industries make it or use it to make other chemicals and when the military uses it as ammunition. It also enters the environment from spills during storage and transport. Because of the discharge of waste water, white phosphorus is likely to be found in the water and bottom deposits of rivers and lakes near facilities that make or use it. It may also be found at sites where the military uses phosphorus-containing ammunition during training exercises. Rainwater washout of these sites may contaminate nearby waterways and their bottom deposits. Hazardous waste sites that contain white phosphorus are also

potential sources of exposure to people. However, because white phosphorus reacts very quickly with oxygen in the air, it may not be found far away from sources of contamination.

The fate of white phosphorus smoke is similar to the fate of reaction products of white phosphorus vapor in air. White phosphorus vapor in air reacts with oxygen and is changed to relatively harmless chemicals within minutes. However, particles in the air may have a protective coating that makes them unreactive for a longer time. White phosphorus reacts mainly with oxygen in water and may stay in water for hours to days. However, chunks of white phosphorus coated with protective layers may stay in water and soil for years if oxygen levels in the water and soil are very low.

In water with low oxygen, white phosphorus may react with water to form a compound called phosphine. Phosphine is a highly toxic gas and quickly moves from water to air. Phosphine in air is changed to less harmful chemicals in less than a day. In water, white phosphorus builds up slightly in the bodies of fish. The other chemicals in white phosphorus smoke are mainly changed to relatively harmless chemicals in water and soil. White phosphorus may stay in soil for a few days before it is changed to less harmful chemicals. However, in deeper soil and the bottom deposits of rivers and lakes where there is no oxygen, white phosphorus may remain for several thousand years. White phosphorus binds moderately to soil and typically doesn’t move deep in soil with oxygen-depleted rainwater.

Chapter 5 provides more information about the fate and movement of white phosphorus in the environment.

1.3 HOW MIGHT I BE EXPOSED TO WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE?

You may be exposed to white phosphorus by breathing in air that contains white phosphorus or by swallowing water or food contaminated with it. White phosphorus has rarely been found in air. Therefore, unless you are near military facilities during training exercises that use white phosphorus ammunition, exposure to it by breathing air will be insignificant. White phosphorus

has not been found in drinking water or any food other than fish caught in contaminated water and game birds from contaminated areas. The maximum level found was 207 millligrams of white phosphorus per kilogram (207 mg/kg) in the muscle of channel catfish caught from the Yellow Lake in Pine Bluff, Arkansas. Some people are exposed to low levels of white phosphorus by eating contaminated food. People who work in industries that produce or use white phosphorus, people who eat contaminated fish or game birds, and people who live near phosphorus-containing waste sites may be exposed to white phosphorus at higher levels than the rest of the population. Other than exposure of certain workers at the Pine Bluff Arsenal in Arkansas, very few studies exist that have information on exposure to high levels of white phosphorus.

Most known cases of fatal or severe exposure to white phosphorus resulted from adults or children accidentally or deliberately swallowing rat poisons or fireworks or handling munitions containing white phosphorus. Other known instances of severe exposure of workers were a result of accidents in white phosphorus loading plants. People, particularly those in the military who use phosphorus-containing ammunitions, may be exposed to white phosphorus smoke during warfare, training exercises, and accidents.

1.4 HOW CAN WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE ENTER AND LEAVE MY BODY?

White phosphorus can enter your body when you breathe air containing white phosphorus. We do not know if white phosphorus in your lungs will enter the blood. White phosphorus can also enter your body when you eat food or drink water containing white phosphorus or when you are burned by it. We do not know if white phosphorus can enter your body through skin that has not been cut or burned. If it enters your body when you eat, drink, or are burned, white phosphorus enters the blood rapidly. We do not know if it changes into other compounds in the blood. Most of the white phosphorus that enters your body leaves in urine and feces after several days. White phosphorus smoke can enter your lungs when you breathe air containing it. When that happens, we do not know if it will enter your blood or how it will leave your body. For more information, please read Chapter 2.

1.5 HOW CAN WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE AFFECT MY HEALTH?

Breathing in white phosphorus can cause you to cough or develop a condition known as phossy jaw that involves poor wound healing in the mouth and a breakdown of the jaw bone. Damage to the blood vessels of the mouth has been observed in rats breathing air containing white phosphorus. Most of what is known about the health effects of breathing this compound is from studies of workers. Current levels of white phosphorus in workplace air are much lower than in the past. If you eat or drink a small amount of white phosphorus (less than one teaspoon), you may vomit; have stomach cramps; have liver, heart, or kidney damage; become extremely drowsy; or die. Most of what is known about the health effects of eating or drinking white phosphorus is from reports of people eating rat poison or fireworks that contained it. White phosphorus is no longer found in rat poison or fireworks. The levels of it that you might be exposed to in food or water are much lower than the levels that were in rat poison or fireworks. We do not know if more serious health effects will occur in people who eat or drink white phosphorus-containing substances for a long time. If burning white phosphorus touches your skin, it will burn you. If you are burned with white phosphorus, you may also develop heart, liver, and kidney damage. We do not know if it can cause cancer or birth defects, or if it affects the ability of people to have children. Because of the lack of cancer studies on animals or people, the EPA has determined that white phosphorus is not classifiable as to human carcinogenicity (that is, whether or not it causes cancer). If you breathe white phosphorus smoke, you may damage your lungs and throat. We do not know how white phosphorus smoke can affect your health if it gets on your skin. For more information, please read Chapter 2**.**

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO WHITE PHOSPHORUS AND WHITE PHOSPHORUS SMOKE?

There are no medical tests to tell if you have been exposed to white phosphorus or its smoke. However, the health effects that can follow exposure may lead your physician to suspect exposure. For more information, please read Chapters 2 and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

EPA requires industry to report spills of white phosphorus of more than 1 pound. White phosphorus levels in workplace air are regulated by the Occupational Safety and Health Administration (OSHA), and recommendations for safe levels have been made by the National Institute for Occupational Safety and Health (NIOSH) and the American Conference of Governmental Industrial Hygienists (ACGIH). All three organizations set the inhalation exposure limit for white phosphorus in the workplace during an 8-hour workday at 0.1 milligram per cubic meter of air (mg/m^3). There are no federal government recommendations for white phosphorus smoke. More information can be obtained from Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of white phosphorus and white phosphorus smoke. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

There are three allotropic forms of elemental phosphorus: white, red, and black phosphorus. At room temperature, pure white phosphorus is a tetrahedral crystal with a molecular formula of P_4. In the pure form, white phosphorus is an ivory-colored, waxy solid. The commercial product is 99.9% pure and may have a slightly yellow color. In the literature, the commercial product is often referred to as yellow phosphorus. In this chapter, the terms white phosphorus and phosphorus are used to refer to P_4, which includes white and yellow phosphorus.

White phosphorus is the most active allotropic form and is extremely toxic when inhaled, ingested, or absorbed through burned areas (Eldad and Simon 1991). It is fat soluble, glows in yellow-green light, and ignites spontaneously upon drying and exposure to air. Storage of white phosphorus in water prevents it from burning spontaneously (Eldad and Simon 1991). White phosphorus can cause thermal injury and hygroscopic damage by absorbing water from surrounding tissues. It reacts with oxygen and water to form strong acids (H_3PO_2, H_3PO_3) and combines with metals like copper to form dark-colored inactive salts (Eldad and Simon 1991).

White phosphorus particles can burn on the surface of the skin or penetrate deep into the tissues when carried on shrapnel particles. Local destruction of tissues continues as long as white phosphorus is exposed to oxygen. White phosphorus smoke with a garlic odor is characteristic of white phosphorus burns (Eldad and Simon 1991). High mortality rates seen following white phosphorus burns can be due to its absorption from the burned surface, which may result in multi-organ failure (mainly liver and kidneys), hyperphosphatemia, hypocalcemia, and electrocardiogram (ECG) abnormalities (ST depression, QT elongation, microvoltage of QRS and bradycardia) (Bowen et al. 1971; Eldad and Simon 1991). Copper

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sulphate is a very effective *in vitro* neutralizer of white phosphorus and has been used to treat white phosphorus burns (Eldad and Simon 1991). However, it is extremely toxic as copper can be absorbed from the burn injury or wound after topical application of copper sulphate to the burnt surface (Bowen et al. 1971; Summerlin et al. 1967). Acute copper intoxication is characterized by hemolytic anemia with intravascular hemolysis, hematuria, proteinuria, glycosuria, oliguria, uremia, tachycardia, hypotension, abnormal liver functions, and jaundice (Summerlin et al. 1967). The hemolytic anemia seen following copper intoxication is a common cause of death. Only tap water irrigations were found to be effective in preventing death after white phosphorus burns (Eldad and Simon 1991).

The garlic-like odor is also detected in the vomitus which is phosphorescent and visible when examined in a dark room. If phosphorus is absorbed as the gas phosphine (PH_3), death can occur rapidly due to cardiac collapse (Blanke 1970). In most cases, white phosphorus is ingested accidentally or when trying to commit suicide. Following absorption, white phosphorus stays in the blood for several days and is slowly oxidized to hypophosphoms and phosphorous acids (Blanke 1970). If death occurs within l-3 days, no significant changes are seen. However, in patients who survive for more than a week, the effect of phosphorus damage is evident by the extreme fatty changes seen on many organs; alterations in both fat and protein metabolism, a yellowish liver with marked fatty degeneration, and severe jaundice are usually present (Blanke 1970).

White phosphorus has been used in the manufacture of rat and cockroach poisons, pesticides, matchheads, firecrackers, and ammunitions in the military. However, other chemicals such as sulfur have replaced phosphorus in matchheads. Phosphorus is also used as a fumigant in the storage of grain in the form of aluminum phosphide pellets. Due to ease of application, pellets of aluminum or magnesium phosphide are commonly used (Garry et al. 1989). Phosphine, a highly toxic gas, is generated from phosphide. The rate of formation of phosphine (permissible exposure limit [PEL], 0.4 mg/m^3) is dependent on the ambient temperature and humidity. In the presence of water (humidity) or acid, the formation of phosphine is greatly enhanced at any given temperature. Phosphine is released rapidly, and it is extremely-fatal to the unprotected worker/person (Garry et al. 1989). An accidental death of a pregnant woman was related to phosphine exposure from stored grain that had been fumigated with aluminum phosphide (AlP_3) pellets (Garry et al. 1993). Phosphine can also be generated when phosphorus is used as a dopant in the microchip processing, where a small amount of phosphorus is added to another substance such as a semiconductor to alter its properties (Garry et al. 1989).

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White phosphorus smoke is generated by burning white phosphorus. The U.S. Army uses white phosphorus smoke as a smoke/obscurant for training and testing activities. The smoke generated from burning white phosphorus consists primarily of oxidation and hydrolysis products of phosphorus, including phosphorus pentoxide and phosphorus trioxide. The moisture in the air reacts with these phosphorus oxides to produce a dynamic mixture of polyphosphoric acids that eventually transform into orthophosphoric acid, pyrophosphoric acid, and orthophosphorus acid. Wind-tunnel tests in which white phosphorus was burned and oxygen was non-limiting produced an average aerosol mass concentration between 2,500 and 3,000 mg/m^3, with the major components being polyphosphates, phosphine, and elemental phosphorus (Van Voris et al. 1987). It should be stressed that while residual-coated white phosphorus is very biologically toxic, there are somewhat stable combustion intermediates (linear and cyclic polyphosphates) that can be persistent under low oxygen conditions and may be toxic to biological organisms.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure - inhalation, oral, and dermal; and then by health effect - death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods - acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observedadverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has

established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals or exposure levels below which no adverse effects have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for white phosphorus. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

White Phosphorus. Studies of human exposure to white phosphorus are limited to those examining occupational exposure to white phosphorus for intermediate or chronic durations. Most of the information on the effects of occupational exposure of humans to white phosphorus was from case reports, rather than epidemiology studies. Phosphorus oxidizes rapidly when exposed to air, and fumes/vapors in phosphorus factories probably contained phosphorus, phosphoric oxide, and phosphorus oxide (Heimann 1946; Hughes et al. 1962; Ward 1928). Exposure levels for white phosphorus and phosphorus compounds were not reported in the occupational studies. However, workers at phosphorus plants were probably also exposed to white phosphorus by the dermal and oral routes.

One study was located regarding toxicity in animals after inhalation exposure to white phosphorus (Ruzuddinov and Rys-Uly 1986). Rats were exposed for an intermediate duration to the atmosphere in a phosphorus plant, reported to contain white phosphorus and its inorganic compounds, and changes in the oral mucosa were examined. However, exposure levels for white phosphorus and phosphorus compounds were not reported in the study.

White Phosphorus Smoke. Several studies have examined the toxicity of white phosphorus smoke in humans and animals (White and Armstrong et al. 1935; Brown et al. 1980, 1981; Starke et al. 1982; Walker et al. 1947). The Walker et al. (1947) study is a report of the health effects observed in workers exposed to white phosphorus smoke during a factory fire. The other studies involve experimental exposures. In these studies, the smoke was generated by burning either the felt that contained white phosphorus or white phosphorus alone. White phosphorus-felt (WP/F) smoke was generated by forcing military-grade white phosphorus under pressure into thick pieces of wool felt. This material was then cut into cubes of specific weights. A cube of the white phosphorus felt on an aluminum-foil pan was placed on an unlit electric hot plate within a chamber. The hot plate was a fast-heating unit capable of reaching temperatures in excess of 700°F (Brown et al. 1980). The smoke was pumped into the exposure chamber or the white phosphorus/felt was burned in the exposure chamber. In some experiments, the subjects were placed in the exposure chamber prior to burning the white phosphorus, and in other experiments the test atmosphere was generated prior to placing the subjects in the exposure chamber. In some of these studies,

subjects were not removed until the smoke had dissipated. Thus, the subjects had the potential to be exposed to a wide range of concentrations of white phosphorus smoke. The temperature in the exposure chambers was higher than room temperature. Another limitation of these inhalation studies is the reporting of air concentrations. Typically air samples were collected on filters, diluted with distilled water, and boiled to convert the phosphorus acids to orthophosphoric acids. The acid content was then determined by titration, and the normality of the acid was then converted to orthophosphoric acid or phosphorus pentoxide equivalents (Brown et al. 1980).

In the Brown et al. (1980, 1981) and Starke et al. (1982) studies, the air concentrations of white phosphorus smoke were expressed in terms of orthophosphoric acid equivalents. In reviewing the methods used to estimate the concentration of orthophosphoric acid, ATSDR detected a calculation mistake. According to the authors' equation for determining the orthophosphoric acid concentration of the sample, the molecular weight was divided by 3 milliequivalents. At pH 9.6, the molecular weight should be divided by 2 milliequivalents. A correction was made to exposure levels for the three studies. White and Armstrong (1935) reported the white phosphorus smoke concentration in terms of phosphorus pentoxide equivalents. In Section 2.2, the air concentrations for the White and Armstrong (1935) studies are also expressed in terms of orthophosphoric acid equivalents. Differences in the exposure protocol between the studies conducted by Brown et al. (1980, 198l), Starke et al. (1982), and White and Armstrong (1935) make it difficult to make comparisons across studies. In White and Armstrong (1935), the continuous-flow method was used, allowing the desired concentrations to be set up and maintained under conditions which avoided exposure of the experimental animals to either excessive temperature rise, oxygen deprivation, or other vitiation of the atmospheres breathed. Exposure duration was for 1 hour. In Brown et al. (1980,1981), exposure times and concentration levels varied. Exposure durations ranged from 5-90 minutes to 13 weeks, and target concentrations varied (200,500, or 1,000 mg/m^3). In Starke et al. (1982), rats were exposed to white phosphorus smoke or control air 15 minutes/day, 5 days/week, for 10 consecutive weeks at concentrations of 0,500, and 1,000 mg/m^3.

2.2.1.1 Death

White Phosphorus. Two white phosphorus-related deaths were reported in a study of workers from three plants involved in the production of fireworks (Ward 1928). Both workers were females exposed to white phosphorus during the molding and wrapping of a paste containing 44% phosphorus. This step in the production of fireworks involved continuous inhalation exposure to airborne white phosphorus, dermal

exposure to the paste, and likely ingestion of airborne white phosphorus and white phosphorus passed from hand to mouth. Apparently, the phosphorus fumes/vapors contained white phosphorus and other phosphorus compounds, including phosphoric oxide and phosphorus oxide. However, exposure levels were not reported. Both women developed phossy jaw, a degenerative condition affecting the soft tissue, bones, and teeth of the oral cavity, after chronic exposure to the atmosphere at the factory. The cause of death in both cases was listed as septicemia, with abscess of a tooth and necrosis of the jaw listed as contributory causes. Thus, death in both cases resulted from infections, probably secondary to the degenerative effects of white phosphorus on the oral cavity (Ward 1928). It is likely that the development of phossy jaw resulted from the local action of white phosphorus on the oral cavity (as discussed in Section 2.2.2.2). It is not known whether white phosphorus inhaled and absorbed into the systemic circulation contributed to the development of phossy jaw in these two workers.

No studies were located regarding death in animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No deaths were observed in humans exposed to concentrations as high as 592 mg phosphorus pentoxide equivalents/m^3 (817 mg orthophosphoric acid equivalents/m^3) for 3.5 minutes or 514 mg phosphorus pentoxide/m^3 (709 mg orthophosphoric acid equivalents/m^3) for 15 minutes (White and Armstrong 1935).

Rats, mice, guinea pigs, and goats have died following acute-duration exposures to white phosphorus smoke (Brown et al. 1980; White and Armstrong 1935). Following a single or multiple 5-60-minute exposures, the lowest lethal concentrations identified in the species examined were 1,742 mg orthophosphoric acid equivalents/m^3 for pregnant rats (Brown et al. 1981; Starke et al. 1982), 1,794 mg orthophosphoric acid equivalents/m^3 for nonpregnant rats (Brown et al. 1980), 310 mg phosphorus pentoxide equivalents/m^3 (428 mg orthophosphoric acid equivalents/m^3) for mice (White and Armstrong 1935), 264 mg orthophosphoric acid equivalents/m^3 for guinea pigs (Brown et al. 1980), and 6,230 mg phosphorus pentoxide equivalents/m3 (8,599 mg orthophosphoric acid equivalents/m^3) for goats (White and Armstrong 1935). For most studies, the cause of death was not determined. In mice, exposure to white phosphorus smoke resulted in death within a few minutes after removal from low concentrations of the smoke (White and Armstrong 1935). The increased mortality may have been the result of the severe respiratory tract damage that was observed, most likely due to cerebral asphyxiation (the nares of the animals were plugged with a heavy mucous discharge). Respiration was obstructed through irritation and swelling of the mucous membranes lining the very small and constricted upper respiratory passages

(White and Armstrong 1935). This rapid death from acute exposure to the smoke was not observed in rats or goats because of their larger upper respiratory tracts. However, much higher smoke concentrations were necessary to produce asphyxial death in rats. In goats, with even larger respiratory tracts, relatively enormous concentrations were required to cause asphyxial symptoms. As in the mice, the same white mucous secretion was seen around their noses and mouths (White and Armstrong 1935).

Increased mortality was also observed in rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 of white phosphorus smoke 15 minutes/day, 5 days/week, for 6-13 weeks (Brown et al. 1981) or 9-10 weeks (Brown et al. 1981; Starke et al. 1982). As with the deaths occurring after acute exposure, the most severe lesions were observed in the respiratory tract. Lesions were most extensive and severe in the larynx and trachea. They consisted mainly of the thickening of the lamina propria (the connective tissue of the mucous membrane) and submucosa by collagen, endothelial cell proliferation, and macrophage infiltration. Occasionally, inflammatory cells were seen in the epithelium (Brown et al. 1981). No chronic duration studies were located.

The LD_{50} values from each reliable study in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

White Phosphorus. No studies were located regarding gastrointestinal, dermal, or ocular effects in humans or animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. Systemic effects of white phosphorus smoke in humans and animals after inhalation exposure are discussed below. The highest NOAEL value and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-1.

No studies were located regarding musculoskeletal or other systemic effects in humans or animals after inhalation exposure to white phosphorus smoke.

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation

Key[a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m^3)	LOAEL (effect) Serious (mg orthophosphoric acid equivalents/m^3)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (NS)	1 hr				1120 (5/10 died 10 days after exposure)	White and Armstrong 1935
2	Rat (Sprague-Dawley)	60-90 min				1794 (2/10 died)	Brown et al. 1980
3	Rat (Sprague-Dawley)	Gd 6-15 15 min/d				1742 (5/24 dams died)	Brown et al. 1981; Starke et al. 1982
4	Mouse (NS)	1 hr				110 (1/20 died)	White and Armstrong 1935
5	Gn pig (Hartley)	30 min				264 (1/5 died within 30 minutes)	Brown et al. 1980
6	Goat (NS)	1 hr				6230 (2/3 died 5 days after exposure)	White and Armstrong 1935

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m^3)		LOAEL (effect) Serious (mg orthophosphoric acid equivalents/m^3)		Reference
	Systemic								
7	Human	15 min	Resp		514	(coughing, headache, nose and throat irritation, chest congestion)			White and Armstrong 1935
8	Human	2-3.5 min	Resp		588	(sensation of tightness in the throat, coughing, headache)			White and Armstrong 1935
9	Human	5 min	Resp		187 [b]	(coughing, throat irritation during talking)			White and Armstrong 1935
10	Rat (NS)	1 hr	Resp		380	(signs of irritation in respiratory tract)	758	(edema)	White and Armstrong 1935
			Hepatic	1120	1170	(slight cloudy swelling and congestion)			
			Renal	2460	2500	(slight cloudy swelling)			

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m^3)		LOAEL (effect) Serious (mg orthophosphoric acid equivalents/m^3)		Reference
11	Rat (Sprague-Dawley)	60-90 min	Resp	2091			3027	(acute diffuse congestion, focal perivascular edema, fibrin thrombi and hemorrhaging in the lungs)	Brown et al. 1980
			Cardio	2091			3027	(diffuse congestion, fibrin thrombi)	
			Hemato	758					
			Hepatic	2091			3027	(diffuse sinusoidal congestion)	
			Renal	2091			3027	(focal proteinuria, intratubular concretions, focal congestion)	
12	Mouse (NS)	1 hr	Resp		110	(signs of irritation)	470	(difficulty in breathing, heavy mucous discharge, congestion, hemorrhages, edema)	White and Armstrong 1935
			Hepatic	310	470	(cloudy swelling)			
			Renal	310	470	(cloudy swelling)			
13	Gn pig (Hartley)	10 min	Resp	984					Brown et al. 1980
			Cardio	984					
			Hemato	984					
			Hepatic	984					
			Renal	984					

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m^3)		LOAEL (effect) Serious (mg orthophosphoric acid equivalents/m^3)		Reference
14	Goat (NS)	1 hr	Resp		540	(mild bronchitis)	3870	(congestion, edema, hemorrhages, pneumonia)	White and Armstrong 1935
					>3000	(harsh respiratory sounds, rales, early pneumonia)			
			Hepatic	7000	7320	(slight congestion, cloudy swelling, vacuolization of some cells)			
			Renal	7000	7320	(marked cloudy swelling, congestion and albuminous fluid in glomeruli and convoluted tubules)			
	Neurological								
15	Mouse (NS)	1 hr		310			470	(increased motor activity, convulsions)	White and Armstrong 1935
	INTERMEDIATE EXPOSURE								
	Death								
16	Rat (Sprague-Dawley)	13 wk 5 d/wk 15 min/d					1742	(27/72 died)	Brown et al. 1981

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)

Key[a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m³)		Serious (mg orthophosphoric acid equivalents/m³)		Reference
17	Rat (Sprague-Dawley)	9-10 wk 15 min/d 5 d/wk					1742	(12/20 males died)	Brown et al. 1981; Starke et al. 1982
	Systemic								
18	Rat (Sprague-Dawley)	13 wk 15 min/d 5 d/wk	Resp	289	884	(moderate laryngitis, moderate tracheitis)	1742	(wheezing, dyspnea)	Brown et al. 1981
			Cardio	1742					
			Gastro	1742					
			Hemato	1742					
			Hepatic	1742					
			Renal	1742					
			Dermal	1742					
			Ocular	1742					
	Neurological								
19	Rat (Sprague-Dawley)	13 wk 15 min/d 5 d/wk		1742					Brown et al. 1981
	Reproductive								
20	Rat (Sprague-Dawley)	10 wk 5 d/wk 15 min/d		1742					Brown et al. 1981; Starke et al. 1982

TABLE 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious (mg orthophosphoric acid equivalents/m^3)	LOAEL (effect) Serious (mg orthophosphoric acid equivalents/m^3)		Reference
21	Rat (Sprague-Dawley)	13 wk 15 min/d 5 d/wk		1742				Brown et al. 1981
22	Rat (Sprague-Dawley)	9-10 wk 15 min/d 5 d/wk		1742				Brown et al. 1981; Starke et al. 1982
Developmental								
23	Rat (Sprague-Dawley)	9-10 wk 15 min/d 5 d/wk		884		1742	(8% decrease in pup weight, 68% decrease in pup survival, and 35% decrease in viability)	Brown et al. 1981; Starke et al. 1982

[a]The number corresponds to entries in Figure 2-1.

[b] Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.02 mg/m^3 for white phosphorus smoke. The adjusted minimal LOAEL of 0.6 mg/m^3 was divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability), resulting in an acute MRL of 0.02 mg/m^3.

Cardio = cardiovascular; d = day(s); Derm = dermal; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; Hemato= hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to White Phosphorous Smoke - Inhalation

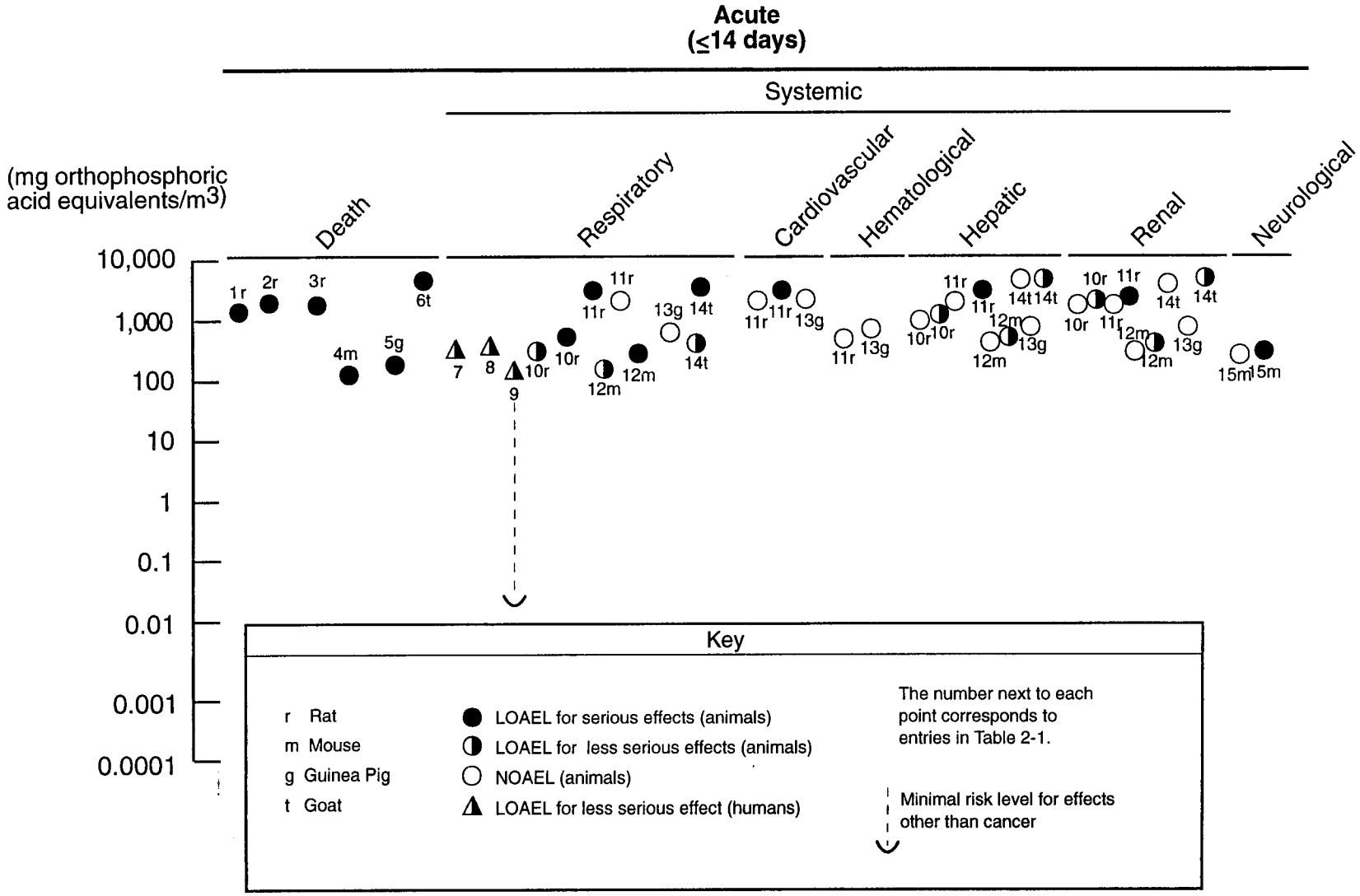
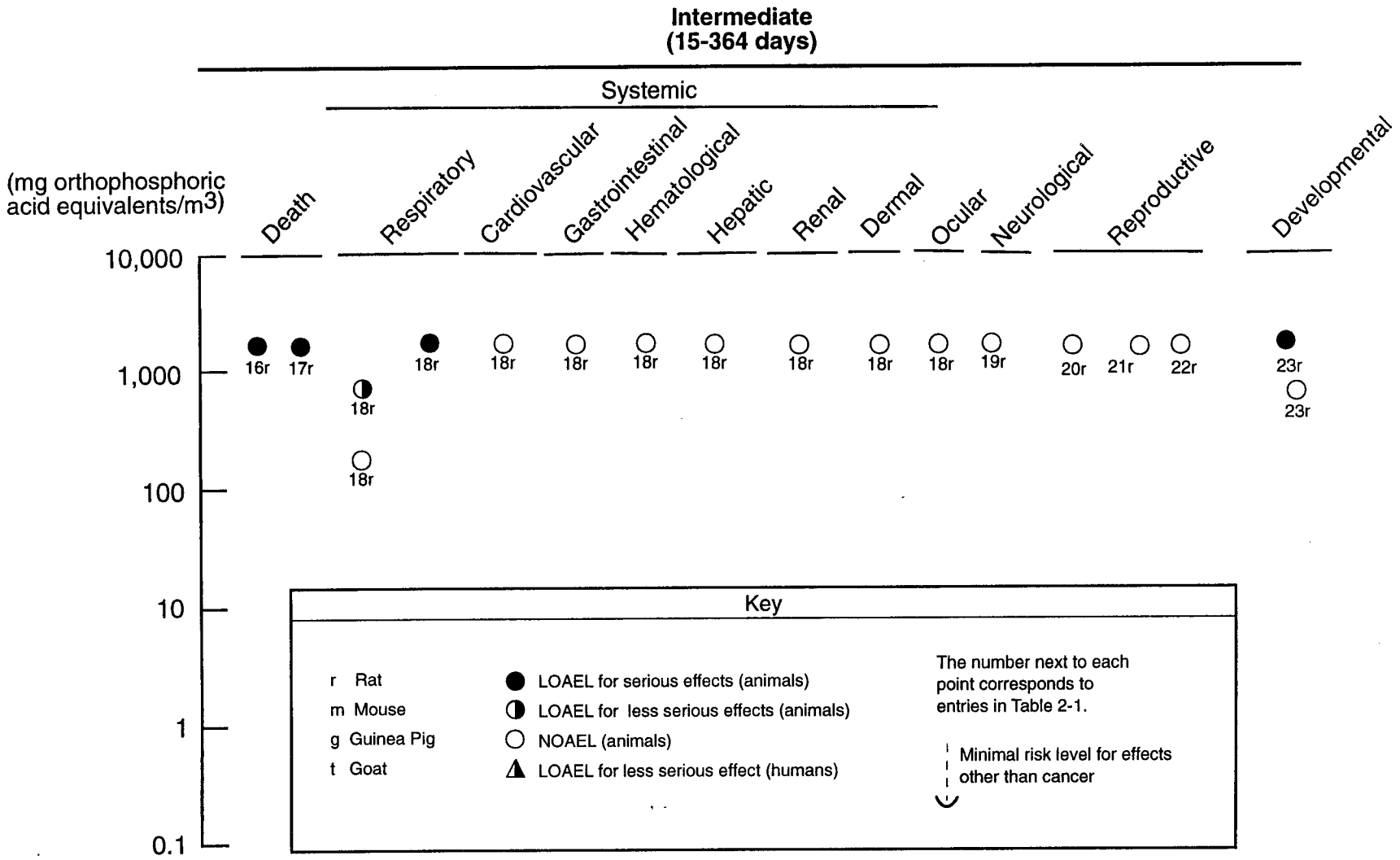


Figure 2-1. Levels of Significant Exposure to White Phosphorus Smoke - Inhalation (continued)



2. HEALTH EFFECTS

Respiratory Effects

White Phosphorus. In a study of 71 humans occupationally exposed to fumes/vapors and paste containing white phosphorus for intermediate or chronic duration, an irritating cough was reported as occurring in a large proportion of the employees (Ward 1928); no further information regarding respiratory effects was reported. Details of this study are provided in Section 2.2.2.2; exposure levels of white phosphorus and other compounds were not reported.

No studies were located regarding respiratory effects in animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. In two acute-duration exposure studies, respiratory effects have been reported by men inhaling white phosphorus smoke for 2-15 minutes (White and Armstrong 1935). At the lowest concentration tested (187 mg phosphorus pentoxide equivalents/m^3 [258 mg orthophosphoric acid equivalents/m^3] for 5 minutes), throat irritation during talking was reported. At higher concentrations ≥514 mg phosphorus pentoxide equivalents/m^3 [709 mg orthophosphoric acid equivalents/m^3]for 15 minutes), coughing and nose irritation were reported (White and Armstrong 1935). Coughing, hoarseness, and erythema and edema of the larynx and vocal cords were reported in women exposed to an unspecified amount of white phosphorus smoke for 15-20 minutes during a factory fire (Walker et al. 1947). No longer-term human exposure studies were located.

In animals, the respiratory tract is one of the primary targets of white phosphorus smoke toxicity. Slight to intense congestion, edema, and hemorrhages were observed in the lungs of rats, mice, and goats (Brown et al. 1980; White and Armstrong 1935). Exposure to 3,027 mg orthophosphoric acid equivalents/m3 for 90 minutes resulted in respiratory tract lesions in rats (Brown et al. 1980). “Unmistakable signs of irritation” were observed in mice, rats, and goats exposed for 1 hour to 110,380, or 540 mg phosphorus pentoxide equivalents/m^3 (152,524, or 754 mg orthophosphoric acid equivalents/m^3), respectively (White and Armstrong 1935). Lung lesions were observed in all of the animals that died early and were necropsied (White and Armstrong 1935). No respiratory tract effects were observed in guinea pigs exposed to concentrations of white phosphorus smoke as high as 984 mg orthophosphoric acid equivalents/m^3 for 30 minutes (Brown et al. 1980). However, only one animal was examined at this exposure level, and it was examined 2 weeks after exposure. Exposure to white phosphorus smoke for

6 or 13 weeks at a concentration of 884 mg orthophosphoric acid equivalents/m^3 for 15 minutes/day, 5 days/week resulted in slight laryngitis and tracheitis in rats (Brown et al. 1981). Exposure to a higher concentration (1,742 mg orthophosphoric acid equivalents/m^3) resulted in wheezing, dyspnea, moderateto-severe laryngitis and tracheitis, and minimal-to-severe interstitial pneumonia (Brown et al. 1981).

Cardiovascular Effects

White Phosphorus. No studies were located regarding cardiovascular effects in humans after inhalation exposure to white phosphorus.

In rats exposed for an intermediate duration to an unknown concentration of airborne white phosphorus from the furnace room of a phosphorus factory, an increase in permeability of capillary walls, lesions in the walls of blood vessels, and evidence of impaired microcirculation were observed in the mouth (Ruzuddinov and Rys-Uly 1986). Severe damage to the oral mucosa was also observed in these animals. No information regarding effects on the heart was located in the animal studies.

White Phosphorus Smoke. No studies were located regarding cardiovascular effects in humans after inhalation exposure to white phosphorus smoke.

No gross or histological alterations were observed in the hearts of rats exposed to white phosphorus smoke at concentrations as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week for 13 weeks (Brown et al. 1981).

Gastrointestinal Effects

White Phosphonrs Smoke. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to white phosphorus smoke.

Exposure of rats to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 for 15 minutes/day, 5 days/week for 13 weeks did not result in gross or histological alterations in the gastrointestinal tract (Brown et al. 1981).

2. HEALTH EFFECTS

Hematological Effects

White Phosphorus. Anemia (marked decrease in red blood cells or hemoglobin) and leukopenia (very low levels of white blood cells or leukocytes) were observed in workers chronically exposed to airborne white phosphorus (Ward 1928). Because the workers handled white phosphorus contaminated rags, it is possible that exposure occurred via oral and dermal routes also. No information on exposure levels was provided. In another occupational exposure study, no alterations in hemoglobin or total or differential leukocyte levels were observed (Hughes et al. 1962).

No studies were located regarding hematological effects in animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding hematological effects in humans after inhalation exposure to white phosphorus smoke.

Two weeks after exposure termination, no significant changes in erythrocyte, hematocrit, hemoglobin, or total and differential leukocyte levels were observed in rats exposed to 3,027 mg orthophosphoric acid equivalents/m^3 for 90 minutes or guinea pigs exposed to 984 mg orthophosphoric acid equivalents/m^3 for 10 minutes (Brown et al. 1980). No changes in erythrocyte, hematocrit, hemoglobin, or leukocyte (total or differential) levels were observed in rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 of white phosphorus smoke for 15 minutes/day, 5 days/weeks, for 13 weeks (Brown et al. 1981).

Musculoskeletal Effects

White Phosphorus. Phossy jaw is a degenerative condition affecting the entire oral cavity including soft tissue, teeth, and bones (Heimann 1946; Hughes et al. 1962; Ward 1928). This condition generally occurs following long term exposure to airborne white phosphorus. The effects of phossy jaw can be extreme, involving severe necrosis of soft tissue, teeth, and bones in the oral cavity. Massive life-threatening infections often occur during the development of phossy jaw. With one exception (Jakhi et al. 1983) (see Section 2.2.2.2), all reported cases of phossy jaw have resulted from occupational exposure to white phosphorus fumes/vapors and/or dust. Because white phosphorus oxidizes rapidly, phosphorus fumes/vapors may contain phosphoric oxide and phosphorus oxide, in addition to phosphorus (Heimann 1946; Hughes et al. 1962; Ward 1928).

2. HEALTH EFFECTS

In a study of workers exposed to white phosphorus for intermediate durations in three fireworks plants, 2 of 44 workers developed definite cases of phossy jaw (Ward 1928). These cases, described as slight necrosis of the lower jaw, took up to 2 years for recovery. In the same study, 13 of 27 workers exposed to white phosphorus for chronic durations developed necrosis of the upper and/or lower jaw, ranging from slight to severe; 2 of the 13 workers developing phossy jaw died from complications related to the necrosis. This study and several case reports discuss the progression of symptoms during the development of phossy jaw (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944). It is likely that the development of necrosis of the jaw in workers exposed to airborne white phosphorus resulted from the local action of phosphorus on the oral cavity. This information is discussed in detail in Section 2.2.2.2.

There is evidence that occupational exposure to white phosphorus affects bones other than those in the jaw; this implies a systemic effect for inhaled white phosphorus. Two middle-aged men occupationally exposed to white phosphorus for 20-30 years had a history of breaking their femurs in accidents not normally expected to result in breakage of bones (Dearden 1899). One man had broken the right and left femurs on two separate occasions by "tripping over a board," while the other broke the right femur by "stumbling down a single step," and the left femur in "just as simple a manner." Examination of bone from the fingertip of one of the two workers indicated an increased "relative proportion of phosphoric acid to lime" compared to healthy bone by nearly 1%. Thus, occupational exposure to white phosphorus may change the composition of bone tissue, decreasing the bones ability to resist fracture; however, the information reported in this study is insufficient to definitively attribute the observed effects to occupational exposure to white phosphorus.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to white phosphorus.

Hepatic Effects

White Phosphorus. Information on hepatotoxicity after exposure to airborne white phosphorus is limited to an occupational exposure study. No alterations in liver function tests were observed in workers chronically exposed to an unreported amount of airborne white phosphorus (Hughes et al. 1962).

No studies were located regarding hepatic effects in animals after inhalation exposure to white phosphorus.

2. HEALTH EFFECTS

White Phosphorus Smoke. No studies were located regarding hepatic effects in humans after inhalation exposure to white phosphorus smoke.

Slight cloudy swelling was observed in the livers of rats exposed for 1 hour to 2 1,170 mg phosphorus pentoxide equivalents/m^3 (≥ 1,615 mg orthophosphoric acid equivalents/m^3) (White and Armstrong 1935) or 3,027 mg orthophosphoric acid equivalents/m^3 for 90 minutes (Brown et al. 1980), mice exposed to 470 mg phosphorus pentoxide equivalents/m^3 (649 mg orthophosphoric acid equivalents/m3) for 1 hour (White and Armstrong 1935), and goats exposed for 1 hour to ≥7,320 mg phosphorus pentoxide equivalents/m^3) (≥10,104 mg orthophosphoric acid equivalents/m3) (White and Armstrong 1935). In the White and Armstrong (1935) studies, only animals dying early were necropsied. Consequently, results were only reported for some of the animals. No hepatic effects were observed in guinea pigs exposed to 984 mg orthophosphoric acid equivalents/m^3 for 10 minutes; only one guinea pig exposed at this concentration was examined 2 weeks after exposure (Brown et al. 1980). A NOAEL of 1,742 mg orthophosphoric acid equivalents/m^3 has been identified for hepatic effects in rats exposed for 15 minutes/day, 5 days/week for 13 weeks to white phosphorus smoke. At this concentration, no alterations in the levels of triglyceride, cholesterol, serum aspartate aminotransferase (AST), or serum alanine aminotransferase (ALT) or gross or histological lesions were observed (Brown et al. 1981).

Renal Effects

White Phosphorus. In an epidemiology study, 48 apparently healthy men working in a phosphorus plant between 1 and 17 years had average creatinine levels in urine (141 mg/L) essentially identical to those of 28 workers (controls) not exposed to white phosphorus (Hughes et al. 1962). However, the groups were apparently not well matched with respect to age and race (details not reported), as only 28 men (controls) volunteered to allow the blood to be drawn (Hughes et al. 1962).

No studies were located regarding renal effects in animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding renal effects in humans after inhalation exposure to white phosphorus smoke.

In rats, mice, and goats exposed to white phosphorus smoke for 1 hour, slight cloudy swelling was observed in the kidneys at ≥1,170,470, and 7,320 mg phosphorus pentoxide equivalents/m^3, respectively

(≥ 1,615, 649, or 10,104 mg orthophosphoric acid equivalents/m^3) (White and Armstrong 1935). In the White and Armstrong (1935) study, a white, mucous secretion was seen around the noses and mouths of animals that died early. Upon necropsy, congestion, hemorrhage, edema, and pneumonia were the principal lesions seen in the lungs, which are all evidence of respiratory obstruction (White and Armstrong 1935). No renal lesions were observed in rats exposed to 3,027 mg orthophosphoric acid equivalents/m^3 for 90 minutes or guinea pigs exposed to 984 mg orthophosphoric acid equivalents/m^3 for 10 minutes (Brown et al. 1980). In the Brown et al. (1980) study, a small number of animals were examined 2 weeks after exposure termination. Exposure to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks did not result in significant changes in levels of serum urea nitrogen, creatinine, or uric acid or in alterations in the gross or histological examination of the kidneys (Brown et al. 1981).

Dermal Effects

White Phosphoncs Smoke. No studies were located regarding dermal effects in humans after inhalation exposure to white phosphorus smoke.

No alterations were observed in the skin of rats exposed to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981).

Ocular Effects

White Phosphorus Smoke. No studies were located regarding ocular effects in humans after inhalation exposure to white phosphorus smoke.

No alterations were observed in the eyes of rats exposed to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981).

2. HEALTH EFFECTS

Other Systemic Effects

White Phosphorus. Decreased serum glucose levels were reported for some workers occupationally exposed to white phosphorus for a chronic duration (Ward 1928). Details of this study are provided in Section 2.2.2.2.

Rats received intermittent exposure to the atmosphere in the furnace room of a phosphorus factory for l-4 months (Ruzuddinov and Rys-Uly 1986). Histology of rats killed monthly revealed progressive morphological degeneration of the tongue and oral mucosa of the cheek, gum, and hard palate. It is likely that the effects of white phosphorus in the oral cavity are local rather than systemic resulting from direct contact of white phosphorus-containing atmosphere with tissues in the mouth. For this reason this study is also discussed in Section 2.2.2.2.

2.2.1.3 Immunological and Lymphoreticular Effects

White Phosphorus. Limited information on the immunotoxicity of inhaled white phosphorus was located. As discussed in Section 2.2.1.2, decreased leukocyte levels were observed in workers exposed to an unknown concentration of white phosphorus via inhalation, oral, and dermal routes (Ward 1928). It is not known if the decrease in leukocyte levels would result in impaired immune function.

No studies were located regarding immunological or lymphoreticular effects in animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding immunological or lymphoreticular effects in humans or animals after inhalation exposure to white phosphorus smoke.

2.2.1.4 Neurological Effects.

White Phosphorus. No studies were located regarding neurological effects in humans or animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding neurological effects in humans after inhalation exposure to white phosphorus smoke.

2. HEALTH EFFECTS

No histological alterations were observed in the brains of rats exposed to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981). This NOAEL for neurological effects in rats exposed for an intermediate duration is recorded in Table 2- 1 and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

White Phosphorus. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding reproductive effects in humans after inhalation exposure to white phosphorus smoke.

No effects on pregnancy rate or number of pups born alive were observed following the mating of male rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 of white phosphorus smoke 15 minutes/day, 5 days/week for 10 weeks with female rats exposed for 3 weeks (similar exposure protocol) (Brown et al. 1981; Starke et al. 1982) or the mating of male rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks to unexposed female rats (Brown et al. 1981; Starke et al. 1982). No exposure-related lesions were seen in the testis, epididymis, ovary, and uterus of rats exposed to 1,742 mg orthophosphoric acid equivalents/m3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981).

These LOAEL values from each reliable study for reproductive effects in rats in each duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.6 Developmental Effects

White Phosphorus. No studies were located regarding developmental effects in humans or animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding developmental effects in humans after inhalation exposure to white phosphorus smoke.

Increases in the incidence of right or reversed ductus arteriosus (9/18 or 50%) and ectopic testicles (3/18 or 33%) were observed in the offspring of unexposed male rats and female rats exposed to 1,742 mg orthophosphoric acid equivalents/m3, 15 minutes/day on gestational days 6-15. Statistical analysis of these data was not presented. No other developmental effects were observed in this study (Brown et al. 1981; Starke et al. 1982). In another study conducted by these authors, no significant increases in the incidence of malformations or anomalies were observed in the offspring of rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3, 15 minutes/day, 5 days/week during the 3-week premating period, mating period, and gestation period. Thus, the authors did not consider these effects to be significant. However continued exposure of the pups and dams to white phosphorus smoke (1,742 mg orthophosphoric acid equivalents/m^3) during the 3-week lactation period resulted in decreased pup growth, pup survival, and pup viability. The authors suggested that the decreased pup growth and survival may have been due to the dams not allowing the pups to nurse, not enough milk being produced, pups not nursing due to respiratory tract irritation, or a direct compound-related effect on the pups (Brown et al. 1981; Starke et al. 1982).

These NOAEL and LOAEL values from each reliable study for developmental effects in rats are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

White Phosphorus. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to white phosphorus.

White Phosphorus Smoke. No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to white phosphorus smoke.
Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

White Phosphorus. No studies were located regarding cancer in humans or animals after inhalation exposure to white phosphorus.

White Phosphonts Smoke. No studies were located regarding cancer in humans or animals after inhalation exposure to white phosphorus smoke.

2.2.2 Oral Exposure

Studies reporting acute oral exposure of humans to white phosphorus were limited to case reports of intentional or accidental ingestion of match heads, rat poison, cockroach poison, firecrackers, or from military operations. Manufacturers of white phosphorus-containing rat poison have claimed that the only active ingredient in the rat poison was white phosphorus (Peacock 1993). It is likely that white phosphorus was the agent producing toxicity following ingestion of cockroach poison, match heads, and fireworks, although the presence of other toxic compounds cannot be ruled out. Many of the case reports involving acute oral exposure of humans to white phosphorus did not report intake levels. High doses of white phosphorus nearly always induced vomiting, expelling much of the ingested white phosphorus from the body. In addition, gastric lavage to remove white phosphorus from the stomach was performed on many poisoned patients. Thus, doses could not be estimated for end points other than vomiting for all but one of the case reports for humans receiving acute oral exposure to white phosphorus.

Several studies reporting intermediate oral exposure of children to white phosphorus were located. In most cases the white phosphorus was administered as a treatment for rickets, but in some cases white phosphorus was administered to healthy children to prevent the development of rickets. In studies reporting the effects of white phosphorus on bones in children, the doses of white phosphorus.. administered (0.026-0.158 mg/kg/day) were several orders of magnitude lower than those reported following intentional or accidental white phosphorus poisoning.

Humans exposed to white phosphorus in the workplace probably ingested some airborne white phosphorus. One retrospective study indicated that oral exposure to white phosphorus passed from hand

to mouth was likely, because the workers constantly handled a paste containing 4-6% white phosphorus, and washroom facilities at the plants were inadequate.

No studies were located regarding health effects in human or animals after oral exposure to white phosphorus smoke.

2.2.2.1 Death

Numerous case reports of death following acute oral exposure of humans to white phosphorus were located (Diaz-Rivera et al. 1950,196l; Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; Rao and Brown 1974; Rubitsky and Myerson 1949; Simmon and Pickering 1976; Talley et al. 1972; Torrielli et al. 1974; Wechsler and Wechsler 1951; Wertham 1932; Winek et al. 1973).

In one case report, circumstances following ingestion of white phosphorus allowed for estimation of dose (Hann and Veale 1910). A woman consumed ≈3.9 g of rat poison containing 4% white phosphorus, but did not vomit until the second day after the poisoning, and the vomitus at that time was clear. Thus, little or none of the white phosphorus ingested was lost due to vomiting. The estimated single dose was 2 mg/kg/day. Four days after ingesting the rat poison, the woman died. The cause of death was not reported, but autopsy revealed fatty degeneration and cell transformation in the liver (Hann and Veale 1910).

In case reports of 56 individuals intentionally ingesting large quantities of white phosphorus (0.19-6.3 g) in rat poison, 48.2% of the individuals died, with a 90% death rate in patients ingesting ≥1.57 g of phosphorus (Diaz-Rivera et al. 1950). Because white phosphorus at these oral exposure levels induced rapid vomiting, the doses for these case reports could not be estimated. In patients that died, symptoms prior to death included irreversible vascular collapse; cyanosis, ashen skin color, and deep pallor (probably secondary to vascular collapse); coma; abnormal electrocardiogram readings; evidence of extreme liver and kidney damage, and hypoglycemia (possible secondary to liver damage); and delirium, psychosis, and hallucinations (possibly secondary to brain damage). The cause of death was not reported for each patient, but appeared in most cases to be related to irreversible failure of the liver, kidney, brain, and/or cardiovascular system (Diaz-Rivera et al. 1950). In other case reports, autopsy of patients dying from white phosphorus poisoning nearly always revealed severe damage to one or more of those four systems

(Diaz-Rivera et al. 1961; Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; Rao and Brown 1974; Wechsler and Wechsler 1951; Wertham 1932). In some cases, pulmonary edema and/or congestion were observed at autopsy (Rao and Brown 1974; Wechsler and Wechsler 1951). In studies reporting the specific cause of death, death was attributed to cardiopulmonary arrest (Diaz-Rivera et al. 1950; Rao and Brown 1974; Simon and Pickering 1976; Winek et al. 1973), peripheral vascular collapse (Diaz-Rivera et al. 1950,1961), liver failure (Diaz-Rivera et al. 1961; McCarron et al. 1981), hypoglycemia (Diaz-Rivera et al. 1961), and gastrointestinal hemorrhage and hemorrhagic bronchopneumonia (Winek et al. 1973).

No deaths were reported in children treated with 0.0264.158 mg/kg/day white phosphorus for as much as 26 months (Compere 1930a; Phemister 1918). An infant became seriously ill during treatment with 0.083 mg/kg/day white phosphorus (timed-weighted average dose for 6 months), but recovered entirely following discontinuation of the dose (Sontag 1938).

Humans occupationally exposed to phosphorus probably ingested some airborne white phosphorus. In a study of 71 humans occupationally exposed to fumes/vapors and paste containing white phosphorus, oral exposure to phosphorus passed from hand to mouth was likely, because the workers constantly handled a paste containing 4-6% white phosphorus, and washroom facilities at the plants were inadequate (Ward 1928). White phosphorus-related deaths occurred in 0 of 44 and 2 of 27 of the workers exposed for intermediate and chronic durations, respectively. In the two cases of death, the workers died from complications related to phossy jaw, a degenerative condition affecting the soft tissue, bones, and teeth of the oral cavity. In this condition, the toxic effects of white phosphorus probably result from the local irritant action of white phosphorus on tissues in the mouth. Thus, white phosphorus paste passed from hand to mouth and the local action of airborne white phosphorus on the oral cavity may have contributed to the development of phossy jaw, and subsequent death, of these two workers. It is not known whether white phosphorus ingested and absorbed into the systemic circulation contributed to the development of phossy jaw in the two workers that died (Ward 1928). Details of this study are provided in Section 2.2.2.2.

A mortality rate of 30% was observed in Wistar rats treated by gavage with 6 mg/kg white phosphorus (Torrielli et al. 1974). The oral LD_{50} value for Charles-River rats was 3.03 mg/kg for females and 3.76 mg/kg for males (Lee et al. 1975). A mortality rate of 20-35% was observed in mice treated by gavage with 5-6 mg/kg (Hurwitz 1972). LD_{50} values of 4.82 mg/kg and 4.85 mg/kg were reported for

female and male mice, respectively (Lee et al. 1975). In two separate one-generation reproduction studies in rats (IRDC 1985; Bio/dynamics 1991), 30-47% and 53%, respectively, of pregnant females treated by gavage with 0.075 mg/kg/day for 145-204 days (intermediate duration) died (or were killed due to morbidity) in late gestation or during parturition; dams exposed to 0.015 mg/kg/day for similar durations did not have an increased mortality rate (IRDC 1985). Compound-related deaths were not observed in male rats exposed to 0.075 mg/kg/day for similar durations (Bio/dynamics 1991; IRDC 1985).

Mortality was observed in 9 of 21 dogs treated once by gavage with an unknown quantity of white phosphorus from firecrackers (Dwyer and Helwig 1925). A cat died 2 hours after ingesting an unknown amount of white phosphorus (Frye and Cucuel 1969).

The LD_{50} values and doses associated with death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Systemic effects of white phosphorus in humans and animals after oral exposure are discussed below. The highest NOAEL value and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

No studies were located regarding ocular effects in humans or animals after oral exposure to white phosphorus.

Respiratory Effects. Studies on respiratory effects following acute oral exposure of humans to white phosphorus were limited to case reports of intentional or accidental consumption of materials containing white phosphorus. Although intake of phosphorus was often reported, dose could be estimated for only one study (Hann and Veale 1910), because vomiting and/or gastric lavage nearly always occurred soon after poisoning, expelling much of the ingested phosphorus from the body.

Tachypnea (increased respiratory rate; 48 breaths/minute) was observed in a woman consuming rat poison containing 4% white phosphorus (Hann and Veale 1910); the woman apparently did not vomit until the second day, and the vomitus was clear. The estimated dose was 2 mg/kg. Four days after ingesting the rat

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Human	once				2 (1/1 died)	Hann and Veale 1910
2	Rat (Charles River CD)	once (GO)				3.03 (LD_{50}-female) 3.76 (LD_{50}-male)	Lee et al. 1975
3	Rat (Wistar)	once (GO)				6 (3/10 died)	Torrielli et al. 1974
4	Mouse (Swiss)	once (GO)				4.82 (LD_{50}-female) 4.85 (LD_{50}-male)	Lee et al. 1975
5	Mouse (Swiss-Webster)	once (GO)				6 (6/17 died by 3 days post-dosing)	Hurwitz 1972
6	Mouse (Swiss-Webster)	once (GO)				5 (20% died after 48 hours)	Hurwitz 1972
	Systemic						
7	Human	once	Gastro		5 (nausea, abdominal pain, vomiting)		Fletcher and Galambos 1963

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
8	Human	once	Gastro		10.2	(nausea, vomiting, and diarrhea)			Fletcher and Galambos 1963
			Hepatic		10.2	(prothrombin time increased to 85 seconds, enlarged liver, increased serum bilirubin, jaundice, and prominant periportal necrosis)			
			Other		10.2	(ascites)			
9	Human	once	Resp				2	(increased respiratory rate)	Hann and Veale 1910
			Cardio				2	(elevated pulse rate to 120, subcutaneous hemorrhages on lower trunk and extremities, hemorrhages of omentum and mesentery in wall of gall bladder)	
			Gastro				2	(vomiting, hemorrhage)	
			Hepatic				2	(acute fatty degeneration and cell transformation)	
			Renal		2	(slight microscopic changes not described)			

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
10	Human	once	Cardio				23	(cardiac arrhythmias decreased blood pressure, and altered EKG readings)	Matsumoto et al. 1972
			Gastro		23	(vomiting, nausea, and diarrhea)			
			Hepatic		23	(increased AST and LDH)			
			Renal		23	(proteinuria and increased urobilinogen)			
11	Human	once	Gastro		6.7	(vomiting, abdominal pain)			McCarron et al. 1981
12	Human	once	Gastro		3	(vomiting and nausea)			Rubitsky and Myerson 1949
13	Human	once (F)	Cardio				7	(circulatory failure and undetectable blood pressure)	Caley and Kellock 1955
			Gastro		7	(vomiting)			
			Hemato				7	(severe anemia requiring blood tranfusion)	
			Hepatic				7	(acute hepatic failure with jaundice, enlarged liver, and greatly increased serum bilirubin)	
			Renal				7	(scanty urine, high levels of albumin and bile pigments in urine, increased blood urea)	
			Other		7	(low serum calcium and potassium levels)			

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		Serious (mg/kg/day)	Reference
14	Human	once (F)	Cardio		8.36	(altered ECG-depression of T waves)		Ehrentheil 1957
			Gastro		8.36	(abdominal cramps and vomiting)		
			Hemato		8.36	(decreased WBC count, decreased percentage of neutrophils, bleeding in nostril)		
			Hepatic		8.36	(jaundice, liver enlargement, increased prothrombin time)		
15	Human	once (W)	Cardio		21.4	(moderate T wave abnormalities)		Newberger et al. 1948
			Gastro		21.4	(vomiting, abdominal cramps, nausea)		
			Hemato		21.4	(transient leukopenia and neutropenia)		
			Hepatic		21.4	(transient abnormal cephalin flocculation test)		
			Renal		21.4	(abnormal BUN, non-protein nitrogen levels)		
16	Rat (Sprague-Dawley)	once (GO)	Hepatic		6	(decreased protein synthesis)		Barker et al. 1963
			Other		6	(decreased pancreatic protein synthesis)		

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
17	Rat (Sprague-Dawley)	once (GO)	Hepatic		10	(increased triglycerides, disaggregation of polyribosomes)			Pani et al. 1972
18	Rat (Wistar)	once (GO)	Hepatic				7.5	(severe fatty degeneration, foci of necrotic cells, increased hepatic triglyceride levels, vesiculation and dispersion of ribosomal granules in the endoplasmic reticulum, increased AST)	Ghoshal et al. 1969
			Other		7.5	(deceased plasma triglyceride levels)			
19	Rat (Wistar)	once (GO)	Hepatic		10	(transient increased triglyceride, AST and ALT)			Paradisi et al. 1984
20	Rat (Wistar)	once (GO)	Hepatic		7.9	(increased fatty acids, cholesterol, phospholipids, 31% increase in liver weight)			Seakins and Robinson 1964
21	Mouse (Swiss-Webster)	once (GO)	Hepatic		7.5	(BSP retention increased 100% after fasting overnight)			Hurwitz 1972
22	Mouse (Swiss-Webster)	once (GO)	Hepatic		5	(BSP retention in blood increased 106% after an initial 24 hour fasting period)			Hurwitz 1972
			Bd Wt		6	(37% decrease in body weight after 4 days after an initial 24 hour fasting period)			

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
23	Dog (NS)	13-14 d 1x/d (GO)	Hepatic				0.2	(impaired liver functions as indicated by decreased serum vitamin A levels; increased prothrombin time and BSP retention; increased urinary excretion of administered choline)	Sigal et al. 1954
	Neurological								
24	Human	once					2	(restlessness and semi-consciousness)	Hann and Veale 1910
	Reproductive								
25	Human	once					2	(uterine hemorrhaging, miscarriage)	Hann and Veale 1910
	Developmental								
26	Rabbit (NS)	9 d (C)			0.3	("phosphorus bands" of increased density in the metaphysis of the tibia and fibula)			Adams 1938a
	INTERMEDIATE EXPOSURE								
	Death								
27	Rat (Charles River COBS CD)	204 d (GO)					0.075	(16/30 died during late pregnancy)	IRDC 1985
28	Rat (CRL:CD)	145 d (G)					0.075	(30-47% mortality during late pregnancy)	Bio/dynamics 1991

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
	Systemic						
29	Human	184 d 7d/wk 1x/d (F)	Hemato	0.83			Sontag 1938
			Bd Wt		0.083 (no gain in body weight for approximately 70 days, decreased appetite)		
30	Rat (Charles River COBS CD)	204 d; 80d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21 ; 10 d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; (GO)	Resp	0.075			IRDC 1985
			Cardio	0.075			
			Gastro	0.075			
			Musc/skel	0.075			
			Hepatic	0.075			
			Renal	0.075			
			Other	0.075			

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference
31	Rat (CRL:CD)	145 d; 80d (pre-mating) 1-21 d (mating) Gd 0-23 Ld 1-21 (G)	Cardio	0.075					Bio/dynamics 1991
			Hepatic		0.075	(slight to moderate necrosis in pregnant rats)			
			Renal	0.075					
			Other	0.075					
32	Rabbit (NS)	<5 mo (GO)	Hepatic		0.25	(eosinophilic granules and hyaline reticulum in hepatocytes)	0.66	(cirrhosis)	Mallory 1933
33	Pig (Duroc-Hampshire cross)	4 wk 5 d/wk (GO)	Hepatic	0.6					Peterson et al. 1991
34	Pig (Duroc-Hampshire cross)	5 d/wk 12 wk (GO)	Hepatic				0.6	(increase in collagenous protein, incomplete bridging fibrosis, widened fibrous bands, thickened and irregular septa and sinusoidal fibrosis)	Peterson et al. 1991
35	Pig (Duroc-Hampshire cross)	5 d/wk 16 wk (GO)	Hepatic				0.6	(cirrhosis)	Peterson et al. 1991
36	Pig (Duroc-Hampshire cross)	8 wk 5 d/wk (GO)	Hepatic		0.6	(thickened fibrous septa)			Peterson et al. 1991

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		Serious (mg/kg/day)		Reference
37	Gn pig (NS)	35 wk 2 or 4x/wk (GO)	Hepatic				0.75	(moderate to marked fibrosis, parenchymal fatty metamorphosis, slight bile duct proliferation, hypertrophy, atrophy)	Ashburn et al. 1948
38	Gn pig (NS)	<5 mo (GO)	Hepatic		0.25	(eosinophilic granules and hyaline reticulum in hepatocytes)	0.66	(cirrhosis)	Mallory 1933
	Neurological								
39	Human	184 d 7d/wk 1x/d (F)			0.083	(lethargy, decreased appetite)			Sontag 1938
40	Rat (Charles River COBS CD)	204 d; 80d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; 10d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; (GO)		0.075					IRDC 1985

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
41	Rat (CRL:CD)	145 d; 80d (pre-mating) 1-21 d (mating) Gd 0-23 Ld 1-21 (G)				0.075 (tremors during late pregnancy)	Bio/dynamics 1991
	Reproductive						
42	Rat (Charles River COBS CD)	204 d; 80d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; 10 d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; (GO)		0.015[b]		0.075 (increased number of stillborn pups)	IRDC 1985
43	Rat (CRL:CD)	145 d; 80d (pre-mating) 1-21 d (mating) Gd 0-23 Ld 1-21; (G)		0.075			Bio/dynamics 1991

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)	Reference
	Developmental							
44	Human	121 d 7 d/wk 2x/d (C)			0.119	(heavy phosphorus bands in bones in a child)		Compere 1930
45	Human	184 d 7d/wk 1x/d (F)			0.083	(broad bands of increased density at the ends of all long bones in a child)		Sontag 1938
46	Rat (Charles River COBS CD)	204 d; 80d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; 10d (pre-mating) 15 d (mating) Gd 1-21 Ld 1-21; (GO)		0.075				IRDC 1985
47	Rat (CRL:CD)	145 d; 80d (pre-mating) 1-21 d (mating) Gd 0-23 Ld 1-21; (GO)		0.075				Bio/dynamics 1991
48	Rat (Wistar)	16 d (F)			1.25	(impairment of osteocytic osteolysis and chondrolysis)		Whalen et al. 1973

TABLE 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)

Key [a] to figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
49	Rabbit (NS)	13-107 d 1x/d (C)				0.3 (decreased growth of the tibial diaphysis, abnormal microscopic histology of epiphyseal cartilage plate and metaphyseal zone)	Adams and Samat 1940

[a] The number corresponds to entries in Figure 2-2.

[b] An intermediate oral Minimal Risk Level (MRL) of $2X10^{-4}$ mg/kg/day was derived. The MRL was actually based on a NOAEL of 0.015 mg/kg/day since 0.075 mg/kg/day was associated with hepatic effects in the Bio/dynamics (1991) study (see text). The dose was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability) resulting in an MRL of $2X10^{-4}$ mg/kg/day.

[c] ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSP = bromosulfophthalein; BUN = blood urea nitrogen; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d=day(s); Derm = dermal; ECG or EKG = electrocardiogram; (F) = feed; (G) = gavage-not specified; Gastro = gastrointestinal; (GO) = gavage-oil; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; kg = kilogram; Ld = lactation day; LDH = lactate dehydrogenase; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; mg = milligram; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; WBC = white blood cell; wk = week(s); x = time(s).

Figure 2-2. Levels of Significant Exposure to White Phosphorus - Oral

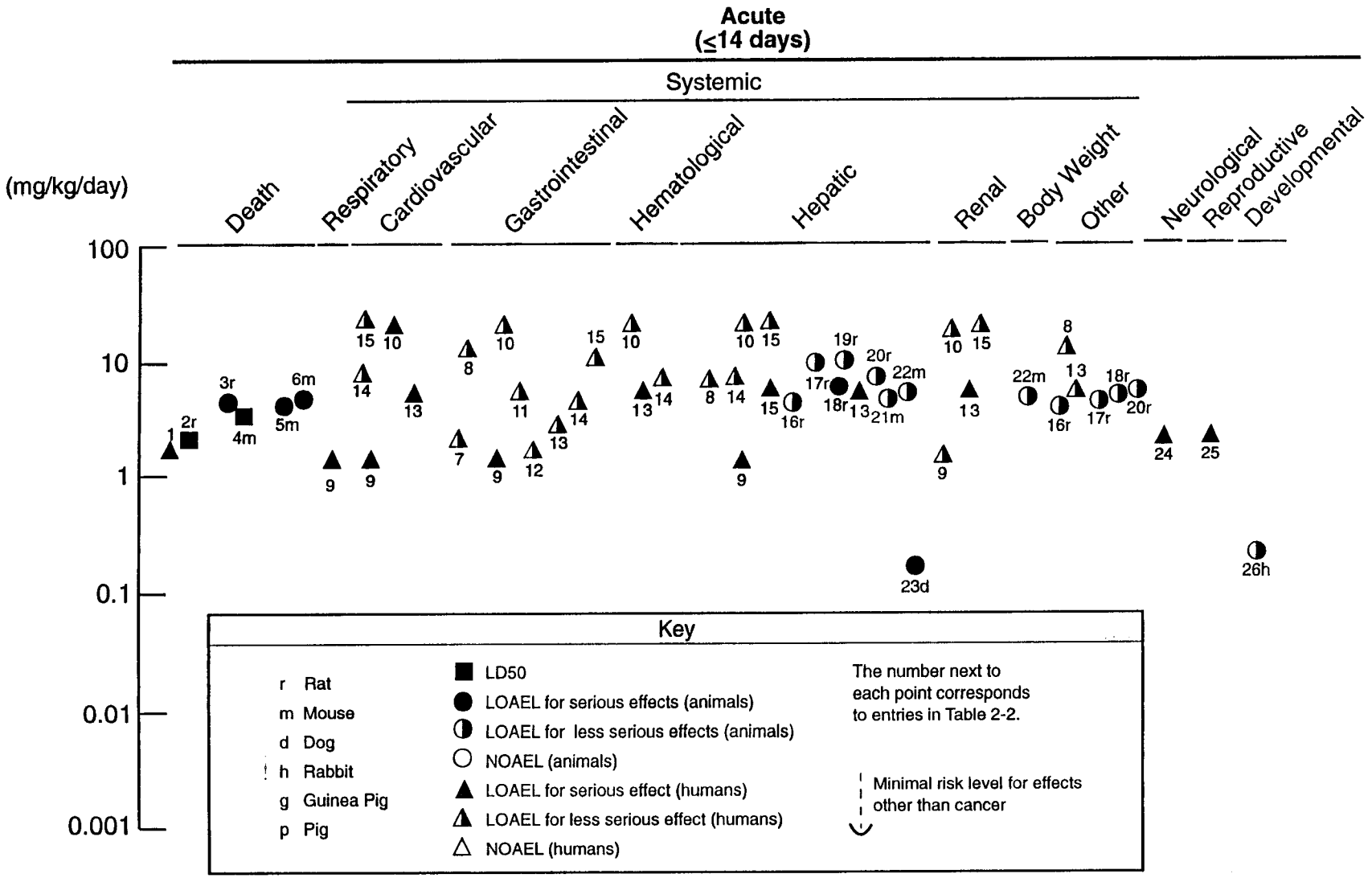
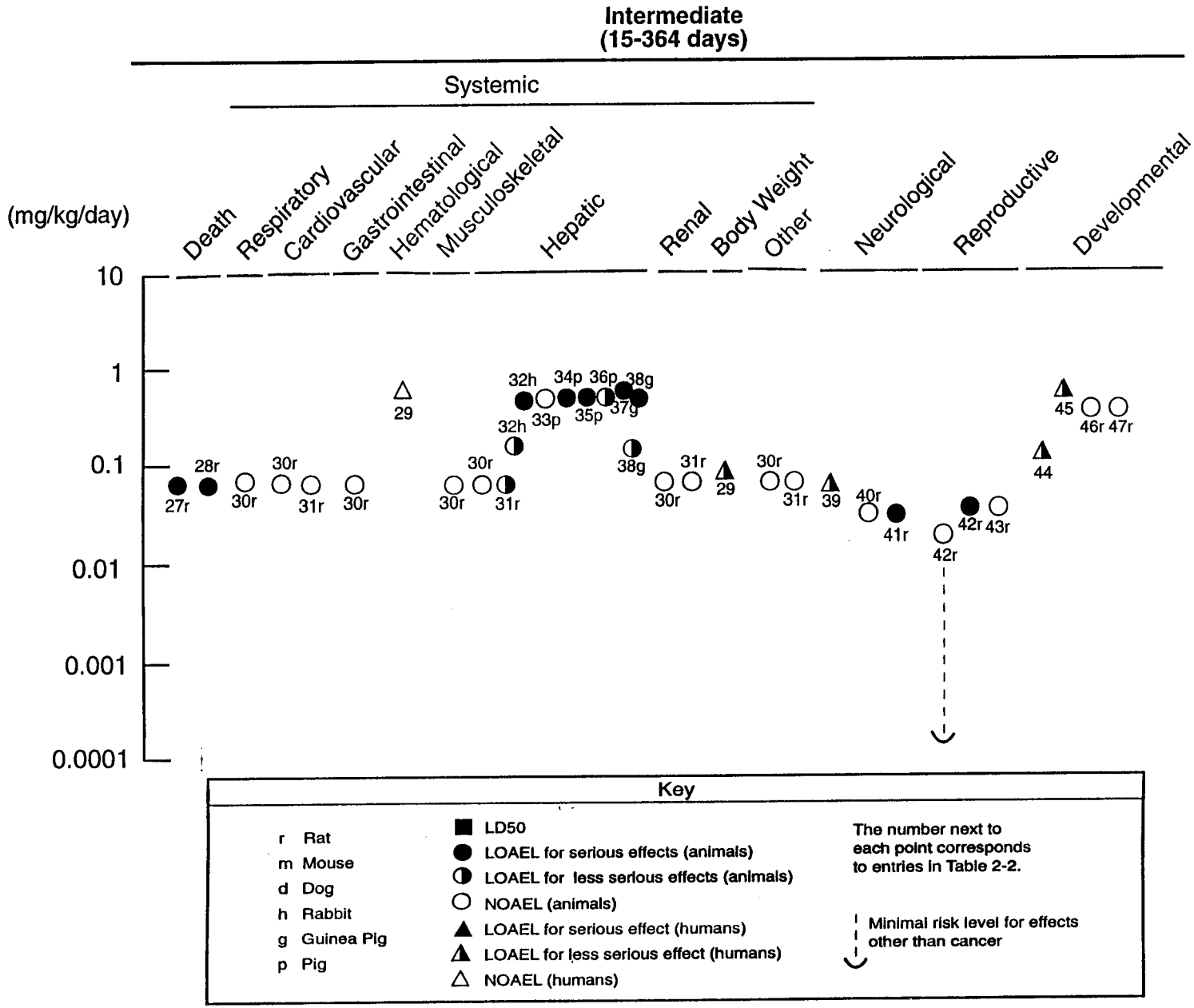


Figure 2-2. Levels of Significant Exposure to White Phosphorus - Oral (continued)



poison, the woman died, apparently from liver failure. Autopsy showed that the pleural cavity was filled with a dark fluid, but no histological abnormalities were observed in the lungs (Hann and Veale 1910).

In the following studies, no doses could be estimated for respiratory effects because of vomiting and/or gastric lavage. In a case report involving ingestion of rat poison containing white phosphorus, the patient arrived at a hospital in a coma and displayed Cheyne-Stokes respirations and rales (Wechsler and Wechsler 1951). The Cheyne-Stokes respirations increased to an extreme degree, and the patient died. Autopsy revealed pulmonary congestion and edema throughout the stroma. Increased respiratory rate (56 breaths/minute) and rales also were observed in an infant ingesting rat poison containing white phosphorus (Rao and Brown 1974). The child died, and autopsy revealed evidence of pulmonary edema. Rales were observed in a child ingesting a fatal dose of white phosphorus in fireworks; autopsy indicated that the lungs were normal except for some fibrous adhesions (Dwyer and Helwig 1925). Hemorrhagic bronchopneumonia was observed following autopsy of a man ingesting a fatal dose of rat poison containing white phosphorus (Winek et al. 1973). Autopsy of a child who died following ingestion of a firecracker revealed fatty deposition in parenchyma, bronchial epithelium, and tracheal epithelium and cartilage (Humphreys and Halpert 1931). Death from cardiopulmonary failure was reported for a 63-year-old woman (Winek et al. 1973), a 2-year-old boy (Simon and Pickering 1976), and a 3-year-old girl (Simon and Pickering 1976) following ingestion of white phosphorus in rat poison; a respiratory rate of 44 breaths/minute was initially observed in the girl (Simon and Pickering 1976). Increased respiratory rate was observed prior to death in two case reports involving ingestion of rat poison (Talley et al. 1972; Winek et al. 1973). Shallow respirations and cyanosis were observed prior to death in an adult female following ingestion of rat/roach poison containing white phosphorus (Rubitsky and Myerson 1949). Rales were observed 1 day after intentional ingestion of rat poison by a 30-year-old man; 2 days later the patient went into shock but survived the poisoning and eventually recovered (Pietras et al. 1968).

No treatment-related respiratory effects were reported in children treated with white phosphorus for intermediate durations.

No treatment-related microscopic changes were observed in the lungs of rats exposed to 0.2 mg/kg/day white phosphorus in the diet for a chronic duration (Fleming et al. 1942) or 0.075 mg/kg/day phosphorus by gavage for an intermediate duration (LRDC 1985). Heavy breathing and apnea were reported following ingestion of a fatal quantity of white phosphorus by a cat (Frye and Cucuell969). Necropsy revealed hyperemia, hemorrhage and edema in the lungs.

2. HEALTH EFFECTS

Cardiovascular Effects. Alterations in electrocardiograms, such as altered or inverted T waves and changes in the QRS complex, and other cardiac changes, such as tachycardia, arrhythmias, atrial fibrillation, and decreased ventricular contractility, have been observed in individuals accidentally or intentionally ingesting a single dose of white phosphorus (Dathe and Nathan 1946; Diaz-Rivera et al. 1950, 1961; Dwyer and Helwig 1925; Ehrentheil 1957; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Simon and Pickering 1976; Talley et al. 1972). Damage to the myocardium was verified by a number of cases in which histological examination of the heart was performed. Prominent cross striations in the myocardium (Dwyer and Helwig 1925), fatty infiltration of muscle (Diaz-Rivera et al. 1961; Humphreys and Halpert 1931; Wertham 1932), necrosis of myocardium (Wechsler and Wechsler 1951), markedly dilated cardiac chamber (Rao and Brown 1974), and interstitial edema of the myocardium and vacuolation of cells (Talley et al. 1972) have been observed. Because of vomiting and gastric lavage, doses cannot be calculated from the human studies. No cardiac effects were reported in longer term human studies.

In addition to the effects on the heart, a number of vascular effects have been observed in humans acutely exposed to white phosphorus. A markedly decreased or undetectable blood pressure (Caley and Kellock 1955; Dathe and Nathan 1946; McCarron et al. 1981; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951), vascular collapse (Diaz-Rivera et al. 1950, 1961), undetectable or decreased pulse (Dwyer and Helwig 1925; Rubitsky and Myerson 1949), and increased pulse (Dathe and Nathan 1946; Hann and Veale 1910; McCarron et al. 1981; Wechsler and Wechsler 1951) have been observed. In addition, individuals have died following cardiopulmonary arrest (Simon and Pickering 1976; Winek et al. 1973), which may be due to effects on the heart or vascular system. A dose of 2 mg/kg/day for vascular effects was identified from the Hann and Veale (1910) report of a woman ingesting a single dose of white phosphorus. Dose levels cannot be estimated for the other case reports. Hemorrhaging in internal organs, as well as the appearance of petechial hemorrhages on the skin, have been reported in a number of acute human exposure cases (Hann and Veale 1910; Humphreys and Halpert 1931; Winek et al. 1973). It is not known whether these effects are due to impairment of the integrity of the blood vessels or due to damage of the affected organ (e.g., liver, stomach) itself.

In rats administered 0.075 mg/kg/day white phosphorus for an intermediate duration, no histological alterations were observed in the heart (Bio/dynamics 1991; IRDC 1985). In rats exposed for an intermediate duration to an unknown concentration of airborne white phosphorus from the furnace room

of a phosphorus factory, an increase in permeability of capillary walls, lesions in the walls of blood vessels and evidence of impaired microcirculation were observed in the mouth (Ruzuddinov and Rys-Uly 1986). These effects probably resulted from the local action of white phosphorus on the oral cavity.

Gastrointestinal Effects. Most of the human case reports listed vomiting as an early effect following ingestion of a single high dose of white phosphorus (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 193 1; Matsumoto et al. 1972; McCarron et al. 1981; McIntosh 1927; Newburger et al. 1948; Pietras et al. 1968; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951; Winek et al. 1973). The doses that induced vomiting ranged from 2 to 23 mg/kg (Caley and Kellock 1955; Ehrentheil 1957; Fletcher and Galambos 1963; Harm and Veale 1910; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Rubitsky and Myerson 1949). Vomiting generally started within hours after ingesting the white phosphorus, and sometimes continued for many days. Other gastrointestinal effects included abdominal cramps or pain (often severe) (Dwyer and Helwig 1925; Ehrentheil1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Humphreys and Halpert 1931; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968), vomiting blood and/or pieces of the gastric mucosa (Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Rubitsky and Myerson 1949), necrosis and erosion of mucosa in the esophagus, stomach, duodenum, and jejunum (Wechsler and Wechsler 1951), and gastrointestinal hemorrhage (Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; Wertham 1932, Winek et al. 1973). These effects, with the exception of necrosis, were probably due to the irritating effects of white phosphorus on the mucosa of the gastrointestinal tract. Vomitus often contained white phosphorus, indicating that vomiting generally occurred before all white phosphorus and/or its oxidation products had been absorbed.

No gastrointestinal effects were reported in children receiving treatment with 0.026-0.158 mg/kg/day white phosphorus for as much as 26 months (Phemister 1918; Compere 1930a). An infant became seriously ill during treatment with 0.083 mg/kg/day white phosphorus (6-month time-weighted average dose), but recovered entirely following discontinuation of the treatment (Sontag 1938). No vomiting or diarrhea was observed during the treatment period.

Gastrointestinal effects were not reported in studies examining longer term occupational exposure to white phosphorus (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944; Ward 1928).

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Erosion and hemorrhages in tissue in the esophagus and stomach were observed following ingestion of a fatal unknown quantity of white phosphorus by a cat (Frye and Cucuel 1969). Vomiting was observed in 6 of 21 dogs treated by gavage with an unknown quantity of white phosphorus from firecrackers (Dwyer and Helwig 1925). No gross or microscopic alterations were observed in the gastrointestinal tract of rats treated by gavage with 0.075 mg/kg/day for 204 days (IRDC 1985).

Hematological Effects. Hematological effects have been reported in a number of case histories of individuals accidentally or intentionally ingesting a single dose of white phosphorus contained in rat (and cockroach) poisons or fireworks. Because most of the individuals vomited or received gastric lavage shortly after ingestion, the amount of white phosphorus available for absorption is not known. Increases in erythrocyte levels (Diaz-Rivera et al. 1950) and hemoglobin levels (Diaz-Rivera et al. 1950; McIntosh 1927); decreases in erythrocyte levels (Dwyer and Helwig 1925) and hemoglobin and/or hematocrit levels (Simon and Pickering 1973); and anemia (Caley and Kellock 1955) have been observed in some of these individuals. A number of individuals had no change in erythrocyte parameters (Ehrentheil 1957; Fletcher and Galambos 1963; Newburger et al. 1948; Simon and Pickering 1976). The decreases in erythrocyte parameters may be a reflection of the hemorrhages observed in specific tissues (e.g., gastrointestinal tract, liver, skin) (Dathe and Nathan 1946; Hann and Veale 1910; Humphreys and Halpert 1931; Wechsler and Wechsler 1951; Winek et al. 1973). In addition to these changes in erythrocyte parameters, changes in total or differential leukocyte levels were reported in a number of individuals acutely exposed to white phosphorus. Decreases in total leukocyte levels (Diaz-Rivera et al. 1950; Ehrentbeil 1957; Fletcher and Galambos 1963; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968) and decreases or increases in the percentage of polymorphonuclear leukocytes (neutrophils) have been reported (Ehrentheil 1957; McCarron et al. 1981; Pietras et al. 1968). No changes in leukocyte parameters were observed in a number of individuals (Fletcher and Galambos 1963; Newburger et al. 1948; Simon and Pickering 1976). Abnormally low protbrombin times or levels (hypo-prothrombinemia) and a moderate decrease in platelets were observed in a number of individuals ingesting single doses of white phosphorus (Caley and Kellock 1955; Dathe and Nathan 1946; Ehrentheil 1957; Fletcher and Galambos 1963; McCarron et al 1981). Most of the patients developed hypoprothrombinemia within 4-8 days (McCarron et al. 1981). This is probably secondary to the liver damage rather than a direct effect on platelets. No changes in hematological parameters were observed in a child ingesting phosphorized cod liver oil (0.083 mg/kg/day phosphorus) for 184 days (Sontag 1938). Anemia and leukopenia were observed in individuals occupationally exposed to white phosphorus chronically (Ward 1928). It is likely that workers were exposed by the inhalation, oral, and dermal routes.

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Because there is very little consistency regarding the length of time that elapsed between ingestion and measurement of hematological parameters and the doses cannot be calculated, it is difficult to compare the results of different studies. There is insufficient information to determine whether white phosphorus has a direct effect on erythrocytes and/or leukocytes. The effects observed may be secondary effects. The decrease in erythrocyte, hemoglobin, hematocrit and leukocyte levels may be secondary to hemorrhaging or hematoemesis (Diaz-Rivera et al. 1950; Rubitsky and Myerson 1949) and the increase in erythrocytes and hemoglobin may be a compensatory mechanism due to tissue anoxia. However, since red blood cell synthesis takes 3-5 days, the observed effects may be direct if they are occurring within l-2 days.

A slight decrease in hemoglobin levels and increase in eosinophil levels were observed in a 30-year-old man who performed magic shows that involved placing white phosphorus pellets in the mucobuccal folds of his mouth for 15 years. He had no other personal habits that might adversely affect his health except for occasional bidi smoking for about 8 years (Jakhi et al. 1983).

Information on hematological effects in animals is limited to one study in which a marked increase in total leukocyte levels and the percentage of monocytes were observed in a guinea pig acutely exposed to 0.9-2.4 mg/kg/day of white phosphorus in a complex dosing regimen (Lawrence and Huffman 1929). The study authors did not specify at which doses the effects occurred.

Musculoskeletal Effects. Following ingestion of a fatal dose of rat poison containing white phosphorus by a woman, autopsy revealed fatty infiltration of essentially all tissues, including the musculature (Wertham 1932). Similar effects were reported following the death of a male child who accidentally ingested a firecracker containing white phosphorus; autopsy revealed fatty deposition in many tissues, included the diaphragmic muscle (Humphreys and Halpert 1931).

Humans occupationally exposed to white phosphorus probably ingested some airborne white phosphorus. In a study of 71 humans occupationally exposed to white phosphorus, oral exposure to white phosphorus via hand-to-mouth activity was likely because the workers constantly handled a paste containing 4-6% white phosphorus and washroom facilities were inadequate (Ward 1928). In workers exposed to white phosphorus for intermediate durations, 2 of 44 developed phossy jaw, described as slight necrosis in the lower jaw. In workers exposed to white phosphorus for chronic durations, 12 of 27 developed phossy jaw, with necrosis ranging from slight to severe; 2 of the 12 workers developing phossy jaw died from complications related to the necrosis. The progression of the disease was similar in the cases described,

usually beginning with the extraction of one or more teeth, poor healing of the socket, followed by necrosis of tissue in the jaw with severe pain and infection. Treatment consisted of repeated removal of destroyed bone tissue and teeth, draining of abscesses, and reconstructive surgery. In severe cases, extensive removal of necrotic bone tissue led to permanent disfigurement. However, exposure levels of white phosphorus were not reported (Ward 1928). Case reports of development of phossy jaw following intermediate or chronic occupational exposure to unreported levels of white phosphorus and phosphorus compounds describe a similar progression of symptoms, with similar results; even in cases of early diagnosis and prompt, intensive treatment of phossy jaw, recovery often took several years (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944).

It is likely that the effect of white phosphorus in the oral cavity is local, resulting from contact of "inhaled" white phosphorus particles with tissue in the mouth. White phosphorus may affect the oral mucosa. Dull, red spots in the oral mucosa, an early sign of phossy jaw, have been reported to precede its development in occupationally exposed workers (Kennon and Hallam 1944). The oral mucosa of workers exposed to white phosphorus has been described as having a dull, red, unhealthy appearance (Hughes et al. 1962). Exposed bones may be especially susceptible to the irritating affects of white phosphorus. It is not known whether white phosphorus ingested and absorbed into the systemic circulation contributed to the development of phossy jaw.

Not all workers exposed to white phosphorus for longer-term durations developed phossy jaw. In a study of 71 workers exposed to airborne white phosphorus for intermediate or chronic durations, 4.5% and 44%, respectively, developed phossy jaw (Ward 1928). Forty-eight male workers with exposure to white phosphorus ranging from 1 to 17 years were found to be normal and healthy with regards to many parameters, including serum levels of calcium and phosphorus, and bone density; none of the men developed phossy jaw (Hughes et al. 1962). Tooth loss often precedes and accompanies the progression of development of phossy jaw (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944; Ward 1928). Tooth loss during the later stages of phossy jaw clearly results from destruction of the-bone structure supporting the teeth (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944; Legge 1920; Ward 1928). It is not known if tooth loss prior to diagnosis of phossy jaw or early in the development of the condition is related to the white phosphorus exposure. Poor dental hygiene alone can result in tooth loss, and in several case reports some of the workers were described as having poor dental hygiene (Kennon and Hallam 1944). Tooth loss followed by poor healing of the socket often precedes development of the necrosis (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944; Ward 1928),

suggesting that poor dental hygiene and exposure to white phosphorus may both be contributing factors to the development of phossy jaw. In a case report, five men developed "precursor signs" (delayed healing of extracted tooth sites and residual sepsis) of phossy jaw developed following tooth extraction and occupational exposure to white phosphorus (Hughes et al. 1962). However, the condition did not develop into "classical" phossy jaw.

A man was repeatedly exposed to white phosphorus pellets, placed in the right mucobuccal cavity for magic shows, for ≈ 15 years (Jakhi et al. 1983). After ≈ 14.5 years of this type of exposure to white phosphorus, right maxillary molars became loose, and were subsequently lost. This was followed by a lack of healing and development of fistulae in the sockets of the right maxillary molars. White phosphorus necrosis of the jaw developed, with massive necrosis of the maxilla and floor of the antrum on the right side of the mouth; perforations were present through which the maxillary sinus and nasal cavity were visible. No effects were observed on the left side of the maxilla or on the mandible. Radiographs revealed no evidence of pathology in the chest and long bones. The damage to the jaw was probably caused by direct local contact of phosphorus with the soft tissue and bone in the oral cavity.

No microscopic or histological abnormalities were observed in the bone of rats treated by gavage with 0.075 mg/kg/day for 204 days (IRDC 1985). Rats exposed for a chronic duration to 0.2 mg/kg/day white phosphorus in the diet had epiphyseal line thickening and greater extension of trabeculae into the diaphysis of unspecified bones, compared to a control group (Fleming et al. 1942). This study is limited by the failure to specify incidences of effects at interval during dosing and by the failure to state the dosing duration explicitly.

Bone effects were observed in children (Compere 1930a; Phemister 1918; Sontag 1938) and young animals (Adams 1938a, 1938b; Adams and Sarnat 1940; Whalen et al. 1973) following acute and intermediate oral exposure to white phosphorus. Because white phosphorus-related effects were observed in growing bones, these effects were considered developmental effects, and are discussed in. Section 2.2.2.6.

Hepatic Effects. Hepatic effects have been observed in most individuals accidentally or intentionally ingesting a single dose of white phosphorus. These effects include jaundice (Caley and Kellock 1955; Diaz-Rivera et al. 1950, 1961; Ehrentheil 1957; Greenberger et al. 1964; Humphreys and Halpert 1931; McCarron et al. 1981), hepatomegaly (Diaz-Rivera et al. 1950; Fletcher and Galambos 1963; Humphreys

and Halpert 1931; Rao and Brown 1974; Simon and Pickering 1976; Wechsler and Wechsler 1951), increased levels of serum bilirubin (Caley and Kellock 1955; Fletcher and Galambos 1963; McCarron et al. 1981; Pietras et al. 1968), impaired liver function test results (Fletcher and Galambos 1963; Newburger et al. 1948; Pietras et al. 1968; Rubitsky and Myerson 1949), and increases in AST, ALT, and/or lactate dehydrogenase (Ehrentheil 1957; Matsumoto et al. 1972; McCarron et al. 1981; Pietras et al. 1968). In addition to these effects, autopsies or liver biopsies have revealed a number of histological alterations in these individuals. Necrosis (Fletcher and Galambos 1963; Rao and Brown 1974; Wechsler and Wechsler 1951), degeneration (Dwyer and Helwig 1925; Greenberger et al. 1964; Wechsler and Wechsler 1951), fibrosis (Greenberger et al. 1964), hemorrhages (Wechsler and Wechsler 1951), and fatty infiltration (Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; Wertham 1932) have been observed in the liver. In addition to these effects, altered prothrombin time or level has been observed in a number of individuals ingesting a single dose of white phosphorus (Caley and Kellock 1955; Dathe and Nathan 1946; Ehrentheill957; Fletcher and Galambos 1963; McCarron et al. 1981). Prothrombin and other plasma proteins that are required for the efficient progression and regulation of blood coagulation are primarily synthesized in the liver. A deficiency of these proteins is often observed in individuals with severe liver disease. A prolongation of prothrombin time is in part due to this impaired synthesis. Liver function tests were normal in workers chronically exposed to unreported levels of airborne phosphorus (Hughes et al. 1962).

Similar hepatic alterations have been observed in animals acutely exposed to white phosphorus. Increases in AST and ALT levels (Paradisi et al. 1984), impaired liver function tests (Ghoshal et al. 1969; Hurwitz 1972; Sigal et al. 1954) increased liver weight (Ghoshal et al. 1969; Seakins and Robinson 1964), increased hepatic triglyceride levels (Ghoshal et al. 1969; Pani et al. 1972; Paradisi et al. 1984; Seakins and Robinson 1964), decreased protein synthesis (Barker et al. 1963; Seakins and Robinson 1964), disaggregation of polyribosomes (Pani et al. 1972), fatty degeneration (Ghoshal et al. 1969) and necrosis (Ghoshal et al. 1969) have been observed. No NOAEL values for hepatic effects following acute animal exposure were identified. In rats, the LOAEL value for liver effects was 6 mg/kg (Barker et al. 1963); in mice it was 5 mgkglday (Hurwitz 1972); and in dogs it was 0.2 mg/kg/day (Sigal et al. 1954). The liver effects occurred shortly after dosing; 3 hours after dosing, a significant decrease in protein synthesis was observed in the liver (Barker et al. 1963), minimal hepatocytic fatty changes were observed after 4 hours (Ghoshal et al. 1969), and severe hepatocytic fatty changes were observed after 12 hours (Ghoshal et al. 1969).

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The following hepatic effects have been observed in animals orally exposed for an intermediate duration: fatty infiltration in guinea pigs exposed to 0.75 mg/kg/day (Ashbum et al. 1948), presence of eosinophilic granules at 0.25 mg/kg/day and cirrhosis at 0.66 mg/kg/day in rabbits and guinea pigs (Mallory 1933), and fibrosis and cirrhosis in pigs exposed to 0.6 mg/kg for 5 days/week (Peterson et al. 1991). In the Peterson et al. (1991) study, no liver effects were observed after 4 weeks of exposure; after 8 weeks, there were early signs of fibrosis, and after 12 weeks, extensive fibrosis was observed. Exposure to 0.075 mg/kg/day for an intermediate duration resulted in slight-to-moderate liver necrosis in dying pregnant rats (Bio/dynamics 1991), but no hepatic effects in the surviving pregnant rats or in male rats (Bio/dynamics 1991). In another reproduction study, liver effects were not observed in dying pregnant rats exposed to 0.075 mg/kg/day (IRDC 1985). Both studies used similar exposure protocols and similar vehicles; the difference in the occurrence of liver damage between the studies cannot be explained.

Renal Effects. Evidence of severe renal effects have been observed in a number of individuals intentionally or accidentally ingesting a single dose of white phosphorus contained in rat (or roach) poison or fireworks. Proteinuria (Matsumoto et al. 1972; Pietras et al. 1968; Rao and Brown 1974), albuminuria (Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Fletcher and Galambos 1963; McCarron et al. 1981; Rubitsky and Myerson 1949), acetonuria (Pietras et al. 1968), increased urobilinogen (Matsumoto et al. 1972), oliguria (Dathe and Nathan 1946; McCarron et al. 1981; Rao and Brown 1974), increased blood levels of urea and/or nitrogen (Diaz-Rivera et al. 1950, 1961; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Rubitsky and Myerson 1949), and increased blood creatinine levels (Dathe and Nathan 1946; McCarron et al. 1981) have been observed in these individuals. Renal insufficiency may be due to a direct toxic effect of phosphorus on the kidneys or to acute renal tubular necrosis from fluid loss and shock. Patients in shock may have a peculiar pallor and cyanosis. These probably reflect extensive cellular damage with poor perfusion of the capillary beds, and are a prognostic sign of serious health effects (Melamon et al. 1981). Several case reports have reported no alterations in kidney function (Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Simon and Pickering 1976). Histological alterations have also been observed in a number of humans ingesting a single dose of white phosphorus. Fatty changes in the tubules and loop of Henle (Dwyer and Helwig 1925; Humphreys and Halpert 1931; Wertham 1932) and engorged glomeruli and intratubular capillaries (Wechsler and Wechsler 1951) have been observed. Because most individuals vomited shortly after ingesting the white phosphorus or were lavaged, accurate doses cannot be calculated except for one study (Harm and Veale 1910). Histological alterations in the kidney were observed in an

individual ingesting 2 mg/kg/day, but the lesion was not described. Creatinine levels were similar among unexposed workers and workers exposed to white phosphorus for chronic durations (Hughes et al. 1962).

In animals, fatty infiltration in the nephron and subcapsular hemorrhages were observed in dogs acutely exposed to an unspecified amount of white phosphorus (Dwyer and Helwig 1925). No renal effects were observed in rats exposed to 0.075 mg/kg/day for an intermediate duration (Bio/dynamics 1991; IRDC 1985).

No chronic exposure animal studies examining renal effects were located.

Dermal Effects. Transient toxic dermatitis (described as a scalartiniform rash) developed 9 days after a man ingested a near-fatal dose of rat poison (Dathe and Nathan 1946). Edema of eyelids was reported in a 13-month-old child after ingestion of a fatal dose of white phosphorus (Rao and Brown 1974). Subcutaneous hemorrhages were visible in the left foot in a woman after consumption of 3.9 g of rat poison containing 4% phosphorus (Hann and Veale 1910). The woman died 4 days after the initial poisoning. At this time, an enormous subcutaneous hemorrhage was visible below the waist line. In this case report, the woman apparently did not expel (via vomiting) any of the ingested dose. Thus, it is likely that the ingested dose (2 mg/kg) was representative of the effective dose. Scattered blue-green petechiae were observed on the abdomen of a male child following accidental ingestion of a fatal dose of white phosphorus mixed with other ingredients from a firecracker (Humphreys and Halpert 1931). The dose level in this study could not be determined; the firecracker was a red composition of phosphorus mixed with other ingredients and was thought to contain about 10% phosphorus (Humphreys and Halpert 1931).

No studies were located regarding dermal effects in animals after oral exposure to white phosphorus.

Other Systemic Effects. A number of other systemic effects have been observed in humans ingesting a single dose of white phosphorus. The effects that are observed most consistently are hypoglycemia (Diaz-Rivera et al. 1950; McCarron et al. 1981; McIntosh 1927; Wechsler and Wechsler 1951), an increase in body temperature (mild pyrexia or fever) (Dathe and Nathan 1946; McIntosh 1927), and a decrease in plasma calcium, potassium, and/or sodium levels (Caley and Kellock 1955; McCarron et al. 1981; Rao and Brown 1974). It is unclear whether the fever seen is a symptom of phosphorus poisoning or a result of the treatment involved. In addition to these effects, metabolic acidosis (Rao and Brown 1974), hypothermia (Simon and Pickering 1976), damage to the spleen (Greenberger et al. 1964), ascites

(Fletcher and Galambos 1963), fatty infiltration of the pancreas (Humphreys and Halpert 193 l), and necrosis of the adrenal medulla and cortex (Wechsler and Wechsler 1951) have been observed. In a child ingesting 0.083 mg/kg/day white phosphorus for an intermediate duration, decreased appetite, impaired body weight gain, and poor turgor (fullness or tension produced by the fluid content of blood vessels, capillaries, and cells) were observed (Sontag 1938). Serum glucose levels were decreased in workers occupationally exposed to white phosphorus for a chronic duration. It is likely that the workers were exposed by the inhalation, oral, and dermal routes (Ward 1928).

In dogs acutely exposed to an unspecified amount of white phosphorus, hypoglycemia was observed (Williamson and Mann 1923). Rats received intermittent exposure to the atmosphere in the furnace room of a phosphorus factory for 14 months (Ruzuddinov and Rys-Uly 1986). Histology of rats killed monthly revealed progressive morphological degeneration of the tongue and oral mucosa of the cheek, gum, and hard palate. Epithelium and connective tissue from different parts of the oral cavity responded similarly to the treatment. Changes in the epithelial layer, observed after only 1 month of exposure, included increases in keratinization and numbers of cell layers, resulting in thickening and hyperkeratosis in the epithelium of the mucosa. Over time, the thickening and hyperkeratosis in the epithelium increased and histological changes were observed in the subepithelial connective tissue base. Eventually, the oral cavity contained areas of thickening of the mucosa from hyperkeratosis and increased epithelial cell layers interspersed with areas of decreased thickness of the epithelial layer due to atrophy, dystrophy, and cellular necrosis. At this time, adverse changes in the subepithelial connective tissue were considered pronounced. These effects occurred in most of the animals exposed to the atmosphere. It is likely that the observed effects of phosphorus on the oral cavity were local rather than systemic, resulting from direct contact of white phosphorus with tissues in the mouth. The study presented essentially no quantitative data, and the types and exposure levels of chemicals in the atmosphere (thought to contain elementary phosphorus and its inorganic compounds) were not reported (Ruzuddinov and Rys-Uly 1986).

2.2.2.3 Immunological and Lymphoreticular Effects.

There is limited information on the immunotoxicity of white phosphorus; however, there is some information that suggests that the immune system may be a target. Thymic hemorrhages were observed in two young children accidentally ingesting white phosphorus-containing fireworks (Dwyer and Helwig 1925; Humphreys and Halpert 1931). In one of these children, hyperplasia of lymphoid tissue in the intestinal wall and abdominal lymph nodes and hyperplastic lymphoid corpuscles in the spleen were

observed (Humphreys and Halpert 193 1). Decreases in leukocyte levels were reported in a number of case reports involving acute ingestion of rat poison or fireworks containing white phosphorus (Diaz-Rivera et al. 1950; Ehrentheil 1957; Fletcher and Galambos 1963; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968). A decrease (Pietras et al. 1968) or an increase in the percentage of polymorphonuclear leukocytes (neutrophils) (McCarron et al. 1981) were also observed in individuals ingesting white phosphorus. Because the individuals vomited shortly after ingesting the white phosphorus and/or received gastric lavage, doses could not be estimated. In workers exposed to an unknown level of white phosphorus via inhalation, oral, and dermal routes, a decrease in leukocyte levels was observed (Ward 1928).

No studies were located regarding immunological or lymphoreticular effects in animals after oral exposure to white phosphorus.

2.2.2.4 Neurological Effects

A number of case reports of individuals accidentally or intentionally ingesting a single dose of white phosphorus have reported neurological effects. Nonspecific neurological effects including lethargy (Dathe and Nathan 1946; Fletcher and Galambos 1963; McCarron et al. 1981; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Talley et al. 1972), sleepiness (Dwyer and Helwig 1925; Ehrentheil 1957; McCarron et al. 1981; McIntosh 1927), irritability (McCarron et al. 1981), restlessness (Diaz-Rivera et al. 1950; Ehrentheil 1957; Harm and Veale 1910), and hypoactivity (Humphreys and Halpert 1931) have been observed. Other symptoms of neurotoxicity that have been observed include coma or semi-coma (Caley and Kellock 1955; Ehrentheil 1957; Hann and Veale 1910; McCarron et al. 1981; McIntosh 1927; Wechsler and Wechsler 1951), toxic delirium and psychosis (Diaz-Rivera et al. 1950), hemiplegia (Humphreys and Halpert 1931; McCarron et al. 1981), abnormal reflexes (Wechsler and Wechsler 1951), hyperesthesia (Humphreys and Halpert 1931), coarse muscle fasciculations (Caley and Kellock 1955), unresponsiveness to painful stimuli (Simon and Pickering 1976), and marked asterixis (flapping tremor) (Greenberger et al. 1964). In addition to these overt signs of neurotoxicity, histological damage in the brain was observed in four individuals ingesting a single dose of white phosphorus. Based on this limited information, the types of cellular damage can be grouped into four categories: (1) cellular changes resulting from ischemic damage found in the Purkinje cells and cerebral cortical cells of the second and third layer of the cortex (Wertham 1932); (2) direct white phosphorus-induced cellular damage to the dentate nucleus and inferior olives (Wertham 1932); (3) fatty infiltration in the ganglion

cells of the cortex, neuroglial cells, Golgi cells of the cerebellum, and the cells in the pia-arachnoid space (Humphreys and Halpert 1931; Wertham 1932); and (4) cerebral edema (Rao and Brown 1974). It is not known if the cerebral edema observed in this one individual was secondary to the other types of damage. A child treated with 0.083 mg/kg/day white phosphorus for an intermediate duration became lethargic 3 months after beginning treatment and remained lethargic until treatment was discontinued ≈70 days later. Following cessation of treatment, the child recovered very rapidly (Sontag 1938).

Overt signs of neurotoxicity were observed in a cat ingesting a single lethal dose (Fry and Cucuel 1969) and in pregnant rats exposed to a lethal dose (0.075 mg/kg/day) of white phosphorus for an intermediate duration (effects only observed during late gestation of parturition) (Bio/dynamics 1991). Tonoclonic convulsions, increased salivation and weakness were observed in the cat (Frye and Cucuel1969), and tremors were observed in pregnant rats (Bio/dynamics 1991). In another developmental toxicity study (IRDC 1985), no signs of neurotoxicity were observed in pregnant rats.

All LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Because vomiting occurred or the individuals received gastric lavage shortly after ingestion, reliable dose estimations could only be made for one individual acutely exposed to 2 mg/kg/day white phosphorus (Hann and Veale 1910).

2.2.2.5 Reproductive Effects

Extensive uterine hemorrhaging was observed in a 2-month pregnant woman following the intentional ingestion of 2 mg/kg white phosphorus in rat poison (Hann and Veale 1910). Autopsy results showed that the uterus was enlarged containing a hemorrhagic mole, which was consistent with a 2-month pregnancy. No effects on reproductive performance or histological alterations in the ovaries, uterus, testis, or epididymis were observed in rats administered 0.075 mg/kg/day or less in a one-generation reproduction study (Bio/dynamics 1991; IRDC 1985).

The highest NOAEL value and all LOAEL values from each reliable study for effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

A healthy infant was administered phosphorized cod liver oil (reported to contain 1.1 mg "pure" phosphorus per fluid ounce) from ages l-7 months (Sontag 1938). The phosphorized cod liver oil was apparently administered for the prevention of rickets. The time-weighted average dose for the 6-month exposure was 0.083 mg/kg/day. During the first 3 months of treatment, the child appeared clinically normal and grew at a normal rate. From the ages of ≈4 to 6 months, the child became clinically ill, gained essentially no weight, and the rate of growth in height decreased from ≈0.1 to 0.04 cm/day. Following replacement of the treatment with normal, nonphosphorized cod liver oil, the child appeared to recover quickly, and began to grow at a normal rate. Radiograms taken at 6 months of age showed bands of increased density at the end of all the long bones with increased thickness and density also observed in the zones of calcification. Radiograms taken between 9 months and 5 years of age showed bands of increased density in the diaphyses of the long bones, and in the pelvic, metacarpal, and metatarsal bones. This study describes formation of "phosphorus" bands of increased density in the ends of long bones and possible decreased growth in a child exposed to 0.083 mg/kg/day phosphorus for 6 months (Sontag 1938). It should be noted that radiologic densities are common at the growing points of long bones in children. However, lead poisoning, administration of nickel, certain chronic diseases like anemia, and hypervitaminosis D may also produce bands in the ends of bones, but these are much thicker and heavier (Sontag 1938).

A child with Perthes' disease was administered 0.056 mgkg/day of phosphorus for two periods of intermediate duration, separated by a period with no exposure (Phemister 1918). "Phosphorus" bands of increased density developed in the ends in the tibia, fibula, and femur during the two exposure periods, without any improvement in the child's condition. A male child with dyschondroplasia was administered 0.026 and 0.046 mg/kg/day white phosphorus for 3 and 8 months, respectively. "Phosphorus" bands of increased density developed in the tibia, fibula, and femur. The density and thickness of the bands were greater at the high-dose level and longer-treatment period. A male child with osteogenesis imperfecta was administered 0.078, 0.063, and 0.059 mg/kg/day phosphorus for 26,3, and 18 months, respectively, separated by a period of time with no white phosphorus exposure. Treatment with white phosphorus produced marked changes, including bands of increased density at the ends of bones and increased transverse diameters of the shafts of bones in the legs and arms (Phemister 1918). Four children with moderate to severe cases of rickets were treated orally with 0.110-0.158 mg/kg/day white phosphorus for

durations ranging from 64 to 149 days (Compere 1930a). "Phosphorus" bands of increased thickness and density were observed in the long bones of 1 of 2 of the children examined.

An arachitic child was treated with 0.119 mg/kg/day white phosphorus for 82 days (Compere 1930b). Following treatment, the child had a "heavy phosphorus line" and increased density of cortices. Treatment with white phosphorus did not generally improve the condition of the bones in children with rickets. Because these children were sickly, the relevance of the observed effects to potential effects of white phosphorus in normal, healthy children could not be ascertained.

Young, growing rabbits exposed to 0.3 mg/kg/day white phosphorus given as a pill for an acute duration had transverse bands of increased density in metaphyseal regions of the tibia and fibula, compared to a control group (Adams 1938a). However, the percentage of calcium and phosphorus, and the calcium/phosphorus ratio in the metaphyseal and cortical regions of the right tibia was similar between treated and control animals. Young, growing rabbits exposed to 0.3 mg/kg/day white phosphorus given as a pill for an intermediate duration had average growth of the tibia of 0.27 mm/day, compared to 0.36 mm/day in the control group; however, no statistical analysis of the results was reported (Adams and Samat 1940). One rabbit had histological abnormalities in the tibia including decreased size of epiphyseal cartilage plate, as well as increased density in the metaphyseal zone with trabeculae that were greater in number and extended further into the diaphysis to a greater extent, compared to a control rabbit. The trabeculae were associated with a greater amount of calcified cartilage matrix. These effects probably resulted from a decrease in the normal rate of bone resorption during bone growth, resulting in decreased rate of growth of the tibia. Weanling rats exposed to 1.25 mg/kg/day white phosphorus in the feed for an intermediate duration had widening of the metaphyseal trabeculae, broadened metaphysis, and a slightly convex lateral contour of the proximal tibia, compared to a control group (Whalen et al. 1973). Osteocytes were small and elongated compared to those in the control group, and osteocytic osteolysis and chondrolysis were decreased or missing. In the treated rats, metaphyseal trabeculae extended deeper into the diaphysis than in the controls. These effects probably resulted from decreased bone resorption during bone growth, resulting in widening trabeculae and a denser metaphysis. Very similar results were observed in studies on growing rats (Adams and Sarnat 1940) and rabbits, but not in an adult rabbit (Adams 1938b). In rats, the doses varied from 0.002% to 0.05% yellow phosphorus (Adams and Sarnat 1940) and in rabbits, from 0.6 to 6 mg (Adams 1938b; Adams and Samat 1940).

A decrease in the number of viable pups and an increase in the number of stillborn pups was observed in the F_{1a} and F_{1b} offspring of rats exposed to 0.075 mg/kg/day; however, the incidence was not significantly ($p<0.05$) different from controls (IRDC 1985). These effects were not seen in a similarly designed reproduction study in which rats were administered 0.075 mg/kg/day (Bio/dynamics 1991). Neither of these studies found any significant differences in the occurrence of malformations or anomalies.

These NOAEL and LOAEL values from each reliable study for developmental effects in rats are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to white phosphorus.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or after oral exposure to white phosphorus.
In the only chronic duration oral study in animals, no treatment-related histopathological lesions were observed in the lungs or other organs (not otherwise specified) in rats given ≤1.6 mg/kg/day white phosphorus in the diet for up to 479 days (Fleming et al. 1942). Only six rats per dose group were used.

2.2.3 Dermal Exposure (Nonburn)

Studies regarding dermal (nonburn) exposure of humans to white phosphorus were limited tojhose involving occupational exposure. In one study, the workers' hands were regularly in contact with paste containing phosphorus (Ward 1928). The extent of dermal exposure in the other occupational studies was not clear, although it is likely there was dermal exposure to airborne particles (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944).

2. HEALTH EFFECTS

One study was located regarding health effects in animals after dermal exposure to white phosphorus; the study tested dermal and ocular irritation of white phosphorus in rabbits (Lee et al. 1975).

No studies were located regarding health effects in humans or animals after dermal exposure to white phosphorus smoke.

2.2.3.1 Death

Dermal exposure to white phosphorus most likely occurred in humans occupationally exposed to fumes/vapors and paste containing white phosphorus. The workers constantly handled a paste containing 4-6% white phosphorus. The workers were most likely exposed by the inhalation, oral, and dermal routes. White phosphorus-related deaths occurred in 0 of 44 and 2 of 27 of the workers exposed for intermediate or chronic durations, respectively (Ward 1928).

No studies were located regarding death in animals after derma.l exposure to white phosphorus.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hepatic, or renal effects in humans or animals after dermal exposure to white phosphorus. The highest NOAEL value and all reliable LOAEL values for systemic effects in each species and duration are recorded in Table 2-3.

Hematological Effects. Anemia and a decrease in leukocytes were observed in workers occupationally exposed to white phosphorus (Ward 1928). Because the workers handled rags coated with white phosphorus, the workers were exposed by inhalation, oral, and dermal routes.

No studies were located regarding hematological effects in animals after dermal exposure to white phosphorus.

Musculoskeletal Effects. Phossy jaw, described as slight-to-severe necrosis of the jaw, was observed in workers exposed to white phosphorus via the inhalation, oral, and dermal routes for intermediate and chronic durations. The workers constantly handled a paste containing 4-6% white phosphorus (Ward 1928). For more information on this effect, see Section 2.2.2.2.

TABLE 2-3. Levels of Significant Exposure to White Phosphorus - Dermal

Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL(effect) Less serious (mg/kg/day)	LOAEL(effect) Serious (mg/kg/day)		Reference
ACUTE EXPOSURE							
Death							
Rat (Hadassah bred)	once				29	(50% died)	Ben-Hur et al. 1972
Rat (NS)	once				100	(50% died)	Ben-Hur and Applebaum 1973
Rat (NS)	once				100	(50% died)	Ben-Hur and Applebaum 1973
Rat (Wistar)	once				181.8	(16/16 died)	Eldad and Simon 1991

TABLE 2-3. Levels of Significant Exposure to White Phosphorus - Dermal(continued)

Species (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/kg/day)	LOAEL(effect) Less serious (mg/kg/day)	LOAEL(effect) Serious (mg/kg/day)		Reference
Systemic							
Rat (Hadassah bred)	once	Cardio			29	(microthrombi in portal veins)	Ben-Hur et al. 1972
		Hepatic			29	(scattered hemorrhagic areas of necrosis, increased ALT, degeneration of hepatocytes, periportal infiltration with inflammatory cells, microthrombi in portal veins)	
		Renal			29	(necrosis, vascular degeneration of proximal convoluted tubules, increased BUN, excessive diuresis, oliguria, anuria, decreased creatinine clearance)	
		Dermal				(necrotic surface)	
Rat (Hebrew University sabra)	once	Renal			200	(ischemic and hypercellular glomerulus, proximal tubular brush border damage, necrosis of proximal tubular cells, kidney malfunction)	Appelbaum et al. 1975

TABLE 2-3. Levels of Significant Exposure to White Phosphorus - Dermal(continued)

Species (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/kg/day)	LOAEL(effect) Less serious (mg/kg/day)	LOAEL(effect) Serious (mg/kg/day)		Reference
Rat (NS)	once	Cardio			100	(microthrombi in portal veins)	Ben-Hur and Applebaum 1973
		Hepatic			100	(periportal infiltration, hepatocellular degeneration, microthrombi in portal veins)	
		Renal			100	(swelling, desquamation and perinuclear vacuolation of cells in proximal tubules, ischemic and hypercellular glomerulus, kidney failure)	
		Dermal			100	(necrosis, delayed wound healing)	
Rabbit (New Zealand)	once	Dermal	0.1%				Lee et al. 1975
		Ocular	0.1%				

ALT = alanine aminotransferase; BUN = blood urea nitrogen; Cardio = cardiovascular; LOAEL = lowest-observed-adverse-effect level; NS = not specified; NOAEL = no-observed-adverse-effect level

No studies were located regarding musculoskeletal effects in animals after dermal exposure to white phosphorus.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to white phosphorus.

No signs of skin irritation were observed in rabbits after a 0.1% solution of white phosphorus in peanut oil was applied to the shaven intact skin (Lee et al. 1975). White phosphorus is highly reactive and is likely to be an irritant. It is possible that the peanut oil vehicle was protective against these potential effects.

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to white phosphorus.

No signs of eye irritation was observed in rabbits after a 0.1% solution of white phosphorus in peanut oil was applied to the eyes (Lee et al. 1975). White phosphorus is highly reactive and is likely to be an irritant. It is possible that the peanut oil vehicle was protective against this potential effect.

Other Systemic Effects. Decreased serum glucose levels were observed in workers occupationally exposed to white phosphorus (Ward 1928). In addition to inhalation and oral exposure, the workers' hands were regularly in contact with paste containing white phosphorus.

No studies were located regarding other systemic effects in animals after dermal exposure to white phosphorus.

2.2.3.3 Immunological and Lymphoreticular Effects

As discussed in Section 2.2.3.2, in workers exposed to an unknown level of phosphorus via inhalation, oral, and dermal routes, a decrease in leukocyte levels was observed (Ward 1928). No other effects suggestive of immunotoxicity were observed in humans.

No studies were located regarding immunological and lymphoreticular effects in animals after dermal exposure to white phosphorus.

2. HEALTH EFFECTS

No studies were located regarding the following health effects in humans or animals after dermal exposure (nonburn) to white phosphorus:

2.2.3.4 Neurological Effects

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to white phosphorus.

2.2.4 Dermal Exposure (Burn)

No studies were located regarding health effects in humans or animals after dermal exposure (burn) to white phosphorus smoke.

2.2.4.1 Death

A high rate of mortality (12 of 27) in humans occurred following accidental explosions from ignited white phosphorus in munitions factories (Walker et al. 1947). The workers that died had third-degree burns over ≈35-90% of their body surface. Those surviving had burns over ≤19% of the body surface. These burn cases followed a course that was “indistinguishable” from that of nonphosphorus related third-degree burns. Thus, death apparently resulted from the burns alone, with no contributing factor from white phosphorus.

In animal studies using experimental white phosphorus burns, there is evidence that white phosphorus or phosphorus compounds remaining in the burn site may contribute to the increased mortality. New Zealand White rabbits received white phosphorus burns or branding burns (control group) over l0-20% of

the body surface (Bowen et al. 1971). The mortality rate was 65-85% in rabbits burned with white phosphorus, compared to 0% in the control group. Most deaths occurred within the first 18-24 hours. Clinical signs prior to death included a generalized depression and twitching. Results from serum chemistry and EKG tests prior to death indicated that white phosphorus burns may produce a decrease in the calcium/phosphorus ratio, with potentially lethal effects on heart function. Animals that died had decreased serum calcium (80% of those that died) and increased serum phosphorus (100% of those that died). Rabbits that died generally had major shifts in EKG readings, while survivors had minor EKG changes.

Three other studies used rats as models of acute dermal burn. Doses of 29 mg/kg/day (Ben-Hur et al. 1972), 100 mg/kg/day (Ben-Hur and Appelbaum 1973), and ≈ 182 mg/kg/day (Eldad and Simon 1991) resulted in 5 of 10 (50%), 4 of 8 (50%), and 16 of 16 (100%) deaths, respectively, in the groups that were burned with white phosphorus. Although each of the studies using rats had a control group, none of the studies reported incidences of mortality in the control group.

Changes in clinical serum and urinary parameters, as well as microscopic examination of tissues, generally indicated severe liver and kidney damage. Acute renal and/or hepatic failure was the probable cause of death. Severe hepatic, renal, and capillary damage was also indicated by light and phase-contrast microscope (Ben-Hur et al. 1972; Ben Hur and Appelbaum 1973).

2.2.4.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, or musculoskeletal effects in humans or animals after dermal (burn) exposure to white phosphorus. The highest NOAEL value and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

Cardiovascular Effects. Transient electrocardiogram alterations, indicative of myocardial-ischemia, were observed in an individual burned by an unknown amount of white phosphorus (Summerlin et al. 1967). The electrocardiogram returned to normal 5 days after being burned.

In rabbits burned by an unknown amount of white phosphorus, electrocardiogram alterations (prolongation of QT interval, ST segment depression, T-wave changes, bradycardia, and low voltage QRS

complex) indicative of myocardial damage were observed; however, no histological alterations were observed in the heart (Bowen et al. 1971).

Hematological Effects. Anemia, hemolysis, and leukocytosis have been observed in individuals burned by an unspecified amount of white phosphorus (Summerlin et al. 1967; Walker et al. 1947). Because copper sulfate is often used to treat white phosphorus burns, it is difficult to determine whether the anemia and hemolysis were due to copper or white phosphorus poisoning. Copper can be absorbed from the burn injury or wound after topical application of copper sulfate to white phosphorus burn surfaces (Bowen et al. 1971; Summerlin et al. 1967). Acute copper intoxication is characterized by hemolytic anemia with intravascular hemolysis (Summerlin et al. 1967)

No studies were located regarding hematological effects in animals after dermal (burn) exposure to white phosphorus.

Hepatic Effects. Jaundice, hepatomegaly, and increased serum bilirubin levels have been observed in humans with white phosphorus-induced burns (Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947).

In rats burned once with 29 or 100 mg/kg/day white phosphorus, an increase in ALT levels, necrosis, ballooning degeneration of hepatocytes, and microthrombi in the portal veins have been observed (Ben-Hur and Appelbaum 1973; Ben-Hur et al. 1972). In rabbits burned by white phosphorus (dose not reported), semm calcium and phosphorus levels were normal, and no morphological damage was observed (Bowen et al. 1971). No longer-term human and animal studies examining hepatic effects were found.

Renal Effects. Evidence of renal damage was observed in individuals burned once with white phosphorus. Increased blood urea nitrogen (Summerlin et al. 1967), increased urinary levels of protein and urea nitrogen (Walker et al. 1947), and signs of acute renal failure (Song et al. 1985) have been observed. No longer term human studies were identified. Some of the blood/serum chemical changes are also found in thermal burn patients and cannot necessarily be ascribed to white phosphorus toxicity. However, controlled animal studies (discussed below) have shown similar effects that have been attributed to white phosphorus.

2. HEALTH EFFECTS

The severe histological alterations that have been observed in animals acutely burned with 29-200 mg/kg/day white phosphorus, support the effects observed in humans. Necrosis and vascular degeneration of the proximal tubule and ischemic changes in the glomerulus of rats were observed (Applebaum et al. 1975; Ben-Hur and Applebaum 1973; Ben-Hur et al. 1972). In addition to these histological alterations, increased blood urea nitrogen levels, excessive diuresis, oliguria, decreased creatinine clearance, and renal failure have been observed (Ben-Hur et al. 1972). No histological alterations were observed in the kidneys of rabbits burned once with an unreported amount of white phosphorus (Bowen 1971). No longer-term derrnal (burn) animal studies were located.

Dermal Effects. Dermal effects have resulted from white phosphorus-induced burns during pesticide manufacture and from incendiary munitions explosions (Konjoyan 1983; Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). Many white phosphorus-induced burns are second and third degree. Burn damage to the skin tissue is believed to result not only from heat but also from the corrosive action of phosphoric acid and the hygroscopic (moisture-absorbing) properties of phosphorus pentoxide, which is generated by the oxidation of white phosphorus (Ben-Hur and Appelbaum 1973). Severe white phosphorus burns also tend to heal more slowly than other types of third-degree thermal burns.

Rat models of acute dermal burn exposure revealed necrosis of the skin at exposure levels of 29 mg/kg/day (Ben-Hur et al. 1972) and 100 mg/kg/day (Ben-Hur and Applebaum 1973), and delayed wound healing at 100 mg/kg/day.

Ocular Effects. Ocular effects have resulted from white phosphorus-induced burns during pesticide manufacture and from incendiary munitions explosions (Konjoyan 1983; Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). Many white phosphorus-induced burns are second and third degree. Burn damage to the skin tissue is believed to result not only from heat, but also the corrosive action of phosphoric acid and the hygroscopic (moisture-absorbing) properties of phosphorus pentoxide which is generated by oxidation of white phosphorus (Ben-Hur and Appelbaum 1973). Also, severe white phosphorus burns tend to heal more slowly than other types of third-degree thermal burns.

Transient local necrosis and congestion were reported after smoking particles of white phosphorus were discovered in the tarsal and bulbar conjunctival sacs of a dermal burn patient (Scherling and Blondis 1945). The conjunctival effects were completely absent by 4 days post-exposure.

No studies were located regarding ocular effects in animals after dermal (burn) exposure to white phosphorus.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after dermal (burn) exposure to white phosphorus.

In rabbits burned once with an unknown amount of white phosphorus, serum hypocalcemia and hyperphosphatemia were observed (Bowen et al. 1971). No longer term dermal (burn) exposure studies were located.

2.2.4.3 Immunological and Lymphoreticular Effects

Leukocytosis was observed in individuals burned by an unspecified amount of white phosphorus (Walker et al. 1947).

No studies were located regarding immunological or lymphoreticular effects in animals after dermal (burn) exposure to white phosphorus.

2.2.4.4 Neurological Effects

An individual lapsed into a deep coma a number of hours after being burned by white phosphorus (Walker et al. 1947). Depression, poor responsiveness to stimuli, shivering, twitching, and anorexia were observed in rabbits burned by white phosphorus (no dose reported) (Bowen et al. 1971).

No studies were located regarding the following health effects in human or animals after dermal (burn) exposure to white phosphorus:

2.2.4.5 Reproductive Effects

2.2.4.6 Developmental Effects

2.2.4.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.4.8 Cancer

No studies were located regarding cancer in humans or animals after dermal (burn) exposure to white phosphorus.

2.3 TOXICOKINETICS

The toxicokinetics of white phosphorus are poorly understood. There are several reasons for this. First, both organic and inorganic molecules containing phosphorus perform a vastly intricate web of functions in the animal body. Organic phosphorus is metabolically important for energy storage and transfer in adenosine triphosphate (ATP) and phosphocreatine, for information transfer and ultimately protein synthesis in nucleotides and nucleic acids, and for carbohydrate metabolism in hexose- and triosephosphates (Latner 1975). Phospholipids have an important structural role, forming integral parts of cell and organelle membranes, including the matrix that properly orients mitochondrial oxidative enzymes (Dryer 1970). Inorganic phosphorus occurs as phosphate in the blood's buffering system, in interstitial fluid, and in intracellular fluid where it is the major anionic constituent (Guyton 1976). Second, a method for quantifying white phosphorus per se in body tissues has not been developed. Therefore, quantitative assessments of white phosphorus absorption, distribution, metabolism, and excretion are necessarily measurements of possible white phosphorus metabolites and not of white phosphorus itself. Even the qualitative detection of white phosphorus in bodily fluids and tissues is equivocal. The one published method for detecting the presence of white phosphorus in tissue gives unequivocal negative results but can give false positives with unreported frequency (Blanke 1970). Also, phosphorescence observed in tissues of white phosphorus-exposed animals may or may not be indicative of the presence of white phosphorus as such.

The fate of white phosphorus following exposure by any route is an open question. White phosphorus is an inorganic chemical that is poorly soluble in water, soluble in nonpolar organic solvents such as benzene, soluble in more polar organic solvents such as CS_2 (Cotton and Wilkinson 1966), and is lipid-soluble. White phosphorus is the most reactive allotropic form of elemental phosphorus, oxidizing spontaneously in the air at room temperature, and hydrating under certain conditions (Cotton and Wilkinson 1966). Although it has not been demonstrated, it is probable that, since white phosphorus is highly reactive in the presence of oxygen, it is rapidly converted to its oxidation products prior to

absorption into the body. Inorganic conversion (e.g., to phosphates, phosphorus peroxide, and orthophosphates) may occur as white phosphorus sits on the skin exposed to the air, travels through the air to the moist surfaces of the lungs and mouth, or moves through the highly acidic and then basic environments of the mammalian gut. However, absorption of some white phosphorus by oral, inhalation, and dermal routes is likely since it is lipid-soluble. If white phosphorus as such is absorbed, then the inorganic reactions may occur *in vivo* in the blood, interstitial fluid, and intracellular fluid, although this has not been demonstrated. Further, there are no studies either definitively supporting or refuting the possibility that white phosphorus is broken down enzymatically.

The formation of white phosphorus metabolites is probably limited by the inorganic, aqueous dissociation of white phosphorus. Following the dissociation of white phosphorus (either prior to absorption or in the body fluids), the individual phosphorus atoms are probably incorporated first into phosphates and then into a variety of biochemicals as secondary metabolites. The fate of the phosphorus would then follow that of all common phosphorus-containing molecules in the body. At least 96% of excreted phosphorus (both urine and feces) is excreted as inorganic phosphate, and the remainder is organic phosphorus (e.g., phosphoproteins, nucleoproteins, nucleotides, and phospholipids) (Latner 1975).

The toxicokinetics of white phosphorus smoke are likewise unknown. White phosphorus smoke is primarily oxides and acids of phosphorus, with some residual unburnt white phosphorus (refer to Chapter 3 for a detailed description of the composition of white phosphorus smoke). The fates of airborne white phosphorus, and the phosphorus oxides and phosphorus-containing acids originating from the combustion of white phosphorus, are largely unknown.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

White Phosphorus. No studies were located regarding absorption in humans or animals after inhalation exposure to white phosphorus. Human serum concentrations of phosphate (relevance to absorption of white phosphorus is unknown) following inhalation exposure are discussed in Section 2.3.3 (Metabolism).

White Phosphorus Smoke. No studies were located regarding absorption in humans or animals after inhalation exposure to white phosphorus smoke. White phosphorus smoke probably contains some

residual unburnt white phosphorus (see Chapter 3 for composition information). Human serum concentrations of phosphate (relevance to absorption of white phosphorus smoke is unknown) following occupational inhalation exposure to white phosphorus are discussed in Section 2.3.3 (Metabolism). Health effects observed after inhalation of white phosphorus smoke are most likely portal of entry effects, and, therefore, do not indicate that absorption of white phosphorus occurred. However, the oxides and acids of white phosphorus that occur in the smoke are probably absorbed to an unknown degree.

2.3.1.2 Oral Exposure

White Phosphorus. No studies were located that quantify absorption of white phosphorus in humans following oral exposure to white phosphorus. Qualitative evidence of oral absorption in humans abounds in case reports of intentionally and accidentally ingested white phosphorus from rat poison or fireworks. Systemic signs of toxicity following such ingestion range from simple gastrointestinal upset to liver failure to death within hours of ingestion (see Section 2.2 for further details). These reports suggest that either white phosphorus, or one of its inorganic breakdown products, is absorbed.

Orthophosphate is a stable end-product of the inorganic oxidation or hydrolysis of white phosphorus (see Section 2.3.3 [Metabolism]), and is possibly produced in the gut to some degree prior to absorption. During normal digestion, phosphate is released from phosphate-containing biochemicals in food and actively absorbed in the upper small intestine, and somewhat less in the more basic environment of the lower small intestine (Latner 1975). Phosphate absorption is significantly higher in acid pH environments than in alkaline environments (Tietz 1970). Human and animal data on serum levels of phosphate (technically, one of two ionic forms of orthophosphate [H_3PO_4]) are included for completeness in Section 2.3.3 (Metabolism). Intestinal absorption of phosphate normally fluctuates widely. It is decreased by high intake of calcium, magnesium, or iron, which form insoluble phosphates in the gut, by unusually high intestinal alkalinity, and by low vitamin D intake (Latner 1975). Thus, the relevance of serum phosphate levels as they relate to absorption of white phosphorus is not known.

Renwick (1989) notes species differences in gastric pH, ranging from 1.9 in rabbits to between 3.8 and 5.0 in rats. Such differences in gut environments may affect species differences in absorption rate of white phosphorus or its inorganic breakdown products, although quantitative comparisons between species were not located.

2. HEALTH EFFECTS

Absorption of ^{32}P-labeled white phosphorus or one of its breakdown products is very rapid following oral administration to animals. Cameron and Patrick (1966) observed ^{32}P systemically in female rats, female rabbits, and male mice for 48 hours following a single oral dose by gavage of ^{32}P-labeled white phosphorus. Absorption of ^{32}P was high in the liver, renal cortex, bowel mucosa, epidermis, hair follicles, pancreas, and adrenal cortex, and was low in the brain, striped muscle, myometrium, fat, and bone.

In a later study, Ghoshal et al. (1971) demonstrated that phosphorus was rapidly absorbed in male rats following a single oral gavage of ^{32}P-labeled white phosphorus mixed with a "toxic dose" of unlabeled white phosphorus. By 15 minutes post-dosing, radioactivity was detected in the blood and liver (<5% of administered ^{32}P). At 2-3 hours, the percentage of total dose in the liver reached its maximum of 65-70%. At that time, the percentages of administered ^{32}P recovered from blood (12%), kidney (4%), spleen (0.4%), pancreas (0.4%), and brain (0.39%) were significantly lower than for the liver ($p<0.001$; n=4 for each). The fraction of the administered dose accounted for in these tissues at 2-3 hours post-dosing was ≈82-87%.

Finally, Lee et al. (1975) gavaged rats once with ≈10% of the oral LD_{50} of ^{32}P-labeled white phosphorus (LD_{50} in males = 3.76 mg/kg LD_{50}; in females = 3.03 mg/kg) and found that total ^{32}P absorbed reached a maximum of 60-65% of the administered radioactivity at =24 hours post-dosing.

White Phosphoncs Smoke. No studies were located regarding absorption in humans or animals after oral exposure to white phosphorus smoke or white phosphorus smoke condensates.

2.3.1.3 Dermal Exposure

White Phosphorus. No studies were located regarding absorption in humans or animals after dermal (no burn) exposure to white phosphorus.

No studies were located that quantify absorption in humans or animals following exposure to white phosphorus by dermal burning. Qualitative evidence of absorption in humans and animals in the form of systemic effects suggests absorption of white phosphorus or one of its combustion products following dermal white phosphorus burns (see Section 2.2). Human and animal serum concentrations of phosphate following dermal white phosphorus burns are discussed in Section 2.3.3 (Metabolism), although their

2. HEALTH EFFECTS

White Phosphorus Smoke. No studies were located regarding absorption in humans or animals after dermal exposure to white phosphorus smoke or white phosphorus smoke condensates.

2.3.2 Distribution

Naturally occurring phosphorus is widely distributed in the healthy human body. Approximately 80% of phosphorus in the human body is bound with calcium in the bones and teeth. Pyrophosphates and polyphosphates are associated with bone formation by maintaining the mineral phase of bone, hydroxyapatite ($3Ca_3(PO_4)_2Ca(OH)_2$), in supersaturated solution in the extracellular fluid (Latner 1975). Phosphorus-containing organic compounds in the blood and muscle such as proteins, lipids, and carbohydrates constitute another 10% of body phosphorus. Nearly all organic forms of phosphorus in blood, such as 2,3-diphosphoglyceric acid, adenosine triphosphate, and fructose 1,6-diphosphate, occur in erythrocytes (Henry 1967). The remaining 10% has an extensive distribution in the fluids of the body (Harper 1969). Serum inorganic phosphates are present at levels of 3.0-4.5 mg/l00 mL (Harper 1969) as $H_2PO_4^{-1}$ (80%) and as HPO_4^{-2} (20%) at normal pH of 7.4 (Tietz 1970). Walser and Mudge (1960) report that ≈7% of plasma phosphate is in direct association with calcium. Transient hypo- or hyperphosphatemia frequently occurs in the healthy human body following meals. Plasma inorganic phosphate increases following ingestion of calcium and decreases during periods of increased carbohydrate metabolism (Latner 1975). Vitamin D can increase phosphate absorption in the gut; during vitamin D deficiency, plasma phosphate falls (Latner 1975). In ill individuals, hypophosphatemia is caused by vomiting and severe diarrhea, and is associated with various liver diseases (Latner 1975).

2.3.2.1 Inhalation Exposure

White Phosphorus. No studies were located regarding distribution in humans or animals after inhalation exposure to white phosphorus. Human serum concentrations of phosphate (relevance to distribution is unknown) following inhalation exposure are discussed in Section 2.3.3 (Metabolism).

White Phosphorus Smoke. No studies were located regarding distribution in humans or animals after inhalation exposure to white phosphorus smoke. White phosphorus smoke probably contains some residual unburnt white phosphorus (see Chapter 3 for composition information). Human serum concentrations of phosphate (relevance to distribution of white phosphorus, oxides of phosphorus, or acids of phosphorus is unknown) following occupational inhalation exposure to white phosphorus smoke are

discussed in Section 2.3.3 (Metabolism). Health effects observed in humans and animals after inhalation of white phosphorus smoke (see Section 2.2) are most likely portal of entry effects, and, therefore, do not indicate that absorption and subsequent distribution of white phosphorus occurred. However, a percentage of the oxides and acids of white phosphorus that occur in the smoke is probably absorbed and distributed systemically.

2.3.2.2 Oral Exposure

White Phosphorus. No studies were located that quantify distribution in humans following oral exposure to white phosphorus, but several studies have examined the distribution of ^{32}P in animals following oral administration white phosphorus. Human and animal serum concentrations of phosphate (relevance to distribution is unknown) following oral exposure are discussed in Section 2.3.3 (Metabolism).

An acute exposure study by Cameron and Patrick (1966) showed qualitatively and quantitatively that the 48 hour distribution of ^{32}P after oral administration of ^{32}P-labeled white phosphorus was similar in rats, rabbits, and mice. Using qualitative autoradiography results, they assigned the liver, renal cortex, bowel mucosa, epidermis, hair follicles, pancreas, and adrenal cortex to the high uptake category. The ovary, renal medulla, spleen, endometrium, myocardium, thymus, lung, and adrenal medulla were assigned to the medium uptake category following autoradiography. Striated muscle, brain, myometrium, fat, and bone were each assigned to the low uptake category on the basis of autoradiography. Autoradiography showed that in both the kidney and adrenal gland, the cortex was more heavily labeled than the medulla, and that the centrilobular region of the liver showed greater uptake of ^{32}P than other areas of the liver.

Cameron and Patrick (1966) generally confirmed their own autoradiography results quantitatively. At 48-hours post-dosing, data showed the same distribution of radioactivity for both perfused and unperfused tissue samples. A comparison of radioactivity concentration between blood and other tissues was not possible, since the units of radioactivity concentration in the blood were unclear. Among the tissues other than blood, the bowel had the highest level of radioactivity, followed in generally decreasing order by the liver, kidney, spleen, lung, heart, muscle, pancreas, adrenal, brain, thymus, thyroid, testes, ovary, uterus, fat, bone, aorta, trachea, and pituitary.

In a later acute exposure study, Goshal et al. (1971) examined both gross distribution and subcellular hepatic distribution of ^{32}P at 2-3 hours post-dosing. At 2-3 hours, the percentage of total dose in the liver

reached its maximum of 65-70%. At that time, the percentages of administered ^{32}P recovered from blood (12%), kidney (4%), spleen (0.4%), pancreas (0.4%), and brain (0.39%) were significantly lower than for the liver ($p<.001$; n=4 for each). A substantial amount (≈40%) of the administered ^{32}P remained in the liver for several hours. The subcellular distribution of ^{32}P within the liver at 2 hours post-dosing was 54%, 18%, 16%, and 10% of total liver radioactivity in the supematant, microsomal, nuclear, and mitochondrial fractions, respectively. Each of these subcellular fractions was treated in turn with 10% trichloracetic acid (TCA) to precipitate essentially all macromolecules in the fraction, leaving only the water-soluble components in solution. The radioactivity of TCA-precipitable material in the supematant, microsomal, nuclear, and mitochondrial fractions was approximately 1.7%, 5.1% (significantly higher than in the other fractions; $p<0.0l$), 1.2%, and 0.3% of total hepatic radioactivity, respectively. Most of the radioactivity of the liver was recovered from the phosphate fraction after TCA treatment. Although the radioactivity recovered from total hepatic lipids increased up to 2-3 hours post-dosing, total hepatic lipids represented a maximum of only 1.4-3% of the administered dose of ^{32}P. Lipids were also extracted from the microsomal fraction of the liver homogenate at the 4- and 10-hour sacrifices (n=4 for each). Total radioactivity of hepatic microsomal lipid significantly increased ($p<0.025$; n=4) between 4 and 10 hours post-dosing, whether expressed as percent of total liver activity (increased from about 2.7% to 4.1%) or as a percent of total ^{32}P administered (increased from about 1.1% to 1.9%)

Following a single oral administration of ^{32}P-labeled white phosphorus (dose not specified) to female rats, Lee et al. (1975) found that administered ^{32}P was distributed unevenly among sampled tissues, and the distribution among tissues changed with the timing of sacrifice after dosing. The liver consistently had the highest total ^{32}P as a percent of the administered dose, with 16.1%, 16.9%, and 6.3% at 4 hours, 1 day, and 5 days post-dosing. The percent of the administered ^{32}P recovered from whole blood, liver, and lungs decreased as the time between dosing and sacrifice increased. The percent of the administered ^{32}P recovered from skeletal muscle increased slightly with time after dosing. Administered ^{32}P recovered from kidneys, spleen, and brain tissue remained relatively constant from 4 hours to 5 days post-dosing. The tissue/plasma radioactivity radio (radioactivity in 1 g wet tissue per radioactivity in 1 mL plasma) increased in all tissues examined (liver, kidney, spleen, brain, lung, skeletal muscle, and bone) during the period 4 hours to 5 days post-dosing. Relative ^{32}P concentration in the liver was far higher than in any other tissue from 4 hours to 5 days post-dosing, and increased from 18.7 to 103.2 times the concurrent plasma ^{32}P concentration. The greatest increase in relative ^{32}P concentration during that period was seen in bone, from under twice to over 65 times the concurrent plasma concentration. Total radioactivity at

24 hours after a single oral dose was 19.3, 5.4,4.8, 2.9, 2.4, 2.2, 0.68, and 0.25 dpm($x10^{-5}$)/g in liver, kidney, bone, blood, spleen, lungs, skeletal muscle, and brain, respectively.

In another acute exposure study, Lee et al. (1975) reported that the distribution of radioactivity in these tissues was similar whether rats received a single dose or five daily doses. They measured total radioactivity at 24 hours after the last of five daily doses to be 79.4,39.3,36.8,28.4,22.2, 17.7,5.9, and 2.6 dpm($xl0^{-5}$)/g in liver, kidney, bone, blood, lungs, spleen, skeletal muscle, and brain, respectively. Although the highest absolute level of radioactivity was in the liver, the increase in radioactivity 24 hours after the last of the five daily doses compared to a single dose, was 10.5, 10.2,9.8, 8.7, 7.7,7.4,7.2, and 4.1 times the single-dose level in the brain, lungs, blood, skeletal muscle, bone, spleen, kidney, and liver, respectively.

White Phosphorus Smoke. No studies were located regarding distribution in humans or animals after oral exposure to white phosphorus smoke or smoke condensates.

2.3.2.3 Dermal Exposure

White Phosphorus. No studies were located regarding distribution in humans or animals after dermal (no burn) exposure to white phosphorus.

No studies were located that quantify distribution in humans or animals following exposure to white phosphorus by dermal burning. Human and animal serum concentrations of phosphate following dermal white phosphorus burns are discussed in Section 2.3.3 (Metabolism). Their relevance to white phosphorus distribution is unknown.

White Phosphorus Smoke. No studies were located regarding distribution in humans or animals after dermal exposure to white phosphorus smoke or smoke condensates.

2.3.2.4 Other Routes of Exposure

White Phosphorus. Whitely et al. (1953) compared phosphorus (allotropic form not specified) uptake *in viva* by rabbit skin between areas of actively growing hair and areas where hair is not growing. Accumulation of ^{32}P was measured in the skin only. Rabbits were administered 75 μCi of ^{32}P/kg body weight in

phosphate-buffered saline by intravenous injection. Accumulation of ^{32}P in the skin following intravenous injection was more rapid in areas with actively growing hair than in areas where hair was not growing, and the ratio of radioactivity between those areas increased with time after exposure, up to 72 hours post-dosing. The ratio of total radioactivity between the growing and quiescent areas as estimated by autoradiography was approximately 1.6 at 5 minutes (three rabbits), 2.4 at 1 hour (nine rabbits, 2.7 at 24 hours (four rabbits), and 3.4 at 72 hours (number of rabbits not reported). A similar pattern over time between the zones of hair growth was also observed in the total radioactivity as calculated from liquid scintillation counter data. The ratio of total radioactivity between the growing and quiescent areas as estimated by scintillation counting (or electron flux calculated in part from counts per minute) was approximately 1.8 at 5 minutes, 2.3 at 1 hour, and 2.9 at 24 hours.

In a more detailed examination of ^{32}P distribution in rabbit skin, Whitely et al. (1953) examined the "phosphate fractions" of the skin following intravenous injection. The mean tissue concentration of total phosphate in nucleic acid is significantly greater in the growing zone than in the quiescent zone ($p<0.01$), both in terms of weight (0.46 and 0.27 mg phosphate/g skin wet weight, respectively) and area (0.07 and 0.02 mg phosphate/cm^3 skin, respectively). The mean tissue concentration of total acid-soluble phosphate was significantly greater in the growing zone than in the quiescent zone ($p<0.0l$), only when expressed in terms of the area of skin examined (0.07 and 0.04 mg phosphate/cm^3 skin, respectively). The difference between the growing and quiescent zones in terms of mean specific activity of total phosphate (counts per minute/mg phosphate; this appears to be a relative index of the fraction of total phosphate that is radiolabeled) grew over time in the nucleic acid fraction and decreased in the acid-soluble fraction.

White Phosphorus Smoke. No studies were located regarding distribution in humans or animals after other routes of exposure to white phosphorus smoke or smoke condensates.

2.3.3 Metabolism

Studies that specifically address the metabolism of white phosphorus are very limited. Nothing is known about the enzymatic catalysis of white phosphorus. The inorganic chemistry of white phosphorus has been fully described, but its relevance *in vivo* has not been specifically addressed.

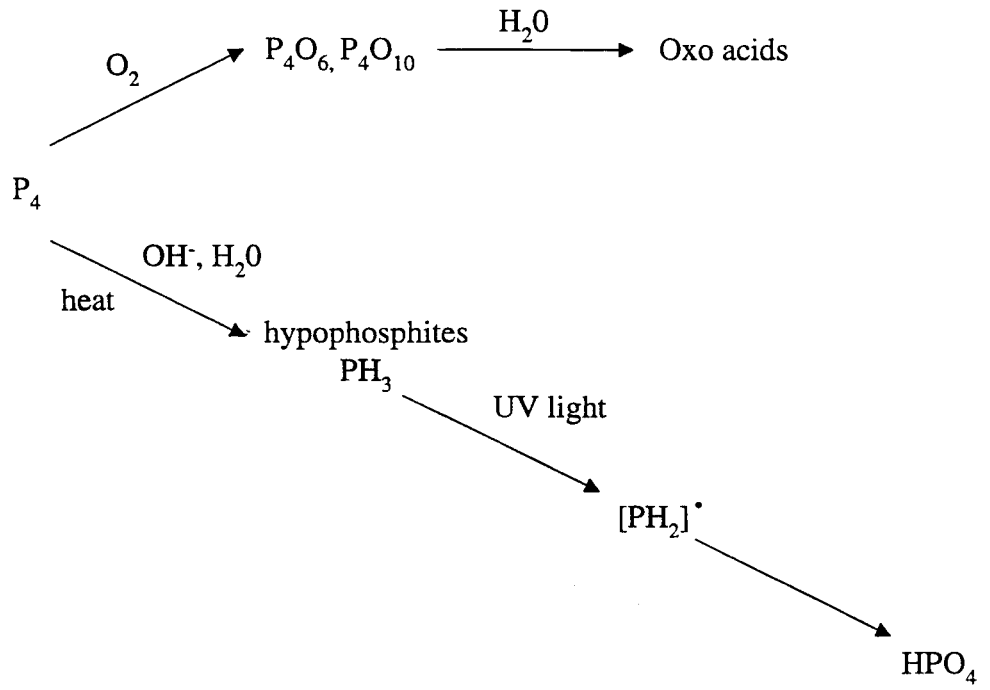
White phosphorus is the most reactive allotropic form of elemental phosphorus, combusting (oxidizing) spontaneously in the presence of oxygen to form P_4O_{10} and P_4O_6 (Figure 2-3), which in turn are easily

hydrated to form oxo acids of phosphorus (Cotton and Wilkinson 1966). Orthophosphate (H_3PO_4) is the most prevalent oxo acid of phosphorus found in the blood (Guyton 1976). In turn, orthophosphate occurs in human serum in its monobasic (HPO_4^{-2}) and dibasic (H_2PO_4) forms in a ratio of about 4: 1 (Tietz 1970). Blanke (1970) claims that phosphorus is slowly oxidized in the blood to hypophosphorous and phosphorous acids (hypophosphite and phosphite, respectively), but does not cite a source, and does not address the problem of special thermal or pH conditions. Hypophosphorous and phosphorous acids in turn may ultimately be oxidized (heat requirement not specified) to orthophosphate in the presence of water (Cotton and Wilkinson 1966). A variety of other higher oxo acids of phosphorus exist, such as pyrophosphates and polyphosphates (which are involved in bone formation) (Latner 1975), cyclic phosphates, and cyclic polyphosphates (Cotton and Wilkinson 1966). It is conceivable that any combination of these may be formed either prior to absorption, or in the blood as minor reaction products in the formation of orthophosphate from white phosphorus, although there is no solid evidence that these co-products are formed.

White phosphorus also may be hydrolyzed in an alkaline aqueous environment with the addition of heat (see Figure 2-3) to give a mixture of hypophosphite and phosphite, with hydrogen and phosphine, respectively, as co-products (Cotton and Wilkinson 1966). Hudson (1965) reports similar reactions, but does not mention that added heat is required, implying instead that a highly alkaline environment may drive the reaction. The jejunum of the mammalian gut may provide an appropriate environment for either of these reactions. Although the reactions forming these lower 0x0 acids of phosphorus seem unlikely to occur in human serum due to the extreme thermal or pH requirements, it is possible that enzymatic catalysis may occur. Indeed, there is some circumstantial evidence suggesting that these reactions do occur in human blood.

Phosphine is a co-product of the formation of phosphite ($HP0_3^{-2}$) by alkaline hydrolysis of white phosphorus (Hudson 1965) and is a highly toxic gas. Phosphine can cause cardiac collapse (Blanke 1970), and severe cardiac problems have been observed in several cases involving human ingestion of white phosphorus (see Section 2.2). It is also genotoxic in humans (Garry et al. 1989). An accidental death of a pregnant woman was related to phosphine exposure from stored grain which had been fumigated with aluminum phosphide (AIP_3) pellets (Garry et al. 1993).

FIGURE 2-3. Pathways of Oxidation and Hydrolysis of White Phosphorous (P_4)*



***Derived from Cotton and Wilkinson 1966**

2. HEALTH EFFECTS

In *in vitro* studies, phosphine decreased red blood cell or plasma cholinesterase activity, and similar effects were seen *in vivo* in workers using phosphine fumigant (Potter et al. 1993). Phosphine also reacted *in vitro* with intact red blood cells to form dense aggregates of denatured hemoglobin known as "Heinz bodies" (Potter et al. 1991).

No studies were located regarding metabolism in humans or animals after inhalation, dermal, or other routes of exposure to white phosphorus smoke or smoke condensates. White phosphorus smoke and condensates of the smoke probably contain some residual unburnt white phosphorus (see Chapter 3 for composition information). For further discussion of white phosphorus metabolism, see Sections 2.3.3.1, 2.3.3.2, and 2.3.3.3 below.

2.3.3.1 Inhalation Exposure

No studies were located that specifically address white phosphorus metabolism in humans or animals after inhalation exposure. However, since orthophosphate is a stable end-product of the inorganic oxidation and hydrolysis of white phosphorus, it is appropriate to examine data on serum phosphate levels in humans and animals (these data are discussed further in Section 2.2).

An epidemiology study (Hughes et al. 1962) compared the mean serum phosphate level of five occupationally-exposed phosphorus plant workers with the mean serum phosphate level of five healthy control men not exposed to phosphorus. The exposure duration ranged from 1 to 17 years in the exposed group. Although the route of exposure was not reported, it is assumed to be inhalation of airborne phosphorus. It is likely that oral exposure (ingestion of airborne phosphorus) also occurred. The serum phosphorus levels of phosphorus plant workers and controls were reported to be 2.85 and 2.9 mg/l00mL, respectively. Both values are below the normal range for adult humans of 3.0-4.5 mg/l00 mL (Harper 1969). There was no statistical difference between the workers' and controls' serum phosphate levels (test and p value not reported).

The serum phosphate level of a worker with phossy jaw was within the normal range of values for an adult human (Hughes et al. 1962). Excretion of phosphate via urinary and fecal routes was reported qualitatively to be approximately normal. The daily output of phosphorus in the feces was about l/4 to l/3 of the total output in both urine and feces.

2.3.3.2 Oral Exposure

No studies were located that specifically address white phosphorus metabolism in humans after oral exposure. However, since orthophosphate is a stable end-product of the inorganic oxidation and hydrolysis of white phosphorus, it is appropriate to examine data on serum phosphate levels in humans following oral ingestion of white phosphorus (these data are discussed further in Section 2.2). Although orthophosphate is the stable end-product, linear and cyclic phosphorus compounds do exist that are stable for relatively long periods, and these may be metabolic blockers especially where phosphorus metabolism is on-going.

Generally, there were no obvious patterns in human serum phosphate level with respect to oral dose or time of measurement after ingestion. Many case reports of adults who intentionally ingested rat poison containing white phosphorus are discussed in Section 2.2. Over 25 of these cases reported serum phosphate levels ranging from 1.2 to 8.6 mg/l00 mL 3 hours to 36 days after exposure. Twelve cases reported sufficient data to calculate oral doses, which ranged between 7.1 and 22.9 mg/kg/day. The normal serum concentrations of phosphate in adult humans are reported to range from 3.0 to 4.5 mg/l00 mL (Harper 1969). However, the doses in these adult suicide cases are confounded by the fact that virtually all the persons either vomited or were lavaged fairly soon after dosing. At least 10 additional case reports involve children who accidentally ingested single unspecified doses of white phosphorus, or were administered phosphorus (between 0.095 and 0.212 mg/kg/day) (allotropic form not explicitly stated) medicinally for rickets for an intermediate duration. Serum phosphate levels following ingestion in children were similar to normal serum phosphate levels in children [4.0-7.0 mg/l00 mL (Harper 1969)].

Limited quantitative and qualitative evidence of the metabolic fate of white phosphorus after acute oral exposure was located. In an acute oral study in rats with ^{32}P-labeled white phosphorus, Lee et al. (1975) determined that urinary and fecal elimination routes respectively accounted for 17.1% and 2%, 34.5% and 16.6%, and 46.7% and 33.0% of the administered dose at 4 hours, 1 day, and 5 days post-dosing, respectively. White phosphorus is insoluble in water, and about 96% of the phosphorus bound in urine is inorganic phosphate (Latner 1975). Based on this, it is reasonable to conclude that ≈20% of the administered white phosphorus is excreted as phosphate in urine within 4 hours post-dosing, showing that in viva metabolism of white phosphorus is extremely rapid.

Lee et al. (1975) also qualitatively studied urinary metabolites of ^{32}P-labeled white phosphorus in rats. They used thin-layer chromatography (TLC) at 4 and 24 hours after a single oral dose to show that radioactive urinary metabolites consisted of two classes of compounds. One of the compounds corresponded to inorganic phosphate, the other compound was less polar and suggested an organic phosphate, although the composition of this class of metabolites was not determined. TLC analysis of liver extract also showed two classes of compounds with similar properties.

Since phosphate is a metabolite of the breakdown of white phosphorus and since phosphate is incorporated into a variety of organic molecules, these biomolecules may be considered molecular successors (or secondary metabolites of white phosphorus) and may provide information regarding the fate of white phosphorus after absorption. Ghoshal et al. (1971) studied the effect of acute oral administration of white phosphorus in male Wistar rats on hepatic microsomal glucose-6-phosphatase activity. The activity was reported as milligram inorganic phosphate split from glucose-6-phosphate in 20 minutes per equivalent gram of microsomes. Glucose-6-phosphatase activity was significantly increased by 29% ($p<0.025$; n=6) and 39% ($p<0.01\%$; n=6) over control values at 12 and 24 hours post-dosing, respectively. Activity was not significantly different from controls at 4 hours post-dosing (p value not reported; n=6).

2.3.3.3 Dermal Exposure

No studies were located regarding metabolism in humans or animals after dermal (no burn) exposure to white phosphorus.

No studies were located that specifically address white phosphorus metabolism in humans or animals following dermal white phosphorus burns. However, orthophosphate is a stable end-product of the oxidation and hydrolysis of white phosphorus. Thus, it is appropriate to examine data on serum phosphate and urinary phosphate in humans and animals following dermal white phosphorus burns (these data are discussed further in Section 2.2).

Serum phosphate was reported in three human cases of dermal white phosphorus burn following explosion of incendiary munitions. Serum phosphate ranged between 1.34 and 8.7 mg/l00 mL. The normal range of adult human semm phosphate is 3.0-4.5 mg/l00 mL (Harper 1969). No patterns with respect to burn intensity or time after exposure were evident.

Urinary phosphate was measured in eight human cases of dermal white phosphorus burn following explosion of incendiary munitions. It was not possible to estimate doses. The rate of urinary phosphate excretion varied widely, ranging between 0.08 and 5.83 g/day. The normal adult human output of inorganic phosphate in urine is 0.34-1.0 g/day (Henry 1967). In five of these cases, levels were measured daily for up to 27 of the first 30 days post-exposure. Overall, the rate of urinary excretion of phosphate was not related to the percent of the area of body burned, the percent of the body with third-degree burns, the survival of the patients, or the time after exposure.

In a series of controlled studies using rats (Applebaum et al. 1975; Ben-Hur and Applebaum 1973; Ben-Hur et al. 1972) significant increases ($p<0.01$) in 72-hour serum phosphate ranging from 100% to 120% over controls were observed. Anesthetized animals were burned in inguinal incisions after application of 26-200 mg/kg white phosphorus.

Anesthetized rabbits were burned on intact skin with 5,700 mg/kg white phosphorus (Bowen et al. 1971). Those that died after white phosphorus burns showed significant ($p<0.001$) increases in serum phosphate levels over pre-burn levels. The pre-burn levels ranged between 4.5 and 5.5 mg/l00 mL, and postexposure levels measured at 12 hours to 3 days ranged between 6.5 and 10.5 mg/l00 mL. Phosphate levels in phosphorus-burned animals that survived remained normal throughout the study.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

White Phosphorus. No studies were located regarding excretion in humans or animals after inhalation exposure to white phosphorus. Human urinary excretion of phosphate (relevance to absorption of white phosphorus is unknown) following inhalation exposure is discussed in Section 2.3.3 (Metabolism).

White Phosphorus Smoke. No studies were located regarding excretion in humans or animals after inhalation exposure to white phosphorus smoke.

2. HEALTH EFFECTS

2.3.4.2 Oral Exposure

White Phosphorus. No studies were located that specifically address white phosphorus excretion in humans after oral exposure However, two animal studies (Cameron and Patrick 1966; Lee et al. 1975) indicate rapid urinary and fecal excretion of white phosphorus, metabolites, or unabsorbed inorganic breakdown products.

Lee et al. (1975) measured urinary and fecal elimination of ^{32}P in rats after oral administration of labeled white phosphorus. The total radioactivity excreted in urine and feces was assessed in three different groups of rats sacrificed at 4 hours or 1 or 5 days after dosing. Total excretion of ^{32}P was far higher via the urinary route by 4 hours post-dosing. Excretion of ^{32}P via the fecal route increased rapidly between 4 hours and 5 days post-dosing. By 5 days post-dosing, combined urinary and fecal excretion accounted for ≈ 80% of the administered dose of ^{32}P.

Cameron and Patrick (1966), showed that radioactivity in the urine of rabbits at 48 hours post-dosing was five times the level observed in the blood, while radioactivity in the feces of rabbits, rats, and mice was higher than the tissue concentration in the bowel by a factor of = 13.

2.3.4.3 Dermal Exposure

White Phosphoras. No studies were located regarding excretion in humans or animals after derrnal (no burn) exposure to white phosphorus.

No studies were located regarding excretion in animals after derrnal burn exposure to white phosphorus. Human urinary excretion of phosphate (relevance to absorption is unknown) following dermal burn exposure is discussed in Section 2.3.3 (Metabolism).

White Phosphorza Smoke. No studies were located regarding excretion in humans or animals after dermal exposure to white phosphorus smoke or smoke condensates.

2. HEALTH EFFECTS

2.4 MECHANISMS OF ACTION

No quantitative information on absorption, distribution, metabolism, and excretion of white phosphorus following inhalation, oral, dermal, and dermal burn exposure was located. Studies in which ^{32}P-labeled white phosphorus was orally administered to animals demonstrated that the label was widely distributed throughout the body, with some of the highest concentrations in the liver, kidney, blood, spleen, and brain (Cameron and Patrick 1966; Lee et al. 1975).

Liver damage in animals exposed to white phosphorus progresses rapidly. Four hours after receiving a single oral dose of white phosphorus, minimal fatty changes in hepatocytes were observed; by 12 hours fatty changes were extensive (Ghoshal et al. 1969). Exposure to white phosphorus has been shown to damage the rough endoplasmic reticulum and cause a disaggregation of polyribosomes (Ganote and Otis 1969; Pam et al. 1972). This damage results in impairment of protein synthesis, in particular, a decrease in the synthesis of the apolipoprotein portion of very low density lipoproteins (VLDL), which are required for the transport of triglycerides. A significant decrease in protein synthesis has been detected as early as 3 hours after oral exposure (Barker et al. 1963). The smooth endoplasmic reticulum is also involved in the formation of the VLDLs, and damage to the smooth endoplasmic reticulum also impairs the formation of VLDLs. The net result of these ultrastructural changes is an accumulation of triglycerides in the liver (Ghoshal et al. 1969). This results in steatosis and fibrosis, which is one of the mechanisms involved in the hepatotoxicity of white phosphorus. The mechanism behind the damage to the endoplasmic reticulum is not known; also, it is not known whether white phosphorus itself or a metabolite of white phosphorus is the damaging agent. In addition to these damages, white phosphorus or a metabolite causes damage to the mitochondria and nuclei in the livers of animals orally exposed to white phosphorus (Ghoshal et al. 1969). The damage to the mitochondria may impair the cell's ability to produce ATP, thus resulting in necrosis of the cell.

Fatty infiltration and/or cellular damage has also been observed in the kidney, brain, and hear& It is possible that white phosphorus (or a metabolite) also impairs the ability of cells in these organs to produce ATP. The mitochondrial damage may also inhibit fatty acid oxidation (also contributing to the decreased availability of ATP) which could result in an accumulation of fat in the organs.

Normal growth of long bones involves bone deposition and bone resorption. Bone deposition during growth, also known as endochondral ossification, involves the formation of osseous tissue (bony tissue)

with cartilage. In long bones, endochondral ossification is seen at the epiphyseal cartilage plate by formation of bone trabeculae on a frame work of unresorbed cartilage, by the action of osteoblasts. The trabeculae extend out from the epiphysis towards the diaphysis or shaft of the bone. The trabeculae and cartilage make up an intercellular calcified cartilage framework. The area of the bone containing this framework is the metaphysis or metaphyseal zone. Normal bone growth involves the resorption of intercellular calcified cartilage matrix, which is left when the cartilage cells are released and disappear on the diaphyseal side of the epiphyseal cartilage plate. Normally a large percentage of this matrix is reabsorbed, leaving only a few spicules on which bone is deposited. The process of tubulation (or formation of the tube in a growing bone) is dependent on the peripheral and central resorption of metaphyseal bone and cartilage. Additional new bone is deposited only in the portion designed to become the cortex of the shaft (Guyton 1981).

The effects of orally administered phosphorus on growth of the long bones has been well documented in the animal literature, and to a lesser extent in humans. Phosphorus apparently decreases the absorption of intercellular calcified cartilage matrix by osteoclasts, in the metaphyseal region of growing bones. Administration of phosphorus to growing animals or children produces “phosphorus bands” of increased bone density and thickness that are visible grossly or from radiograms (Adams 1938a, 1938b; Adams and Samat 1940; Compere 1930a; Sontag 1938; Whalen 1973). The “phosphorus bands” are observed in the metaphyseal region of growing bones, and represent areas of decreased absorption of the calcified cartilage matrix. Histological examination of “phosphorus bands” in young, growing rabbits revealed decreased size of epiphyseal cartilage plate, as well as increased density in the metaphyseal zone, with trabeculae that were greater in number and extended further into the diaphysis, compared to a control rabbit (Adams and Sat-t-tat 1940).

The trabeculae were associated with a greater amount of calcified cartilage matrix. Growing rats exposed to phosphorus had widening of the metaphyseal trabeculae, broadened metaphysis, and a slightly convex lateral contour of the proximal tibia, compared to a control group (Whalen et al. 1973). Osteocytes were small and elongated compared to those in the control group, and osteocytic osteolysis and chondrolysis were decreased or missing. Metaphyseal trabeculae extended deeper into the diaphysis than seen in controls. These effects probably resulted from decreased bone resorption during bone growth, resulting in widening trabeculae and a denser metaphysis. Because normal growth of the bone depends on the resorption of the calcified cartilage matrix, phosphorus decreases the rate of growth of long bones (Adams

1938a, 1938b; Adams and Samat 1940). These "phosphorus bands" were not observed in an adult rabbit or at repaired fracture sites in long bone (Adams 1938b).

The mechanism of action of white phosphorus on the oral cavity has been determined primarily from human occupational studies. The condition progresses slowly and has only been observed in workers exposed for intermediate or chronic durations (Heinmann 1946; Hughes et al. 1962; Kennon and Hallam 1944). It is likely that the effect of phosphorus in the oral cavity is local, resulting from contact of "inhaled" phosphorus particles with tissue in the mouth. Rats exposed to the atmosphere in a phosphorus factory displayed progressive histopathological degeneration of the oral mucosa, reported as pronounced after only 4 months of exposure (Ruzuddinov and Rys-Uly 1986). The oral mucosa of occupationally exposed workers has been described as having a dull, red, unhealthy appearance (Hughes et al. 1962; Kennon and Hallam 1944). These effects on the oral mucosa may result from the general irritant effects of white phosphorus. The condition usually begins with the extraction of one or more teeth, poor healing of the socket, followed by necrosis of tissue in the jaw with severe pain and infection (Heinmann 1946; Hughes et al. 1962; Kennon and Hallam 1944). Tooth loss is thought to contribute to the condition, by exposing the bone in the socket to the irritant effects of white phosphorus. It is not known whether tooth loss (possibly related to poor dental hygiene) precedes the condition, or whether the tooth loss is the result of white phosphorus exposure. It is also not known whether phosphorus ingested and absorbed into the systemic circulation contributed to the development of this condition known as phossy jaw. Evidence exists that long bones of occupationally exposed workers fracture more easily under stress, suggesting a systemic effect of white phosphorus on bones.

2.5 RELEVANCE TO PUBLIC HEALTH

Phosphorus is found in every cell of the body, but most of it (about 80% of the total) is combined with calcium as $Ca_3(PO_4)_2$ in the bones and teeth (Harper 1969; Tietz 1970). Phosphorus is present in cells mainly as organic phosphate, with a small amount in serum as inorganic phosphate (Tietz 1970). Phosphorus is involved in the intermediary metabolism of carbohydrates (Tietz 1970). About 10% is found in combination with proteins, phospholipids, and carbohydrates and in other compounds in the blood and muscle (Harper 1969). The remaining phosphorus is widely distributed in various chemical compounds such as nucleic acids, nucleotides, and adenosine triphosphate (ATP) (Tietz 1970).

2. HEALTH EFFECTS

The metabolism of phosphorus (P) is largely related to that of calcium (Ca). The Ca:P ratio in the diet affects the absorption and excretion of these elements (Harper 1969). Any increase in serum phosphorus results in a decrease of serum calcium by mechanisms which are still unknown. For example, increased serum phosphorus levels and decreased serum calcium levels are seen in uremia (renal retention of phosphorus), hypoparathyroidism, hypocalcemia (decreased serum calcium levels), and hyperphosphatemia (increased serum phosphorus levels), and the reverse is seen in hypercalcemia (increased serum calcium levels) and hyperparathyroidism. Hypophosphatemia (low serum phosphorus levels) is seen in ricketts (vitamin D deficiency) (Harper 1969; Tietz 1970).

The recommended ratio of phosphorus to calcium is 1:1, except in infants it is 2:1. For older infants, the recommended intake of phosphorus is increased to 80% of the calcium requirement, so that the ratio is similar to cow's milk (Harper 1969). Both phosphorus and calcium are distributed similarly in foods, hence a sufficient intake of calcium ensures a sufficient intake of phosphorus. The exception is cows' milk, which contains more phosphorus than calcium (Harper 1969). The adult daily requirement for phosphorus is about 700 mg. A balanced diet provides sufficient amounts of phosphorus because it is commonly found in foods (phosphoproteins and phospholipids, inorganic phosphate), especially milk and milk products, wheat, meats and fish (Latner 1975). In the body, normal serum (inorganic) phosphorus levels are 4-7 mg/l00 mL in children and 34.5 mg/l00 mL in adults and the elderly. In body fluids and tissues, normal serum phosphorus levels found are 40, 170-250, 360, and 22,600 mg/l00 mL in blood, muscle, nerve, and both bones and teeth, respectively (Harper 1969; Tietz 1970).

White Phosphorus. White phosphorus does not naturally occur in the environment. It has been manufactured in the past for use in such products as matches, fireworks, pest poisons, and incendiary munitions. It is primarily in the manufacture and use of these products where human exposure has occurred. White phosphorus is also commonly called yellow phosphorus.

Chemically, white phosphorus is an allotropic form of elemental phosphorus containing four phosphorus atoms. It is a solid at room temperature and may be stored as a solid in water without breaking down or significantly dissolving, yet it is soluble in oils and lipids. It is unstable in air, either volatilizing or spontaneously cornbusting at room temperature. Oxidized inorganic forms of phosphorus include phosphorus pentoxide, which is a known hygroscopic compound. The oxidized forms of phosphorus are also reactive, forming various higher oxo acids in the presence of water, and various lower oxo acids in an alkaline aqueous environment with the addition of heat.

2. HEALTH EFFECTS

Biologically, white phosphorus is highly lipid-soluble indicating that it is probably absorbed easily via all routes of exposure, although this has not yet been demonstrated. Most of the absorbed white phosphorus is then probably quickly broken down by some of the inorganic reactions described above.

White phosphorus is highly toxic. People have attempted suicide by ingesting matches, fireworks, roach poison, or rat poison containing white phosphorus. Unless emergency poison treatments are applied within 2-3 hours, death is likely. Animal data are consistent with human data after acute oral exposure. Further, a life-threatening condition called phossy jaw has been described following intermediate or chronic occupational exposure to white phosphorus.

Systemic effects following oral ingestion in humans and animals usually begin with severe gastrointestinal distress within several hours, probably due to extreme irritation of the gastrointestinal lining. This may be followed during the next 3 weeks by life-threatening organ impairments that are manifested by severe cardiovascular, hepatic, renal, hematological, and neurological effects. Respiratory, dermal, ocular, reproductive, and immunological effects have generally not been severe after acute oral exposure. Histological changes in the mucous membranes of the mouth and susceptibility to death among pregnant females during birth are also possible following longer term exposure.

Similar systemic effects have been observed following dermal white phosphorus-induced burns. This route of exposure also inflicts 2nd and 3rd degree burns that may be slow to heal.

White Phosphorus Smoke. There is limited information on the toxicity of white phosphorus smoke. Based on this information, the respiratory tract appears to be the most sensitive target. Because white phosphorus smoke contains a number of phosphorus compounds and a small amount of white phosphorus, the toxicity of white phosphorus smoke cannot be extrapolated from human and animal studies involving exposure to white phosphorus.

Minimal Risk Levels for White Phosphorus

Inhalation MRLs

No MRLs have been derived for inhalation exposure to white phosphorus because none of the inhalation studies reported exposure levels.

2. HEALTH EFFECTS

Oral MRLs

- An MRL of $2x10^{-4}$ mg/kg/day has been derived for intermediate-duration oral exposure to white phosphorus based on a NOAEL of 0.015 mg/kg/day (IRDC 1985).

In animals, the lowest LOAEL value was 0.075 mg/kg/day (Bio/dynamics 1991; IRDC 1985). At this dose level, there were significant increases in mortality during late pregnancy and parturition (Bio/dynamic 1991; IRDC 1985), liver necrosis (Bio/dynamics 1991), and neurotoxicity (Bio/dynamics 1991). The IRDC (1985) study also identified a NOAEL of 0.075 mg/kg/day for systemic, developmental, and reproductive effects, and the Bio/dynamics (1991) study identified a NOAEL of 0.075 mg/kg/day for developmental and reproductive effects. At first examination, it appeared that no intermediate oral MRL could be derived because the lowest dose indicated in Table 2-2 was 0.075 mg/kg/day, which was associated with increased mortality in pregnant rats in two reproductive studies one by Bio/dynamics (1991) and one by IRDC (1985). However, in the IRDC (1985) study, 0.075 mg/kg/day was a NOAEL for systemic end points (Table 2-2); therefore, the lower doses in the study did not appear in the LSE table. Further examination of the study revealed no effects in rats at lower doses of 0.005 and 0.015 mg/kg/day. Therefore, the 0.015-mg/kg/day dose, which was not associated with increased mortality and produced no other effects, was the NOAEL for the intermediate database. In the Bio/dynamics (1991) study, only the 0.075-mg/kg/day dose was used, which in addition to increased mortality, was associated with hepatic toxicity (Table 2-2). Therefore, the critical end point is hepatic. It should be noted that the MRL was actually based on a NOAEL of 0.015 mg/kg/day since 0.075 mg/kg/day was associated with hepatic effects in the Biojdynamics (1991) study. The resultant intermediate MRL would be $2x10^{-4}$ mg/kg/day. It was noted that the EPA derived an RfD from the same NOAEL of 0.015 mgikg/day in the same study.

The lowest LOAEL value (0.083 mg/kg/day) in healthy humans ingesting white phosphorus for an intermediate duration was identified in the Sontag (1938) study. Lower LOAEL values have been identified in children with rickets (Phemister 1918). Because these children had a pre-existing condition, these data were not considered reliable. Other systemic effects and neurological effects were observed at this dose. This study was not selected as the basis of an intermediate-duration oral

MRL because it is a case report of a single child and no assessment of hepatic or renal toxicity (liver and kidneys are two primary targets of white phosphorus toxicity) was made.

No acute oral MRL could be derived for exposure to white phosphorus. A number of case reports of individuals accidentally or intentionally ingesting a single dose of white phosphorus identified LOAEL values for gastrointestinal effects. No NOAEL values were identified in the human studies. The lowest LOAEL value for systemic and reproductive effects identified in humans was 2 mg/kg/day (Harm and Veale 1910); however, this is a lethal dose. The lowest LOAEL values in animals were 0.2 mg/kg/day for impaired liver function in dogs (Sigal et al. 1954) and 0.3 mg/kg/day for developmental effects in rabbits (Adams 1938a); both studies reported data for a small number of animals. No acute oral MRL could be derived because serious effects (impaired liver function) occurred in dogs at 0.2 mg/kg/day, the lowest dose in the acute oral database.

No chronic-duration MRL for oral exposure to white phosphorus could be derived. Information on exposure levels was not reported in the human chronic-duration studies. A LOAEL value of 0.2 mg/kg/day was identified in a chronic dog study for skeletal effects (Fleming et al. 1942). However, this study was not selected as the basis for a chronic-duration oral MRL because the study authors did not specify which organs were examined, and thus it is not known whether the liver and kidneys (two primary targets of white phosphorus toxicity) were examined. In addition, this LOAEL value is higher than the intermediate LOAEL value for increased mortality in pregnant dams (Bio/dynamics 1991; IRDC 1985).

Minimal Risk Levels for White Phosphorus Smoke

Inhalation MRLs

- An MRL of 0.02 mg/m^3 has been derived for acute-duration inhalation exposure to white phosphorus smoke from a minimal LOAEL of 187 mg/m^3 for 5 minutes for throat irritation in humans (White and Armstrong 1935). Although a 5minute exposure duration is usually too brief to consider for MRLs and expanding over a 24-hour period would result in an exposure level of 0.6 mg/m^3, further experiments indicated exposure for longer durations would result in more severe effects. In the field, white phosphorus smoke was generated at 0.1 mg/m^3 to protect soldiers from detection. In addition, the OSHA PEL is 0.1 mg/m^3. Therefore, expanding the 5minute duration over 24 hours is reasonable.

2. HEALTH EFFECTS

The acute toxicity of airborne white phosphorus smoke has been studied in humans and a number of animal species. The human exposure studies assessed respiratory toxicity only (Walker et al. 1947; White and Armstrong 1935). The animal exposure studies were primarily lethality studies (Brown et al. 1980; White and Armstrong 1935). In the Brown et al. (1980) study, rats and guinea pigs were killed 2 weeks after the single exposure, and a small number of animals were examined. The White and Armstrong (1935) study examined a limited number of end points in rats, mice, and goats which died during or after exposure. The human and animal studies suggest that the respiratory tract is the most sensitive end point of toxicity; however, because of study limitations, other sensitive end points cannot be eliminated.

No intermediate-duration inhalation MRL was derived. Only one intermediate-duration inhalation study was identified. In this study, rats were exposed to several concentrations of white phosphorus smoke for 15 minutes/day (Brown et al. 1981). The study suggests that the respiratory tract is the most sensitive end point of toxicity.

No chronic-duration inhalation exposure studies were located; therefore, an MRL for chronic-duration exposure to white phosphorus smoke could not be derived.

Death

White Phosphorus. White phosphorus is highly toxic via the oral route. Many case reports of deaths resulting from intentional or accidental ingestion of white phosphorus in rat and cockroach poison and firecrackers were located (Diaz-Rivera et al. 1950, 1961; Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Tally et al. 1972; Torrielli et al. 1974; Wechsler and Wechsler 1951; Wertham 1932; Winek et al. 1973). The classical progression of symptoms from fatal oral white phosphorus poisoning in humans involves three stages (McCarron et al. 1981). Symptoms in the first stage include vomiting (with vomitus sometimes containing blood and/or pieces of the gastric mucosa) and extreme abdominal cramps and pain. These symptoms probably result from the extreme irritant effects of white phosphorus on the gastrointestinal lining. In the second stage the patient improves symptomatically and appears to be recovering. The third stage usually consists of a rapid decline in condition, with death resulting from failure of one or more organ systems, usually the liver, kidney, and cardiovascular and central nervous systems. Autopsy often reveals massive damage to one or more of these organ systems

(Diaz-Rivera et al. 1961; Dwyer and Helwig 1925; Harm and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; Rao and Brown 1974; Wechsler and Wechsler 1951; Wertham 1932). Not all cases of fatal white phosphorus poisoning follow the classic scenario. Death from cardiac arrest may occur rapidly (Diaz-Rivera et al. 1961). Because vomiting often expels much of the ingested dose, the effective dose usually cannot be estimated. In one case report, a woman ingested a fatal dose of white phosphorus, but did not expel the ingested dose before dying (Hann and Veale 1910). In this case the ingested dose (2 mg/kg/day) probably approximates the effective dose producing death. This study identifies a LOAEL of 2 mg/kg/day for a single oral dose of white phosphorus in humans. No deaths occurred in children receiving daily doses of ≤0.158 mg/kg/day for intermediate durations (Compere 1930a; Phemister 1918; Sontag 1938). No studies were located regarding death in humans after chronic oral exposure to white phosphorus.

Longer term occupational exposure to white phosphorus can result in a condition (phossy jaw) that is potentially life-threatening. Two white phosphorus-related deaths were reported in a study of 71 workers from three plants involved in the production of fireworks (Ward 1928). Both workers developed phossy jaw, a degenerative condition affecting the soft tissue, bones, and teeth of the oral cavity, after chronic exposure to the atmosphere at the factory. It is likely that white phosphorus-related necrosis results from a direct local effect following contact of phosphorus with tissues in the oral cavity. The cause of death in both cases was listed as septicemia, with abscess of a tooth and necrosis of the jaw listed as contributory causes. Thus, death in both cases resulted from infections, probably secondary to the degenerative effects of white phosphorus on the oral cavity (Ward 1928).

Animal data support the acute oral toxicity of white phosphorus. Mortality rates of ≥20% were reported for rats (Lee et al. 1975; Torrielli et al. 1974) and mice (Hurwitz 1972) exposed to single gavage doses ranging from 3 to 6 mg/kg phosphorus, compared to the LOAEL of 2 mg/kg identified in the case report of a woman intentionally ingesting rat poison (Hann and Veale 1910). In two one-generation reproduction studies in rats, 30-47% (IRDC 1985) and 53% (Bio/dynamics 1991) of the pregnant females treated by gavage with 0.075 mg/kg/day for an intermediate duration (145-204 days) died (or were killed due to morbidity) in late gestation or parturition. Dams exposed to 0.015 mg/kg/day for similar durations did not have an increased mortality rate (IRDC 1985). Compound-related deaths were not observed in male rats exposed to 0.075 mg/kg/day for similar durations (IRDC 1985; Bio/dynamics 1991). The high mortality rates in pregnant rats may indicate a parturition-related sensitivity to the toxic effects of white phosphorus. Upon histopathological evaluation of selected tissues (heart, liver, kidneys, uterus, ovaries, and

testes/epididymides), the only finding considered treatment related was an increased incidence of centrilobular liver necrosis in 8/30 treated females (Bio/dynamics 1991).

No studies were located regarding death in animals after inhalation or dermal (nonburn) exposure to white phosphorus.

Information that was located regarding the contribution of white phosphorus to death after acute white phosphorus-induced burns suggests a possible difference between humans and animal models. A high rate of mortality (l2/27) in humans occurred following accidental explosions from ignited white phosphorus in munitions factories (Walker et al. 1947). The workers that died had third-degree burns over ≈35-90% of their body surface. Those surviving had burns over ≤19% of the body surface. The authors noted that these burn cases followed a course that was "indistinguishable" from that of nonphosphorus related third-degree burns. The contribution of white phosphorus to the increased mortality is not known.

In animal studies using experimental white phosphorus burns, there is evidence that phosphorus compounds remaining in the burn site may contribute to the increased mortality. Experimental burns with white phosphorus have resulted in abnormal EKGs in rabbits (Bowen et al. 1971) and extensive renal and hepatic damages in rats (Ben-Hur et al. 1972; Ben-Hur and Appelbaum 1973). Increased mortality in these studies was attributed to the systemic effects of white phosphorus or phosphorus compounds, rather than to the toxicity of the burn. White phosphorus is probably absorbed to a much greater degree from severe burns than from normal dermal exposure.

White Phosphorus Smoke. No deaths were reported in humans inhaling white phosphorus smoke at concentrations as high as 592 mg phosphorus pentoxide equivalents/m^3 (817 mg orthophosphoric acid equivalents/m^3) for 3.5 minutes or 514 mg pentoxide equivalents/m^3 (709 mg orthophosphoric acid equivalents/m^3) for 15 minutes (White and Armstrong 1935). In animals exposed to white phosphorus smoke, deaths have been observed following acute- and intermediate-duration inhalation exposure or acute oral exposure. The lowest lethal concentrations identified in animals exposed once to white phosphorus smoke are 1,943 mg orthophosphoric acid equivalents/m^3 for rats (Brown et al. 1980), 310 mg phosphorus pentoxide equivalents/m^3 (428 mg orthophosphoric acid equivalents/m^3) for mice (White and Armstrong 1935), 677 mg orthophosphoric acid equivalents/m^3 for guinea pigs (Brown et al. 1980), and 6,230 mg phosphorus pentoxide equivalents/m^3 (8,599 mg orthophosphoric acid equivalents/m^3) for goats (White and Armstrong 1935). Similar lethal concentrations (1,742 mg orthophosphoric acid equivalents/m^3) were

observed in rats exposed to white phosphorus smoke 15 minutes/day, 5 days/week, for 6-13 weeks (Brown et al. 1981; Starke et al. 1982). For the most part, the cause of death was not determined. An exception is the mouse acute exposure study. A thick mucous discharge was observed in the nares of dying mice. This discharge plugged the nares, and the mice died of asphyxiation (White and Armstrong 1935). For the other species tested, the most prominent nonlethal effect was moderate-to-severe respiratory tract irritation. It is possible that the respiratory tract damage was severe enough to be life-threatening.

Based on this information on deaths in animals, it is likely that exposure to high concentrations of white phosphorus smoke would be fatal to humans.

Systemic Effects

Respiratory Effects

White Phosphorus. In a study of 71 humans occupationally exposed to fumes/vapors and paste containing white phosphorus for intermediate or chronic durations, an irritating cough was reported as occurring in a large proportion of the employees (Ward 1928). No quantitative information was provided. No information on respiratory effects was reported in other occupational exposure studies (Heinmann 1946; Hughes et al. 1962; Kennon and Hallam 1944). White phosphorus has an irritating effect on other soft tissues, including the oral mucosa and gastrointestinal tract. Thus, inhalation of white phosphorus might be expected to produce irritation in the tissue of the lungs.

No studies were located regarding respiratory effects in animals after inhalation exposure to white phosphorus.

Various changes in respiration were reported in humans following intentional or accidental ingestion of life-threatening doses of white phosphorus. During the initial stage following oral white phosphorus poisoning, the patient is usually anxious and in a great deal of pain. Increases are observed in many vital signs, including respiratory rate (Hann and Veale 1910; Rao and Brown 1974; Simon and Pickering 1976; Talley et al. 1972; Winek et al. 1973). Rales have been reported in several cases of serious white phosphorus poisoning (Dwyer and Helwig 1925; Pietras et al. 1968; Rao and Brown 1974; Wechsler and Wechsler 1951). If the condition worsens, the patient often becomes comatose and may display decreased,

shallow respirations (Rubitsky and Myerson 1949) or Cheyne-Stokes respiration (Wechsler and Wechsler 195 1). Autopsy has revealed pulmonary damage including a small amount of dark fluid in the pleural cavity (Hann and Veale 1910), pulmonary congestion and edema throughout the stroma (Wechsler and Wechsler 1951), hemorrhagic bronchopneumonia (Winek et al. 1973), and fatty deposition in parenchyma, bronchial epithelium, and tracheal epithelium and cartilage (Humphreys and Halpert 1931). Death from cardiopulmonary failure was reported following ingestion of white phosphorus in rat poison (Simmon and Pickering 1976; Winek et al. 1973); however, the pulmonary effect was probably secondary to cardiovascular failure. Death due to acute oral white phosphorus poisoning is generally attributed to organ systems other than the respiratory tract (Diaz-Rivera et al. 1961; Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; Rao and Brown 1974; Wechsler and Wechsler 1951; Wertham 1932).

No treatment-related microscopic changes were observed in the lungs of rats exposed to 0.2 mg/kg/day white phosphorus in the diet for a chronic duration (Fleming et al. 1942) or 0.075 mg/kg/day white phosphorus by gavage for an intermediate duration (IRDC 1985). Heavy breathing and apnea were reported following ingestion of a fatal quantity of white phosphorus by a cat (Frye and Cucuell969). Necropsy revealed hyperemia, hemorrhage, and edema in the lungs.

No studies were located regarding respiratory effects following dermal exposure, both for burn and nonburn.

White Phosphorus Smoke. Respiratory tract irritation has been observed in humans exposed to white phosphorus smoke for 2-15 minutes. Throat irritation during talking, coughing, nose irritation, and erythema and edema of the larynx and vocal cords have been reported (Walker et al. 1947; White and Armstrong 1935).

Respiratory tract irritation has been observed at concentrations of 187 mg phosphorus pentoxide equivalents/m^3 (258 mg orthophosphoric acid equivalents/m^3) for 5 minutes or longer (White and Armstrong 1935). Damage to the respiratory tract has also been observed in animals exposed to white phosphorus smoke for acute and intermediate durations. Slight-to-intense congestion, edema, and hemorrhages were observed in the lungs of rats, mice, and goats dying during or following a l-hour exposure to concentrations of 1,350,470, and 3,870 mg phosphorus pentoxide equivalents/m^3, respectively (1,863,649, and 5,342 mg orthophosphoric acid equivalents/m^3) (White and Armstrong

1935) and rats exposed to 3,027 mg orthophosphoric acid equivalents/m^3 for 90 minutes (Brown et al. 1980). Exposure to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks resulted in minimal-to-severe interstitial pneumonia in rats (Brown et al. 1981). In addition to these effects in the lungs, slight tracheitis and laryngitis has been observed in rats exposed to 884 mg orthophosphoric acid equivalents/m^3 for 15 minutes/day, 5 days/week, for 6-13 weeks. The severity of these effects on the trachea and larynx increased at higher concentrations (Brown et al. 1981). Dermal studies examining the respiratory tract were not located. Because the respiratory tract effects observed following inhalation exposure to white phosphorus smoke are probably the result of direct contact with the respiratory tissue, it is not likely that similar respiratory tract effects would be observed following dermal exposure.

Cardiovascular Effects

White Phosphorus. Effects on the myocardium have been observed in humans exposed to a single oral dose of white phosphorus, humans exposed to molten phosphorus, and rabbits burned by phosphorus. Alterations in electrocardiogram readings, tachycardia, arrhythmias, atrial fibrillation, and decreased ventricular contractility have been observed in humans orally exposed to white phosphorus or burned by phosphorus (Dathe and Nathan 1946; Diaz-Rivera et al. 1950,196l; Dwyer and Helwig 1925; Ehrentheil 1957; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Simon and Pickering 1976; Summerlin et al. 1967; Talley et al. 1972) and rabbits burned by white phosphorus (Bowen et al. 1971). These alterations may be due to a direct effect on the heart as evidenced by the fatty infiltration, necrosis, cross striations, and interstitial edema that have been observed in the hearts of affected individuals (Diaz-Rivera et al. 1961; Dwyer and Helwig 1925; Humphreys and Halpert 1931; Talley et al. 1972; Wechsler and Wechsler 1951; Wertham 1932) or may be secondary to peripheral vascular collapse that can cause a decrease in the coronary blood flow resulting in severe myocardial ischemia. Longer-term human studies did not examine cardiac end points. No evidence of myocardial damage were observed in rats orally exposed to relatively low concentrations of white phosphorus (Bio/dynamics 1991; IRDC 1985).

Effects on the vascular system have also been observed in humans and animals. One of the more prominent effects following acute human exposure to white phosphorus is shock, manifested by a marked decrease in blood pressure, vascular collapse, marked decrease in pulse, cyanotic nail beds, cold clammy skin, and cardiopulmonary arrest (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al.

1950,196l; Dwyer and Helwig 1925; Hann and Veale 1910; McCarron et al. 1981; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951; Winek et al. 1973). The mechanism involved in the development of shock in these individuals is not known. Hemorrhaging in internal organs as well as the appearance of petechial hemorrhages on the skin have been reported in a number of acute human exposure cases (Harm and Veale 1910; Humphreys and Halpert 1931; Winek et al. 1973). In addition, an increase in permeability of capillary walls and lesions in the walls of blood vessels have been observed in the mouth of rats exposed for an intermediate duration to an unknown concentration of airborne phosphorus (Ruzuddinov and Rys-Uly 1986), and proliferation of the tunica intima and occlusion of the blood vessel lumen were observed in the cortical blood vessels of rabbits receiving intravenous injections of ≥15 mg/kg/day of white phosphorus for an intermediate duration (Ferraro et al. 1938).

White Phosphorus Smoke. There is limited information on the potential of white phosphorus smoke to induce cardiovascular effects in humans. No human exposure studies examining the cardiovascular system were located. No gross or histological alterations were observed in the hearts of rats exposed to white phosphorus smoke at concentrations as high as 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981). No dermal exposure studies examining the cardiovascular system were located.

Gastrointestinal Effects

White Phosphorus. No information on the gastrointestinal effects in humans or animals following inhalation, dermal, or dermal burn exposure is available. In humans acutely ingesting poisons containing white phosphorus, the most prominent gastrointestinal effect was vomiting (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 1931; Matsumoto et al. 1972; McCarron et al. 1981; McIntosh 1927; Newburger et al. 1948; Pietraset al. 1968; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951; Winek et al. 1973). Reported doses that induced vomiting ranged from 2 to 23 mg/kg/day. The vomiting usually started shortly after ingesting the white phosphorus and persisted for several days. Abdominal pain or cramps often accompanied the vomiting. The effects on the gastrointestinal tract were probably due to the irritating effects of white phosphorus. This is supported by the necrosis and erosion of the esophagus, stomach, duodenum, and jejunum (Wechsler and Wechsler 1951) and the gastrointestinal hemorrhage

(Dwyer and Helwig 1925; Hann and Veale 1910; Humphreys and Halpert 1931; Wertham 1932; Winek et al. 1973) that have been observed in humans. Gastrointestinal effects have not been observed in children ingesting white phosphorus for an intermediate duration (Compere 1930a; Phemister 1918; Sontag 1938).

Similar gastrointestinal effects have been observed in animals ingesting white phosphorus. Vomiting was observed in dogs ingesting an unreported amount of white phosphorus (Dwyer and Helwig 1925) and erosion of the esophagus and stomach was observed in a cat ingesting a single dose (amount not reported) of phosphorus (Fry and Cucuel 1969). No gross or microscopic alterations were observed in rats exposed to a relatively low dose (0.075 mg/kg/day) of white phosphorus for an intermediate duration (IRDC 1985).

White Phosphorus Smoke. No studies were located regarding gastrointestinal effects in humans after exposure to white phosphorus smoke. No gross or histological evidence of gastrointestinal tract damage was observed in rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week for 13 weeks (Brown et al. 1981). No dermal exposure studies examining gastrointestinal effects were located.

Hematological Effects

White Phosphorus. Hematological effects have been observed in a number of individuals accidentally or intentionally ingesting white phosphorus containing poisons or fireworks. The effects on erythrocytes appear to be inconsistent. Increases and decreases in erythrocyte levels, increases and decreases in hemoglobin levels, and anemia have been observed (Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Caley and Kellock 1955; McIntosh 1927; Simon and Pickering 1976). The changes in erythrocyte parameters may be a reflection of the hemorrhages observed in a number of individuals (Datbe and Nathan 1946; Hann and Veale 1910; Humphreys and Halpert 1931; Wechsler and Wechsler 1951; Winek et al. 1973) or a compensatory mechanism because of tissue anoxia. Anemia has also been observed in individuals occupationally exposed to airborne white phosphorus via inhalation, ingestion, an-d dermal contact (Ward 1928). Increases or decreases in the levels or percentage of polymorphonuclear leukocytes (neutrophils) have been observed in individuals acutely exposed to ingested white phosphorus (Diaz-Rivera et al. 1950; Ehrentheil 1957; Fletcher and Galambos 1963; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968). No hematological effects were observed in a number of individuals acutely exposed to phosphorus (Fletcher and Galambos 1963; Simon and Pickering 1976) or in a child exposed for an intermediate duration (Sontag 1938).

2. HEALTH EFFECTS

Anemia, hemolysis, and leukocytosis have been observed in individuals burned by white phosphorus (Summerlin et al. 1967; Walker et al. 1947). Because copper sulfate is often used to treat white phosphorus burns, it is difficult to determine whether the anemia and hemolysis were due to copper or white phosphorus poisoning.

A small number of the available animal studies have measured hematological effects. An increase in total leukocyte and monocyte levels were observed in guinea pigs acutely exposed to ingested white phosphorus (Lawrence and Huffman 1929) An increase in the levels of monocytes was also observed in guinea pigs receiving white phosphorus via subcutaneous injection for an acute duration (Lawrence and Huffman 1929). Hemosiderosis has been observed in the spleens of rats subcutaneously exposed to 1.2 mg/kg/day for an acute duration, exposed to 0.8 mg/kg/day for an intermediate duration, and 0.05 mg/kg/day for a chronic duration (Fleming et al. 1942).

White Phosphorus Smoke. Hematological end points were not examined in the three human exposure studies that were located (Walker et al. 1947; White and Armstrong 1935). No significant changes in erythrocyte, hematocrit, hemoglobin, or total and differential leukocyte levels were observed in rats exposed to 3,027 mg orthophosphoric acid equivalents/m^3 for 90 minutes (Brown et al. 1980), guinea pigs exposed to 984 mg orthophosphoric acid equivalents/m^3 for 10 minutes (Brown et al. 1980), or rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 of white phosphorus smoke for 15 minutes/day, 5 days/week for 13 weeks (Brown et al. 1981). No dermal exposure studies examining hematological effects were located. This information is not adequate for determining the potential of white phosphorus smoke to induce hematological effects in humans.

Musculoskeletal Effects

White Phosphorus. White phosphorus produces two entirely different effects on bone, depending on the type of exposure. Longer-term occupational exposure to airborne phosphorus can produce a degenerative condition (phossy jaw) affecting the entire oral cavity including soft tissue, teeth, and bones (Heimann 1946; Hughes et al. 1962; Ward 1928). The effects of phossy jaw can be extreme, involving severe necrosis of soft tissue, teeth, and bones in the oral cavity. Massive life-threatening infections often occur during the development of phossy jaw. The progression of the disease was similar in the cases described, usually beginning with the extraction of one or more teeth, poor healing of the socket, followed by necrosis of tissue in the jaw with severe pain and infection. Treatment consisted of repeated removal of

destroyed bone tissue and teeth, draining of abscesses, and reconstructive surgery. In severe cases, extensive removal of necrotic bone tissue led to permanent disfigurement. It is likely that the effect of white phosphorus in the oral cavity is local, resulting from contact of inhaled white phosphorus particles with tissue in the mouth. Workers in phosphorus factories have oral mucosa described as having a dull, red, unhealthy appearance (Hughes et al. 1962). Placement of a white phosphorus pellet in the right mucobuccal cavity of a man employed as a magician, eventually (after ≈ 14 years) resulted in massive necrosis of the maxilla and floor of the antrum on the right side of the mouth; perforations were present through which the maxillary sinus and nasal cavity were visible. No effects were observed on the left side of the maxilla or on the mandible. Radiographs revealed no evidence of pathology in the chest and long bones. The damage to the jaw was highly localized affecting only the side the mouth exposed to the pellet. Exposed bones, such as sockets following tooth extraction, may be especially susceptible to the irritating affects of white phosphorus. Thus, poor dental hygiene might be a contributing factor to the development of phossy jaw. It is not known whether white phosphorus ingested and absorbed into the systemic circulation contributed to the development of phossy jaw. There is evidence that occupational exposure to white phosphorus weakens the long bones in the body, as indicated by fractures following minimal stress (Dearden 1899).

Ingested white phosphorus does not affect the oral cavity. However, bone effects were observed in children (Compere 1930a; Phemister 1918; Sontag 1938) and young animals (Adams 1938a, 1938b; Adams and Surnat 1940; Whalen et al. 1973) following acute- and intermediate-duration oral exposure to phosphorus. Because white phosphorus-related effects were observed in growing bones, these effects were considered developmental in nature and are described under Developmental Effects in Section 2.2.2.4.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to white phosphorus.

Chronic oral exposure to 0.2 mg/kg/day white phosphorus in the diet resulted in epiphyseal line thickening and greater extension of trabeculae into the diaphysis of unspecified bones, compared to a control group (Fleming et al. 1942). This study is limited by the failure to specify incidences of effects at intervals during dosing and by the failure to state the dosing duration explicitly. Thus, it is not known if these bone effects occurred in young or adult rats.

2. HEALTH EFFECTS

White Phosphorus Smoke. No studies were located regarding musculoskeletal effects in humans and animals after inhalation or dermal exposure to white phosphorus smoke.

Hepatic Effects

White Phosphorus. One of the primary targets of white phosphorus is the liver. Hepatotoxicity has been observed in humans orally exposed to white phosphorus and burned by white phosphorus and in animals exposed orally and parenterally and burned by white phosphorus. No information on hepatotoxicity in animals following exposure to airborne white phosphorus was located. The following indicators of hepatic damage have been noted in humans acutely exposed to white phosphorus: jaundice, hepatomegaly, increased serum levels of bilirubin, impaired liver function tests, and increases in AST and ALT (Caley and Kellock 1955; Diaz-Rivera et al. 1950, 1961; Ehrentheil 1957; Fletcher and Gahunbos 1963; Greenberger et al. 1964; Humphreys and Halpert 1931; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951). Autopsies or liver biopsies were performed in a number of these individuals, and marked liver damage was observed. Necrosis, fibrosis, hemorrhages and fatty infiltration were observed (Dwyer and Helwig 1925; Fletcher and Galambos 1963; Greenberger et al. 1964; Harm and Veale 1910; Humphreys and Halpert 1931; Rao and Brown 1974; Wechsler and Wechsler 1951). Similar hepatic effects were observed in humans burned by white phosphorus (Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). No alterations in liver function tests were observed in workers chronically exposed to an unreported amount of airborne white phosphorus (Hughes et al. 1962). Although there is extensive information on the hepatotoxicity of white phosphorus in humans ingesting a single dose of white phosphorus, there is very limited information on dose-effect relationships. Most of the individuals vomited or received gastric lavage shortly after ingesting the white phosphorus; thus, reliable doses could not be calculated. No dose information is available for the inhalation, dermal, or dermal burn routes.

Similar hepatic effects have been observed in animals orally exposed for acute and intermediate durations (Ashburn et al. 1948; Ghoshal et al. 1969; Hurwitz 1972; Mallory 1933; Pani et al. 1972; Paradisi et al. 1984; Peterson et al. 1991; Seakins and Robinson 1964; Sigal et al. 1954) and dermally burned with white phosphorus once (Ben-Hur et al. 1972; Ben-Hur and Appelbaum 1973). The lowest LOAEL value for hepatic effects identified in animals orally exposed to white phosphorus is 0.2 mg/kg/day (Sigal et al. 1954) for acute duration and 0.25 mg/kg/day (Mallory 1933) for intermediate duration. No NOAEL value

for acute oral exposure was identified. As discussed in Section 2.2.2.2, conflicting results in the Bio/dynamics (1991) and IRDC (1985) studies preclude identifying the 0.075 mg/kg/day dose as a NOAEL or LOAEL value. The lowest LOAEL value for dermal burn exposure is 29 mg/kg/day. No NOAEL values for dermal burn exposure were identified.

Animal data provide information on the progression of the hepatic effects. Four hours after dosing, minimal hepatocytic fatty changes were observed; by 12 hours extensive hepatocytic fatty changes were observed (Ghoshal et al. 1969). The severity of the liver effects was duration related, with early signs of fibrosis being detected after 8 weeks of exposure and extensive fibrosis after 12 weeks (Peterson et al. 1991). The steatosis (fatty infiltration) observed in the livers of humans and animals is likely to be the result of impaired protein synthesis of the liver. One of the earliest signs of liver toxicity is a decrease in protein synthesis (Barker et al. 1963); the impaired protein synthesis is probably due to the damage to the rough endoplasmic reticulum and disaggregation of polyribosomes (Garrote and Otis 1969; Pani et al. 1972). The decrease in synthesis of apolipoproteins results in a decrease in the transport of triglycerides out of the liver. Twelve hours after ingestion of a single dose of white phosphorus, significant increases in liver triglyceride and decreases in plasma triglyceride levels were observed (Ghoshal et al. 1969). The damage observed in the smooth endoplasmic reticulum (site for conjugation of different components of lipoproteins) (Ganote and Otis 1969; Ghoshal et al. 1969) may also play a role in the decreased ability to remove triglycerides from the liver. Other damage in the liver (e.g., fibrosis) may be due to the ultrastructural changes that are observed in the mitochondria (focal matrical rarefaction, loss of cristae, and rupture of peripheral membranes) (Ghoshal et al. 1969).

White Phosphorus Smoke. There is limited information on hepatotoxicity following exposure to white phosphorus smoke. No human exposure studies examining hepatic end points were identified. In animals, cloudy swelling of the liver was observed following 60-90-minute exposures to 1,170 mg phosphorus pentoxide equivalents/m^3 (1,615 mg orthophosphoric acid equivalents/m^3) (White and Armstrong 1935) or 3,027 mg orthophosphoric acid equivalents/m^3 in rats (Brown et al. 1980), 470 mg phosphorus pentoxide equivalents/m^3 (649 mg orthophosphoric acid equivalents/m^3) in mice (White and Armstrong 1935), and 7,320 mg phosphorus pentoxide equivalents/m^3 (10,104 mg orthophosphoric acid equivalents/m^3) in goats (White and Armstrong 1935). Hepatic effects were not observed in rats exposed to 1,742 mg orthophosphoric acid/m^3 15 minutes/day, 5 days/week for 6 or 13 weeks (Brown et al. 1981). No studies examining hepatic end points following dermal exposure were located.

2. HEALTH EFFECTS

Renal Effects

White Phosphorus. No changes in urinary creatinine levels were observed in workers exposed to an unspecified amount of airborne white phosphorus (Hughes et al. 1962). Evidence of severe renal effects have been observed in humans orally exposed to white phosphorus and burned by white phosphorus. In animals, renal effects have been observed following oral and dermal burn exposure. There is no information on the potential of white phosphorus to induce renal effects in humans dermally exposed to white phosphorus or animals exposed by inhalation and dermal routes.

The presence of protein, albumin, and acetone in the urine and increases in blood levels of urea nitrogen, nonprotein nitrogen, and creatinine have been observed in individuals acutely ingesting rat (or roach) poisons or fireworks containing white phosphorus (Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Fletcher and Galambos 1963; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Rubitsky and Myerson 1949). These clinical symptoms suggest a severe decrease in renal function. In addition to these indicators of renal function, histological damage consisting of fatty changes in the tubules and loop of Henle and engorged glomeruli and intratubular capillaries have been observed in humans acutely exposed to white phosphorus (Dwyer and Helwig 1925; Humphreys and Halpert 1931; Wechsler and Wechsler 1951; Wertham 1932). Several case reports have reported no alterations in kidney function (Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Simon and Pickering 1976). Histological alterations have also been observed in a number of humans ingesting single dose of white phosphorus. Fatty changes in the tubules, loop of Henle (Dwyer and Helwig 1925; Humphreys and Halpert 1931; Wertham 1932) and engorged glomeruli and intratubular capillaries (Wechsler and Wechsler 195 1) have been observed. Indicators of impaired renal function (increased blood urea nitrogen, and increased urinary protein and urea nitrogen) have also been observed in humans acutely burned by white phosphorus (Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). No longer-term human oral or dermal burn studies examining renal effects were located.

Histological alterations in the kidneys have been observed in animals acutely ingesting white phosphorus and burned by white phosphorus. Fatty infiltration in the nephron and subcapsular hemorrhages were observed in dogs orally exposed to an unspecified amount of white phosphorus (Dwyer and Helwig 1925). Necrosis and vascular degeneration of the proximal tubule and ischemic changes in the glomerulus were observed in animals burned once with 29-200 mg/kg/day white phosphorus (Appelbaum et al. 1975; Ben-

Hur and Appelbaum 1973; Ben-Hur et al. 1972). Evidence of impaired renal function (increased blood urea nitrogen levels, excessive diuresis, oliguria, decreased creatinine clearance) have also been observed in animals burned with white phosphorus (Ben-Hur et al. 1972). No renal effects were observed in rats exposed to 0.075 mg/kg/day for an intermediate duration (Bio/dynamics 1991; IRDC 1985). No chronic oral exposure studies or intermediate and chronic dermal burn exposure studies examining the renal system were located.

The mechanism of action of white phosphorus on the kidney is not known. Changes in the integrity of blood vessels have been observed in humans and animals exposed to phosphorus (see Cardiovascular discussion). It is possible that changes in the glomemlar capillaries allow protein from the blood to enter the glomemlar filtrate. The mechanism behind the necrosis in the proximal tubules is not known.

These data suggest that the kidneys are one of the primary targets of white phosphorus toxicity. It is likely that white phosphorus, which is absorbed through the lungs and skin, would also affect the kidneys

The severe histological alterations that have been observed in animals acutely burned with 29-200 mg/kg/day white phosphorus, support the effects observed in humans. No histological alterations were observed in the kidneys of rabbits burned once with an unreported amount of white phosphorus (Bowen et al. 1971). No longer-term dermal burn animal studies were located.

White Phosphorus Smoke. Renal effects were not examined in the three acute-duration white phosphorus smoke inhalation human studies (Walker et al. 1947; White and Armstrong 1935). Slight cloudy swelling in the kidneys was observed in rats, mice, and goats exposed to white phosphorus smoke for 1 hour at concentrations of 1,170,470, and 7,320 mg phosphorus pentoxide equivalents/m^3, respectively (1,615, 649, and 10,104 mg orthophosphoric acid equivalents/m^3) (White and Armstrong 1935). No renal lesions were observed in rats exposed to 3,027 mg orthophosphoric acid/m^3 for 90 minutes (Brown et al. 1980), or rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 6 or 13 weeks (Brown et al. 1981). Because of differences in the exposure protocols, comparisons between the White and Armstrong (1935) study and the Brown et al. (1980, 1981) studies cannot be made. No dermal exposure studies examining renal effects were located.

2. HEALTH EFFECTS

Dermal Effects

White Phosphorus. There is limited information on the dermal toxicity of white phosphorus. Dermal effects were not reported in humans or animals following inhalation exposure. Very few human studies reported dermal effects following acute ingestion of white phosphorus. Toxic dermatitis (Dathe and Nathan 1946) and subcutaneous hemorrhages (Hann and Veale 1910; Humphreys and Halpert 1931) have been reported. It is not known if the dermatitis is related to phosphorus exposure, or due to a pre-existing condition. The subcutaneous hemorrhages are consistent with other studies which found hemorrhages in the liver, brain, and kidneys. No evidence of skin irritation was observed in animals exposed to white phosphorus in peanut oil placed on the skin (Lee et al. 1975). The peanut oil vehicle may have been protective against the potential irritating effects of white phosphorus.

Following dermal burn exposure to white phosphorus, damage to the skin has been reported in humans and animals (Konjoyan 1983; Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). Many white phosphorus-induced burns are second and Third degree. Burn damage to the skin tissue is believed to result not only from heat but also from the corrosive action of phosphoric acid and the hygroscopic (moisture-absorbing) properties of phosphorus pentoxide, which is generated by oxidation of white phosphorus (Ben-Hur and Appelbaum 1973). Also, severe white phosphorus burns tend to heal more slowly than other types of third-degree burns.

Rat models of acute dermal burn exposure revealed necrosis of the skin at 29 mg/kg/day (Ben-Hur et al. 1972) and 100 mg/kg/day (Ben-Hur and Appelbaum 1973), and delayed wound healing at 100 mg/kg/day.

White Phosphorus Smoke. There is limited information on the potential of white phosphorus smoke to induce dermal effects. No human exposure studies examining dermal end points were located. In rats, no histological damage in the skin was observed following inhalation exposure to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981).

Ocular Effects

White Phosphorus. There is limited information on the ocular toxicity of white phosphorus. Ocular effects were not reported in humans or animals following inhalation exposure. Very few human studies reported ocular effects following acute ingestion of white phosphorus. Edema of the eyelids (Rao and

Brown 1974) has been reported. It is not known if the edema is related to phosphorus exposure, or due to a pre-existing condition. No evidence of eye irritation was observed in animals exposed to white phosphorus in peanut oil placed on the eye (Lee et al. 1975). The peanut oil vehicle may have been protective against the potential irritating effects of white phosphorus.

Transient local necrosis and congestion were reported after smoking particles of white phosphorus were discovered in the tarsal and bulbar conjunctival sacs of a dermal burn patient (Scherling and Blondis 1945). The conjunctival effects were completely absent by 4 days post-exposure.

No studies were located regarding ocular effects after dermal burn exposure.

White Phosphorus Smoke. There is limited information on the potential of white phosphorus smoke to induce ocular effects in humans. No human exposure studies examining ocular end points were located. In rats, no histological damage in the eye was observed following exposure to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981).

Other Systemic Effects.

White Phosphorus. A number of other systemic effects have been observed in humans and animals exposed to white phosphorus. Hypoglycemia was observed in humans ingesting a single dose of white phosphorus (Diaz-Rivera et al. 1950; McCarron et al. 1981; McIntosh 1927; Wechsler and Wechsler 1951) and in dogs acutely ingesting an unspecified amount of white phosphorus (Williamson and Mann 1923). The hypoglycemia is probably the result of a decrease in the ability for the liver to regulate and/or synthesize glucose.

A decrease in plasma electrolyte levels (calcium, potassium and/or sodium) has been observed in humans acutely ingesting white phosphorus (Caley and Kellock 1955; McCarron et al. 1981; Rao and-Brown 1974), in children ingesting approximately 0.1 mg/g/day white phosphorus for an intermediate duration (Compere 1930a), and in rabbits burned once with white phosphorus (Bowen et al. 1971). No reliable dose information was available from acute duration studies. The alteration in electrolyte levels may be secondary to the vomiting and diarrhea observed following ingestion of white phosphorus. The metabolic acidosis that was observed in an individual ingesting a single dose of white phosphorus (Rao and Brown 1974) and the decrease in pH observed in a child consuming approximately 0.1 mg/kg/day white

phosphorus for an intermediate duration (Compere 1930a) may be related to an alteration in electrolyte levels.

Other systemic effects have been observed in a small number of individuals intentionally or accidentally ingesting white phosphorus containing poison or firework. Some of these effects, such as fatty infiltration of the pancreas (Humphreys and Halpert 1931), splenomegaly (Greenberger et al. 1964), and necrosis of the adrenal medulla and cortex (Wechsler and Wechsler 1951), are consistent with effects that have been widely reported in other tissues. Other effects such as ascites (Fletcher and Galambos 1963), hyperthermia (Dathe and Nathan 1946; McIntosh 1927; McIntosh 1927), and hypothermia (Simon and Pickering 1976), may be the result of a pre-existing condition. No reliable dose information is available from these studies.

The decreased appetite, impaired weight gain, and poor turgor observed in a child who ingested 0.08 mg/kg/day white phosphorus for an intermediate duration (Sontag 1938) may have been caused by damage to the gastrointestinal tract.

Degeneration of the tongue and oral mucosa of the cheek, gum, and hard palate was observed in rats exposed to the atmosphere in a furnace room or a phosphorus factory for an intermediate duration. These effects were most likely the result of a direct contact of white phosphorus with tissues of the mouth an&or indirect contact through particles deposited on the fur which are then ingested by preening (Ruzuddinov and Rys-Uly 1986).

No other systemic effects were reported for humans exposed via inhalation or dermal (nonburn) exposure, humans burned with white phosphorus, or animals dermally (nonburn) exposed.

White Phosphorus Smoke. No studies were located regarding other systemic effects in humans and animals after inhalation or dermal exposure to white phosphorus smoke.

Immunological and Lymphoreticular Effects

White Phosphorus. Information available on the immunotoxicity of white phosphorus is limited. Hemorrhages in the thymus of two young children (Dwyer and Helwig 1925; Humphreys and Halpert 193l), hyperplasia of abdominal lymphoid tissue, lymph nodes, and splenic lymphoid corpuscles in a young child (Humphreys and Halpert 1931), decreases in neutrophil levels (Diaz-Rivera et al. 1950;

Fletcher and Galambos 1963; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968), and a decrease (Pietras et al. 1968) or an increase (McCarron et al. 1981) in the percentage of polymorphonuclear leukocytes (neutrophils) were observed in individuals ingesting a single dose of white phosphorus. Because the individuals vomited shortly after ingesting the white phosphorus and/or received gastric lavage, doses could not be estimated. A decrease in neutrophil levels was also observed in workers exposed to an unknown level of white phosphorus via inhalation, oral, and dermal routes (Ward 1928) and in individuals burned by white phosphorus (Walker et al. 1947). The alterations suggest that the immune system may be a target of toxicity. No information on immunotoxicity in animals was located.

White Phosphorus Smoke. No studies were located regarding immunological or lymphoreticular effects in humans and animals after inhalation or dermal exposure to white phosphorus smoke.

Neurological Effects

White Phosphorus. Signs of neurotoxicity have been observed in a number of individuals ingesting a single dose of white phosphorus. These signs include lethargy, sleepiness, irritability, restlessness, hypoactivity, coma, toxic delirium and psychosis, hyperesthesia, coarse muscle fasciculations, marked asterixis, unresponsiveness to painful stimuli, and hemiplegia (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; McIntosh 1927; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Talley et al. 1972; Wechsler and Wechsler 1951). Coma was also reported in an individual burned by white phosphorus (Walker et al. 1947). Similar signs of neurotoxicity have been observed in animals receiving oral, dermal burn, or parenteral exposure of white phosphorus (Bio/dynamics 1991; Bowen et al. 1971; Bumell et al. 1976; Ferraro et al. 1938; Frye and Cucuel 1969). Histological damage in the brain has also been observed in humans acutely ingesting white phosphorus (Humphreys and Halpert 1931; Rao and Brown 1974; Wertham 1932) and in rabbits receiving intravenous injections of phosphorus far an intermediate duration (Ferraro et al. 1938).

Liver damage was observed in most of the human and animals exhibiting signs of neurotoxicity. In a compilation of case reports of individuals intentionally ingesting single doses of white phosphorus, neurotoxicity was frequently observed in individuals exhibiting signs of liver toxicity (McCarron et al. 1981). Some of the neurological effects observed may have been secondary to the liver damage.

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Disturbances in consciousness (ranging from confusion to stupor to deep coma) and fluctuating neurological signs such as rigidity, hyperreflexia, asterixis, and, rarely, seizures have been observed in individuals with hepatic failure. Histologic alterations observed in these individuals with hepatic failure include hyperplasia of astrocytes (principally in the cortex), cerebral edema, and band-like cerebral cortical necrosis. Many of these histological alterations were observed in the limited number of white phosphorus poisoned individuals in which histopathological examination of the brain was performed (Rao and Brown 1974; Wertham 1932).

However, not all of the histological alterations in the brain appeared to be secondary to liver damage. Fatty deposition (an effect observed in a number of tissues) has been observed in humans (Humphreys and Halpert 1931; Wertham 1932) but not in animals (Ferraro et al. 1938) exposed to white phosphorus. Alterations secondary to ischemic damage were observed in an individual ingesting white phosphorus (Wertham 1932). Proliferation of the tunica intima of small cortical blood vessels that occasionally resulted in occlusion of the vessel was observed (Ferraro et al. 1938). The hemiplegia observed in two individuals may have been the result of occlusion of cortical blood vessels (Humphreys and Halpert 1931; McCarron et al. 1981). Damage to microglial cells (hypertrophy and effects associated with acute swelling) (Ferraro et al. 1938) and damage to cells of the inferior olives (observed in humans and animals) (Ferraro et al. 1938; Wertham 1932) may be a direct effect of white phosphorus.

White Phosphorus Smoke. There is limited information on the neurotoxicity of white phosphorus smoke. No human exposure studies were located. No lesions were observed in the brains of rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 of white phosphorus smoke 15 minutes/day, 5 days/week for 13 weeks (Brown et al. 1981). No other studies examining neurological end points were observed.

Reproductive Effects

White Phosphorus. There is limited information on the reproductive effects of white phosphorus in humans. Uterine hemorrhaging was reported in a 2-month pregnant woman who intentionally ingested a lethal dose (2 mg/kg) of phosphorus (Harm and Veale 1910). In male and female rats orally exposed to white phosphorus, no effects on reproductive performance were observed at relatively low doses (0.075 mg/kg/day) (Bio/dynamics 1991; IRDC 1985). In addition, no histological alterations were observed in reproductive organs of male rats receiving subcutaneous injections of 3.2 mg/kg/day for l-l1 days (Fleming et al. 1942), subcutaneous injections of 0.8 mg/kg/day for 140 days (Fleming et al.

1942), or subcutaneous injections of 0.4 mg/kg/day for 340-610 days (Fleming et al. 1942). Male and female rats orally exposed to 0.075 mg/kg/day for 145 or 204 days (Bio/dynamics 1991; IRDC 1985) and male guinea pigs receiving 0.4 mg/kg/day via subcutaneous injections for 720 days (Fleming et al. 1942) likewise showed no effects in reproductive organs. Increased mortality was observed during late gestation and parturition in rats receiving white phosphorus for an intermediate duration. These effects were discussed previously in Section 2.5 under "Death." No dermal exposure studies examining reproductive toxicity were located. The studies that examined reproductive performance used relatively low doses; it is not known if exposure to higher doses would result in reproductive toxicity. Thus, the potential of white phosphorus to cause reproductive effects in humans cannot be determined.

White Phosphorus Smoke. Reproductive end points were not examined in the available human exposure studies (Walker et al. 1947; White and Armstrong 1935). No histological damage was observed in reproductive tissues of male and female rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 15 minutes/day, 5 days/week, for 13 weeks (Brown et al. 1981). In addition, no effects on reproductive performance were observed in male or female rats exposed to 1,742 mg orthophosphoric acid equivalents/m^3 for 15 minutes/day, 5 days/week, for 3-13 weeks (Brown et al. 1981; Starke et al. 1982). Dermal exposure studies examining reproductive end points were not located.

Developmental Effects

White Phosphorus. Oral white phosphorus administered to two healthy children for intermediate durations for the prevention of rickets resulted in a decreased growth rate in one child (Sontag 1938) and the development of transverse bands of increased density at the ends of the long bones. Increased thickness and density were observed in the zones of calcification in both children (Compere 1930a; Sontag 1938). Following cessation of treatment, the growth rate returned to normal; however, the "phosphorus" bands were still visible 4.5 years later (Sontag 1938).

Young, growing rabbits and rats exposed orally to phosphorus for acute or intermediate durations developed similar transverse bands of increased density in metaphyseal regions of the long bones, compared to a control group (Adams 1938a, 1938b; Adams and Sarnat 1940; Whalen et al. 1973). In addition, some animals had a decreased rate of growth of the long bones (Adams and Samat 1940). Normal growth of long bones requires bone deposition and bone resorption. White phosphorus apparently decreases the absorption of intercellular calcified cartilage matrix by osteoclasts, in the metaphyseal region

of growing bones. The process of tubulation (or formulation of the tube in a growing bone) is dependent on the peripheral and central resorption of metaphyseal bone and cartilage. During white phosphorus administration, areas of increased density are formed and bone growth is inhibited.

Information on the developmental toxicity of white phosphorus, other than effects on growing bones, is limited to two oral exposure studies (Bio/dynamics 1991; IRDC 1985), which administered a relatively low dose of white phosphorus. A nonsignificant ($p>0.05$) decrease in the incidence of viable pups and increase in the incidence of stillbirths was observed in the offspring of rats exposed to 0.075 mg/kg/day. These effects were not observed in a similarly designed study in which rats were exposed to 0.075 mg/kg/day (Bio/dynamics 1991). Anomalies or malformations were not observed in either of these studies. Because these studies used relatively low doses, their usefulness in predicting whether exposure to white phosphorus would result in developmental toxicity is limited.

White Phosphorus Smoke. No data on developmental effects in humans exposed to white phosphorus smoke were located. No developmental effects were observed in rats exposed *in utero* to concentrations of white phosphorus smoke as high as 1,742 mg orthophosphoric acid equivalents/m^3 for 15 minutes/day (Brown et al. 1981; Starke et al. 1982). However, exposure of the dams and pups to white phosphorus smoke *in utero* and during lactation resulted in an 8% decrease in pup body weight, a 68% decrease in pup survival, and a 35% decrease in viability (Brown et al. 1981; Starke et al. 1982). These results may be due to interference with the pups suckling, decreased milk production, decreased suckling due to respiratory tract irritation in the pups, or another compound-related effect. No dermal exposure developmental studies were located.

Genotoxic Effects

White Phosphorus. No studies were located regarding *in vivo* genotoxic effects in humans or animals after inhalation, oral, dermal (nonburn), and dermal (burn) exposure.

Genotoxicity of a saturated solution of white phosphorus in water was evaluated *in vitro* in a standard Ames assay both with and without microsomal activation (Ellis et al. 1978). The tests used *Salmonella typhimurium* tester strains TA1535, TA1537, TA1538, TA98, and TAl00. White phosphorus was not genotoxic in these test systems.

White Phosphorus Smoke. No studies were located regarding *in vivo* or *in vitro* genotoxic effects in humans or animals after inhalation and dermal exposure.

Cancer

White Phosphorus. No information on carcinogenicity of white phosphorus in humans has been located. Data in animals are very limited. In a chronic oral exposure study in rats, carcinogenic effects were not reported (Fleming et al. 1942). However, this study provides limited information on which tissues were examined.

White Phosphorus Smoke. No human or animal exposure studies examining cancer following inhalation or dermal exposure to white phosphorus smoke were located.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989). Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to white phosphorus are discussed in Section 2.6.1.

2. HEALTH EFFECTS

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by white phosphorus are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, "Populations That Are Unusually Susceptible."

2.6.1 Biomarkers Used to Identify or Quantify Exposure to White Phosphorus

White Phosphorus. White phosphorus affects nearly every organ system to some degree, depending on the duration and route of exposure (see Section 2.2). Most of these effects appear to be shared effects and may not be useful individually as characteristic indicators of white phosphorus exposure. However, established clinical diagnostic principles as well as the weight of evidence from this report (see Section 2.2) suggest that a sequence of effects following exposure and a few individual clinical signs or effects may be useful biomarkers of exposure. Data were sufficient to suggest biomarkers indicative of acute oral, acute dermal, and chronic occupational exposures (see Section 2.2 for further details). Data were not sufficient for other routes of exposure.

There are no known quantitative biomarkers unique to acute oral white phosphorus poisoningin an individual. Unfortunately, the metabolism of white phosphorus is not well understood (refer to Section 2.3 for details of metabolism). Studies that identify metabolites of white phosphorus were not located. It seems, however, that most metabolites of white phosphorus are probably inorganic or organic molecules that are commonly found in body tissues and fluids. Two obvious potential biomarkers of exposure are serum and urine phosphate levels, which are parameters that are included in some routine clinical test series. The normal range for human serum phosphate is 3.0-45 mg/l00 mL (Harper 1969),

and the normal range for the rate of human urinary phosphate excretion is 0.34-1.0 g/day (Henry 1967). However, the weight of evidence upon examination of pertinent data (see Sections 2.2 and 2.3) indicates that these parameters are probably not good biomarkers of exposure. Both of them commonly have a high degree of variability within individuals. Also, both the mean and the range of an individuals values vary within a population of individuals. Thus, serum and urine phosphate are contraindicated as biomarkers of exposure. An odor of garlic in the inhaled breath of an individual, possibly accompanied by a pale bluegreen phosphorescence in the vomitus or the feces, and smoke coming out of the mouth and feces are indicative of acute oral white phosphorus poisoning. White phosphorus itself volatilizes and produces the metallic odor of garlic, while the phosphorescence is thought to be evolved during the oxidation of white phosphorus to phosphorus pentoxide (Rabinowitch 1943).

White Phosphorus Smoke. The lack of information on the metabolism and mechanism of action of white phosphorus smoke and the limited information on the toxicity of white phosphorus smoke precludes identifying biomarkers of exposure.

2.6.2 Biomarkers Used to Characterize Effects Caused by White Phosphorus

White Phosphorus. The primary sites of white phosphorus toxicity are the gastrointestinal tract, liver, kidney, cardiovascular system, and bone. The bone effects are only observed following longer-term exposure to white phosphorus, whereas hepatic, renal and cardiovascular effects are observed shortly after exposure to white phosphorus. Following exposure to white phosphorus, a dense phosphorus line can be identified on the bones. The appearance of this phosphorus line may be unique to phosphorus; however, it may only occur in growing bones. The most extensive information on the effects of white phosphorus is from the acute human oral exposure database, primarily case reports of individuals intentionally or accidentally consuming poisons or fireworks containing phosphorus. The biomarkers of liver effects include jaundice, impaired bromsulfophthalein (BSP) (liver function test) results, increased levels of bilirubin, and increased in AST and ALT levels. Increases in blood levels of urea nitrogen and nonprotein nitrogen, proteinuria, albuminuria, and oliguria are some of the biomarkers of kidney damage that have been observed in humans. Indicators of cardiovascular effects include a marked decrease in (or undetectable) blood pressure and/or pulse and hemorrhaging. Shortly after ingesting white phosphorus, most individuals vomit, and often blood is present in the vomitus. Although these biomarkers are not specific for phosphorus exposure, a combination of vomiting, altered serum chemistry values, suggestive of liver and kidney damage, and symptoms of shock may be useful in identifying phosphorus exposure.

2. HEALTH EFFECTS

Quantitative biomarkers of acute oral exposure that are shared with a variety of other toxic compounds are numerous (see Section 2.2 for more details). Clinical pathologic findings include hypoglycemia, decreased total leukocytes, increased serum bilirubin, altered prothrombin time, increased AST and ALT, impaired liver function, increased lactate dehydrogenase, decreased serum triglyceride levels, proteinuria, albuminuria, oliguria, increased blood urea and/or nitrogen, and increased blood creatinine levels. A postmortem quantitative biomarker is increased total hepatic lipids and hepatic triglyceride levels.

Clinical signs of oral toxicity may be the most reliable set of biomarkers of acute oral exposure to white phosphorus. After acute oral exposure to white phosphorus, a typical set of clinical signs ensue (these are discussed in more detail in Section 2.2). Severe gastrointestinal distress follows within several hours, sometimes with gastrointestinal swelling. Usually, it involves persistent and/or violent vomiting, sometimes accompanied by diarrhea. Following these typical initial signs of acute oral exposure to white phosphorus, a number of nonspecific signs may appear within 12 hours of ingestion. These range from no further effects to severe hepatomegaly, jaundice, decreased urine volume, increased respiratory rate, vascular collapse or cardiac arrest, lethargy or sleepiness, transient hemiplegia, shock, coma, and/or death, among others (see Section 2.2 for more detail).

Qualitative biomarkers of acute oral exposure that are shared with other toxic compounds include a variety of electrocardiogram alterations. Postmortem biomarkers include fatty hepatic degeneration, pulmonary edema and/or congestion, widespread internal hemorrhaging, widespread intracellular fatty deposits, various myocardial damage, hepatic necrosis, hepatic fibrosis, and increased liver weight (see Section 2.2 for more detail).

Quantitative biomarkers of dermal burn exposure are generally similar to those seen after acute oral exposure (see Section 2.2 for details). Qualitative biomarkers are also generally similar, but differ on a few relatively obvious points. In white phosphorus burn exposures , gastrointestinal upset is less common and generally less severe, and phosphorescent particles are frequently visible in the area of a white phosphorus burn rather than in vomitus and/or feces. Also if white phosphorus is still present in the burn wound following cleansing procedures, white phosphorus - induced burns may re-ignite spontaneously

There are no known quantitative in-life or postmortem biomarkers that are unique to chronic (primarily inhalation, but also oral and dermal) exposure to white phosphorus. There are also no postmortem quantitative biomarkers of chronic exposure. In-life quantitative biomarkers that are shared with other

toxic compounds include anemia, decreased total leukocytes, and hypoglycemia (see Section 2.2 for details).

Qualitative in-life biomarkers that are characteristic of chronic exposure to white phosphorus include progressive destruction of the jaw bones (phossy jaw), brittleness of long bones, and poor healing of oral cavity lesions including tooth sockets after tooth extraction (see Section 2.2 for details). In-life biomarkers that are probably shared with other toxic compounds include increased permeability of capillary walls and impaired microcirculation. Postmortem qualitative biomarkers include hyperkeratosis of the epithelium of the oral mucosa and lesions of the capillary walls (see Section 2.2 for details). Hyperkeratosis is a microscopic morphological finding that can be seen in biopsy material from a living patient or from an autopsy and is seen in association with phosphorus intoxication.

White Phosphorus Smoke. Based on the limited information on the toxicity of airborne white phosphorus, the respiratory tract appears to be the primary site of toxicity. However, similar respiratory tract effects have been observed following exposure to other airborne irritants.

Additional information regarding biomarkers for effects can be found in OTA (1990) and CDC/ATSDR (1990). A more detailed discussion of the health effects caused by white phosphorus and white phosphorus smoke can be found in Section 2.2 of Chapter 2.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

White Phosphorus. Information that was located on interactive effects of white phosphorus with other compounds focuses on absorption and hepatotoxicity.

Gastrointestinal absorption of white phosphorus may be enhanced by interaction with a liquid vehicle. This is suggested by an increase in mortality rate after ingestion of rat poison, roach poison, or fireworks in a study of 51 suicide cases (Diaz-Rivera et al. 1950). A possible mechanism is the facilitation of the passage of the white phosphorus to the duodenum, where more rapid absorption may occur when the medium of ingestion is itself digested and absorbed. However, the interpretation of the effect of a liquid medium on phosphorus absorption is confounded by the timing of lavage, timing of post-ingestion vomiting, and perhaps interactions between components of the poisons.

In contrast, gastrointestinal absorption was impeded by an interaction with physiologically inert liquid petrolatum (a cathartic) orally administered to dogs (Atkinson 1921). Adverse systemic effects were completely prevented or delayed. Apparently white phosphorus preferentially dissolves in liquid petrolatum, which is itself not digested, and therefore passes through the gastrointestinal tract.

The interactive effects of copper sulfate associated with dermal absorption are equivocal. Information was located suggesting antagonistic effects of copper sulfate solutions in water, glycerol, and oil with respect to phosphorus absorption (Goldblatt and Oakeshott 1943; Jalenko 1974; Rabinowitch 1943). Emulsions of 3% copper sulfate (with 1% hydroxyethyl cellulose, 5% sodium bicarbonate, and 1% lauryl sulfate) applied to white phosphorus burns also appeared to demonstrate an antagonistic interaction in one study by preventing white phosphorus-induced death in rats (Ben-Hur and Appelbaum 1973). However, the same emulsion solution had no beneficial effect in a later repeat of the experiment (Eldad and Simon 1991). The mechanism by which copper sulfate theoretically impedes dermal absorption of phosphorus following white phosphorus burn is the formation of a copper-phosphorus complex (Cu_3P_2) that will not be absorbed, is unstable and may decompose to ionic copper and phosphate when in contact with oxygen in the air (Sontag et al. 1985).

A safer and potentially more reliable antagonist to white phosphorus dermal absorption is a solution of silver nitrate ($AgNO_3$). The mechanism is not known with certainty (Song et al. 1985) but is hypothesized to be formation of Ag_3P, the toxic properties of which are not reported.

Increases in hepatic triglycerides after white phosphorus treatment were apparently potentiated in male rats by pretreatment with intraperitoneal injection of phenobarbital (Jacqueson et al. 1979). The effect was not observed in females. White phosphorus and phenobarbital individually induced statistically significant increases in hepatic triglycerides. The potentiation may occur by phenobarbital increasing the hydroxylation of testosterone, a steroid hormone, or it could also be due to proliferation of the smooth endoplasmic reticulum (ER). A different steroid, 19-nortestosterone phenylpropionate (NTPP), was shown to be moderately antagonistic to increases in white phosphorus-induced hepatic triglyceride levels (Jacqueson et al. 1978). NTPP did not change the mortality rate or the incidence of other systemic effects after white phosphorus treatment (Jacqueson et al. 1978).

Phenobarbitone is not only a potentiator of white phosphorus-induced fatty liver, but is also an antagonist of white phosphorus-induced mortality. Pretreatment with phenobarbitone prevented death in

phosphorus-treated male rats, while white phosphorus alone caused 40% mortality in males (Jacqueson et al. 1979). The mechanism for this is unclear.

Glutathione (GSH) and propyl gallate (PG) are antioxidants and free radical scavengers. Pretreatment with each of these chemicals was antagonistic to white phosphorus-induced increases in hepatic triglycerides and increases in hepatic polyribosome disaggregation (Pani et al. 1972). The overall effect of intraperitoneal pre-treatment with glutathione or propyl gallate was maintenance of hepatic protein synthesis in spite of white phosphorus treatment.

The interaction of phetharbital and white phosphorus is also antagonistic with respect to liver function. Four daily treatments of mice with phetharbital following a single administration of white phosphorus facilitated the return of BSP retention to control levels (Hurwitz 1972).

Three studies examined the mediating effect of phenobarbital on white phosphorus-induced liver function impairment. Pre-treatment with four or five intraperitoneal injections of phenobarbital showed no effect on white phosphorus-induced triglyceride accumulation at 12 hours after white phosphorus administration (Pani et al. 1972), but had an antagonistic effect on white phosphorus-induced increases in BSP retention at 24 hours after treatment with white phosphorus (Hurwitz 1972). The antagonistic effect of phenobarbital pre-treatment on white phosphorus-induced BSP retention disappeared by 48 hours after white phosphorus administration. Another study conducted by Hurwitz (1972) showed the antagonistic effect of 4 daily intraperitoneal post-treatments with phenobarbital on white phosphorus-induced mortality.

White Phosphorus Smoke. No information on the interactive effects of white phosphorus smoke and other compounds was located.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to white phosphorus than will most persons exposed to the same level of white phosphorus in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and

excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, "Populations With Potentially High Exposure."

White Phosphorus. Studies have shown that pregnant rats are more susceptible than nonpregnant female and male rats to the lethal effects of white phosphorus during late gestation or parturition. It is not known if pregnant women would also represent an unusually susceptible population. Human exposure to white phosphorus has shown that the liver, kidney, and cardiovascular systems are some of the primary targets of toxicity. Individuals with pre-existing liver, kidney, heart, or circulatory disorders may be unusually susceptible to white phosphorus toxicity.

White Phosphorus Smoke. There is no information on populations that would be usually susceptible to the toxicity of white phosphorus smoke. Based on human and animal inhalation studies, it is possible that individuals with pre-existing respiratory problems may be more sensitive.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section describes clinical practice and research concerning methods for reducing toxic effects of exposure to white phosphorus. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to white phosphorus. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

White Phosphorus. The first 2 hours following oral ingestion of white phosphorus containing compounds appear to be critical. Mortality rates increase rapidly if gastric lavage is not administered within 2-3 hours after ingestion (Diaz-Riviera et al. 1950). Although emesis has occasionally been contraindicated because white phosphorus may be corrosive to the esophagus and mouth, a study of 51 cases of white phosphorus ingestion indicates that vomiting within 1 hour appears to substantially

increase the probability of survival, and an 80% mortality rate was indicated among individuals who did not vomit at all (Diaz-Rivera et al. 1950). Supporting animal data show that white phosphorus in mineral oil is absorbed in male rats within 15 minutes of ingestion, and within 2-3 hours 82-87% of the administered dose had reached internal organs and fluids (Ghoshal et al. 1971).

Various lavage solutions have been suggested, including mineral oil, saline, and dilute copper sulfate solution. Dilute copper sulfate has been suggested for its emetic properties, as well as for its ability to form an apparently inert complex with phosphorus that reduces white phosphorus absorption (Eldad and Simon 1991; Summerlin et al. 1967).

It has been suggested that dermal absorption may be impeded with dilute aqueous copper sulfate solutions by temporarily inactivating white phosphorus until the copper-phosphorus complexes can be removed by washing or with forceps (Rabinowitch 1943; Goldblatt and Oakeshott 1943; Jelenko 1974). However, mitigation with copper sulfate solution has since been contraindicated because of its own toxicity as a potent hemolytic agent (Eldad and Simon 1991). Indeed, even the effectiveness of 3% copper sulfate emulsions to interfere with dermal absorption is in question, since contradictory results have been reported (Ben-Hur and Appelbaum 1973; Eldad and Simon 1991). Indeed, water was the only flushing treatment that was effective in preventing death in one of the studies (Eldad and Simon 1991). A solution of copper sulfate in oil or glycerol is suggested to deactivate liquid paraffin or benzene-rubber solutions of phosphorus, after successful trials with animals (Goldblatt and Oakeshott 1943). The oil solution reportedly also effectively deactivates solid phosphorus and phosphorus dissolved in carbon sulfide or benzene. The toxicity of the oil solution of copper sulfate itself was not reported. Silver nitrate was suggested as an alternative to copper sulfate, and was successfully applied in 13 cases of white phosphorus burns during 1978-1985 (Song et al. 1985).

It is suggested that oils and greases be excluded from white phosphorus burn areas, since they may dissolve the white phosphorus and assist its penetration into the wound (Rabinowitch 1943). An apparent exception to this is suggested in studies in animals subjected to white phosphorus burns and treated with oil-phosphorus solution. The oil-phosphorus solution was very effective in inactivating white phosphorus (Goldblatt and Oakeshott 1943; Rabinowitch 1943). In cases of limited white phosphorus burn, flushes with aqueous solutions of dilute copper sulfate or sodium bicarbonate are suggested (Rabinowitch 1943). Covering the affected area with liquid petrolatum has also been suggested (Jelenko 1974). Surgical

removal of phosphorus particles with forceps concurrent with the flushes is suggested, since they may reignite once the burn area dries (Rabinowitch 1943).

Common treatments for eye exposure to white phosphorus fumes/vapors include holocaine and epinephrine ointments, a camphor and epinephrine solution, and a solution with epinephrine alone. All of these have been suggested as successful therapeutic agents following exposure of the eye, but their effect on absorption through the eye area is unknown (Scherling and Blondis 1945).

White Phosphorus Smoke. There is no information on methods for reducing peak absorption following exposure to white phosphorus smoke.

2.9.2 Reducing Body Burden

White Phosphorus. The retention of white phosphorus following absorption is poorly understood. Most of the phosphorus is probably quickly converted to orthophosphate, which in turn is rapidly eliminated from the body in urine (see Section 2.3). Supporting animal data show that up to 17% of administered radiolabeled phosphorus was eliminated in the urine of rats 4 hours after oral administration (Lee et al. 1975). By 5 days post-dosing in the same study, 79% of administered radiolabeled phosphorus was excreted in the urine and feces, combined. The fate of the remaining phosphorus is unknown.

Some evidence suggests that white phosphorus or its metabolites are present in the human body after 5 days. A latent period of 4 days to 3 weeks following initial gastrointestinal distress, and preceding severe systemic effects and/or death, has been well described. It is not known whether the relapse is due to retention of active phosphorus or one of its metabolites rather than to delayed effects from an organ impairment that occurred during the initial intoxication.

No studies on body burden reduction methods were located. The state of definitive knowledge of white phosphorus metabolism is too limited to permit extensive speculation on methods for reducing body burden. However, it is possible that increasing selective excretion of phosphate may increase the rate of inorganic conversion of white phosphorus to phosphate (this conversion is described in detail in Section 2.3). Since phosphate is a naturally occurring component of the blood's buffering system, this would effectively deactivate the phosphorus. No methods for selectively increasing phosphate excretion were located.

White Phosphorus Smoke. There is no information on methods to reduce the body burden of toxic components of white phosphorus smoke.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

White Phosphorus. One manifestation of liver damage following ingestion of white phosphorus is an increase in sulfobromophthalein (BSP) retention, indicating impairment of biliary excretion. Both phetharbital and phenobarbital seem to mitigate the white phosphorus-induced increase in BSP retention. Four daily intraperitoneal treatments of mice with either phetharbital or phenobarbital following a single administration of white phosphorus facilitated the return of BSP retention to control levels at 5 days after white phosphorus ingestion (Hurwitz 1972). However, the usefulness of these two compounds as mitigating factors may be very limited, since white phosphorus-induced body weight changes and mortality rate were not affected.

The primary mechanisms of action in the liver are an impairment of protein synthesis (particularly a decrease in apolipoprotein), resulting in an accumulation of triglycerides, which eventually leads to fibrosis and cirrhosis, and mitochondrial damage, which results in diminished ATP levels, and cell necrosis. Similar mechanisms of action probably occur in the kidney, heart, and brain. A compound that would interfere with the white phosphorus-induced ultrastructural damage would mitigate these effects; no compound has been identified that would interfere with this mechanism of action.

White Phosphorus Smoke. There is no information on methods for interfering with the mechanism of action for white phosphorus smoke-induced toxic effects.

2.10 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of white phosphorus and white phosphorus smoke are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of white phosphorus.

2. HEALTH EFFECTS

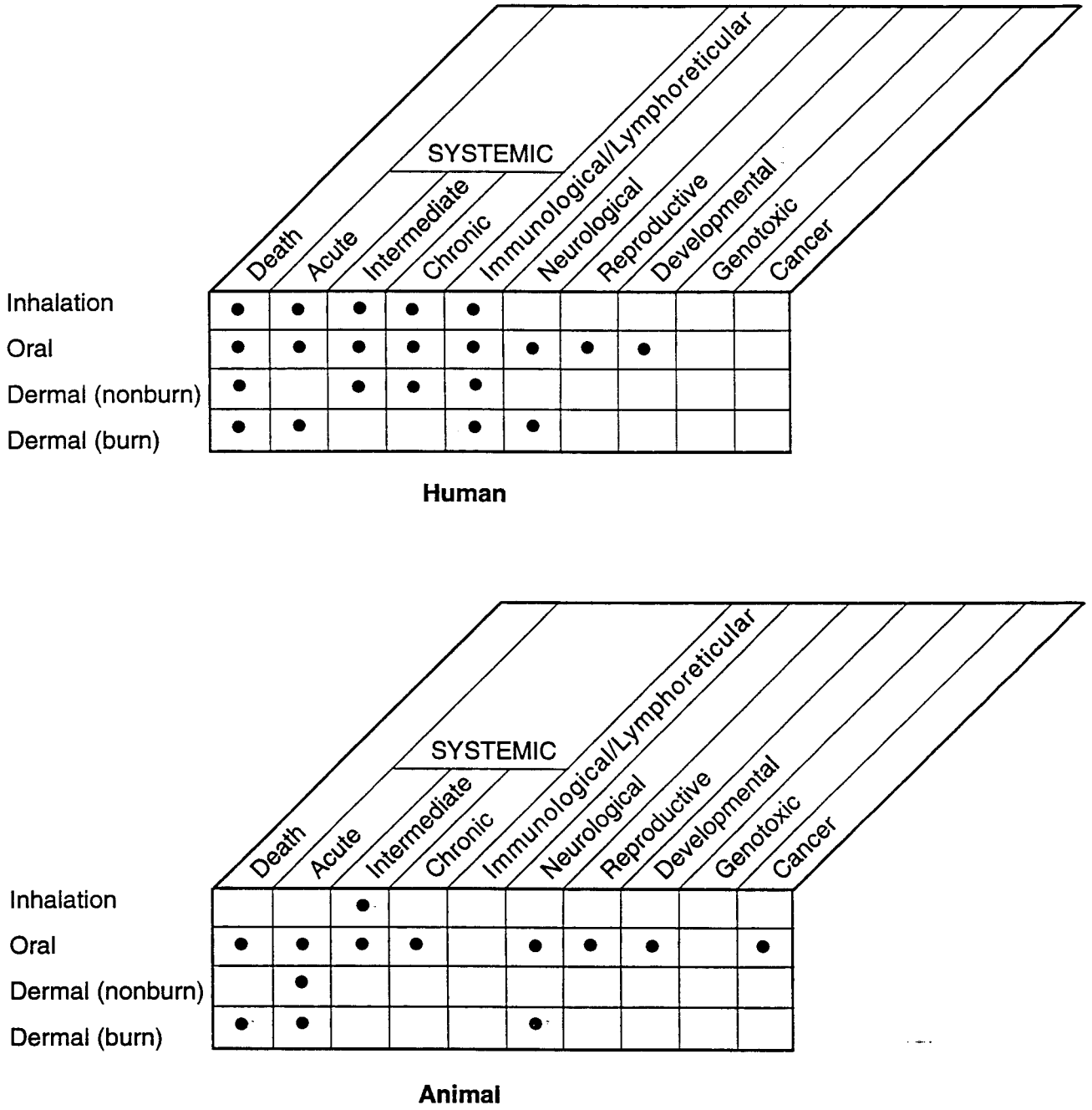
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of White Phosphorus

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to white phosphorus are summarized in Figures 2-4 and 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of white phosphorus. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

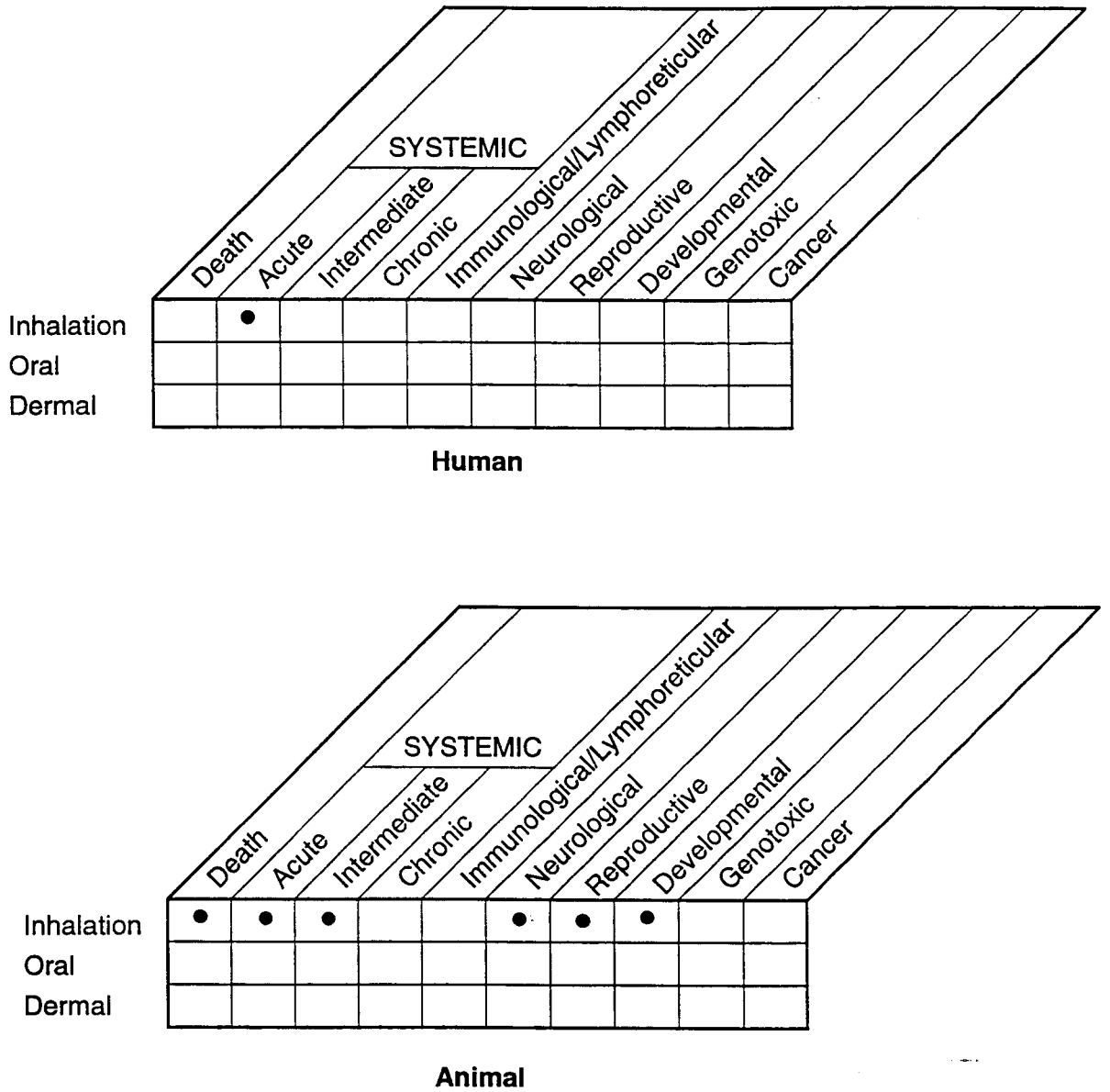
Most of the information on the toxicity of white phosphorus in humans comes from case reports of individuals who intentionally or accidentally ingested a single dose of phosphorus that was a component of poison or fireworks. These case reports provide information on acute systemic effects, possible immunological effects, neurological effects, reproductive effects, and death in humans. In addition to these case reports of single exposures, there are several case reports of children ingesting white phosphorus for an intermediate duration; these studies provide information on intermediate systemic effects and developmental effects. Information on chronic oral and dermal exposure in humans is limited to occupational exposure studies in which workers were exposed to white phosphorus via inhalation, oral, or dermal routes. Some limited information on chronic systemic effects is available from these studies. There is limited information on the toxicity of inhaled white phosphorus in humans. Several occupational exposure studies are available; however, only a limited number of parameters were assessed in these studies. Some information on health effects in humans following dermal burn exposure is available. As with the occupational exposure studies identified for inhalation, oral, and dermal (nonburn), these studies examined a limited number of systemic parameters.

FIGURE 2-4. Existing Information on Health Effects of White Phosphorus



● Existing Studies

FIGURE 2-5. Existing Information on Health Effects of White Phosphorus Smoke



● Existing Studies

2. HEALTH EFFECTS

Information on the toxicity of inhaled white phosphorus in animals is limited to a study that examined some parameters of systemic toxicity following intermediate-duration exposure. Information on death, acute, intermediate, and chronic systemic effects, neurological effects, reproductive effects, and developmental effects has been located. Studies on animals dermally (nonburn) exposed to white phosphorus are limited to an acute exposure study which monitored for dermal and ocular effects. Several dermal burn studies were identified which provided data on death and a limited number of acute systemic effects. Neurological effects were also observed in an acute animal dermal burn study.

White Phosphorus Smoke. There is a limited amount of available information on human toxicity of white phosphorus smoke. These acute-duration human exposure studies monitored for systemic effects following inhalation exposure. Death, systemic effects, and developmental effects have been observed in animals exposed to airborne white phosphorus smoke for acute and intermediate durations. Reproductive and neurological end points have also been monitored following intermediate-duration inhalation exposure. No dermal exposure studies were located.

2.10.2 Identification of Data Needs

Acute-Duration Exposure

White Phosphorus. No acute-duration inhalation exposure data in humans and animals were located; thus, an acute-duration inhalation MRL cannot be derived. There is extensive information on the acute-duration effects of white phosphorus following oral exposure in humans (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950,196l; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 1931; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951). The primary targets of toxicity are liver, kidneys, cardiovascular system, and gastrointestinal system. Acute-duration oral exposure data in animals support the identification of these target organs. An acute-duration oral MRL cannot be derived because most individuals vomit shortly after ingestion of white phosphorus; thus, the dose cannot be calculated. Animal studies cannot be used as the basis of the MRL because the studies that identified the lowest LOAEL values reported data for only a small number of animals (Adams 1938a; Sigal et al. 1954). Only one acute-duration dermal (nonburn) study was located (Lee et al. 1975); this animal study only tested for dermal and ocular effects and did not use multiple

doses. Several human acute-duration dermal burn exposure studies reported effects following exposure to white phosphorus (Konjoyan 1983; Obermer 1945; Scherling and Blondis 1945; Song et al. 1985; Summerlin et al. 1967; Walker et al. 1947). Based on these human studies and animal studies (Appelbaum et al. 1975; Ben-Hur and Appelbaum 1973; Ben-Hur et al. 1972; Bowen et al. 1971), the primary targets following dermal burn exposure to white phosphorus appear to be the skin, liver, and kidneys. Additional studies involving acute exposure to white phosphorus would be helpful to identify the target organs following inhalation and dermal (nonburn) exposure and dose-response relationships for all routes of exposure. There are populations surrounding hazardous waste sites that might be exposed to white phosphorus for brief periods; children living near phosphorus-containing hazardous waste sites may be exposed to white phosphorus by dirt ingestion and/or skin contact while playing at unrestricted dumpsites. Therefore, this information is important.

White Phosphorus Smoke. In humans and animals exposed to airborne white phosphorus smoke for acute durations, the respiratory tract appears to be the most sensitive end point (Brown et al. 1980; Walker et al. 1947; White and Armstrong 1935). An acute inhalation MRL of 0.02 mg/m^3 was derived based on throat irritation in humans (White and Armstrong 1935). Other effects observed in animals include death and hepatic and renal effects (Brown et al. 1980; White and Armstrong 1935). These studies have several limitations; a limited number of end points were examined in the White and Armstrong (1935) study, and animals were held for 2 weeks following exposure termination in the Bowen et al. (1980) study. In addition, these studies expressed air concentrations in terms of orthophosphoric acid or phosphorus pentoxide equivalent concentrations making it difficult to assess the health risk to humans following exposure to white phosphorus smoke. Acute-duration inhalation exposure studies examining a number of end points would be useful in assessing human health risk. No acute-duration dermal exposure studies were located. Dermal exposure studies examining a number of end points would be useful in determining the targets of white phosphorus smoke toxicity.

Intermediate-Duration Exposure

White Phosphorus. Several human intermediate-duration inhalation studies were identified (Hughes et al. 1962; Legge 1920; Ward 1928). Phossy jaw was observed in these workers. Only one animal inhalation study was identified (Ruzuddinov and Rys-Uly 1986). Because these studies only examined a limited number of end points (primarily focused on occurrence of phossy jaw), they cannot be used to determine the targets of toxicity. Several intermediate duration studies in which children were administered white

phosphorus reported abnormalities in the bone (Compere 1930a; Phemister 1918; Sontag 1938). In addition, a study in which workers were exposed to airborne white phosphorus (with some oral and dermal exposure) reported phossy jaw (Ward 1928). Several intermediate-duration animal studies were identified (Adams and Sarnat 1940; Ashbum et al. 1948; Bio/dynamics 1991; IRDC 1985; Mallory 1933; Peterson et al. 1991; Sollmann 1925; Whalen et al. 1973). Based on the human and animal studies, the primary targets of intermediate-duration exposure to white phosphorus appear to be the bone and liver. Most of the animal studies did not examine the renal system; however, based on acute data, it is likely that this is also a target of toxicity following intermediate-duration exposure. An intermediate-duration oral MRL of $2x10^{-4}$ mg/kg/day was derived based on a NOAEL of 0.015 mg/kg/day which increased mortality or other effects in pregnant rats (Bio/dynamics 1991; IRDC 1985). As discussed above, in the workers examined by Ward (1928) (exposed via inhalation, oral, and dermal routes), phossy jaw was observed. No intermediate-duration dermal animal studies were identified. The targets of toxicity following dermal exposure cannot be identified because of the limited number of end points examined in the Ward (1928) study. No intermediate-duration dermal burn studies were identified. Inhalation, oral, and dermal (nonburn and burn) exposure studies would be useful to determine the primary targets of white phosphorus toxicity and dose-response relationships. There are populations surrounding hazardous waste sites that might be exposed to white phosphorus for similar durations.

White Phosphorus Smoke. No human intermediate-duration inhalation exposure studies were located. In rats exposed to white phosphorus smoke for 6-13 weeks, death and respiratory effects were observed (Brown et al. 1981). The very short daily exposure duration (15 minutes/day) precludes using these animal exposure studies as the basis of an intermediate-duration inhalation MRL. It is not known if a longer daily exposure to white phosphorus smoke would be more toxic; intermediate-duration exposure studies examining this effect would be useful. No human or animal intermediate-duration dermal exposure studies were located. Dermal exposure studies examining a number of end points would be useful in determining targets of white phosphorus smoke toxicity.

Chronic-Duration Exposure and Cancer

White Phosphorus. There is limited information on the chronic toxicity of white phosphorus. Increased mortality (Ward 1928), phossy jaw (Hughes et al. 1962; Heimann 1946; Kennon and Hallam 1944; Legge 1920; Ward 1928), chronic cough (Ward 1928), and alterations in hematological parameters (Ward 1928) have been observed in workers chronically exposed to airborne white phosphorus. Frequently these

workers were exposed by oral and dermal routes as well as the inhalation route. No chronic-duration animal inhalation studies were located. The chronic-duration inhalation exposure data suggest that the musculoskeletal system is one of the primary targets of phosphorus; however, because these studies only examined a limited number of end points, other possible targets of toxicity cannot be excluded. The occupational exposure studies (Heimann 1946; Hughes et al. 1962; Kennon and Hallam 1944; Legge 1920; Ward 1928) did not report exposure levels; thus, a chronic-duration inhalation MRL cannot be derived. Phossy jaw and altered hematological parameters were observed in an individual orally exposed to white phosphorus (Jakhi et al. 1983). In the Ward (1928) study, workers were also exposed orally; the results of this study are presented above. One chronic-duration animal study was identified. In this study, musculoskeletal effects were observed (Fleming et al. 1942). Bone changes consisting of thickening of the epiphyseal line and extension of trabeculae into the shaft were noted in all the animals, but not in the controls (Fleming et al. 1942). The skeletal system appears to be a target of white phosphorus toxicity. Other potential targets of toxicity (i.e., liver and kidney) cannot be identified because the Jakhi et al. (1983) and Ward (1928) human studies examined a limited number of end points, and it is unclear which tissues were examined in the Fleming et al. (1942) study. Because targets of toxicity have not been fully identified, a chronic-duration oral MRL could not be derived. Information on chronic-duration toxicity of white phosphorus following dermal (nonburn) exposure to white phosphorus is limited to the occupational exposure studies discussed above for inhalation. No chronic-duration nonburn dermal animal studies were identified. No chronic-duration dermal burn human or animal studies were located. Studies designed to identify potential targets of chronic white phosphorus toxicity could be useful because water and soil sources near hazardous waste sites can be contaminated with white phosphorus.

No information on the carcinogenic potential of white phosphorus was located. Studies designed to assess carcinogenicity in animals after inhalation, oral, and dermal (nonburn and burn) exposure would be useful.

White Phosphorus Smoke. No chronic-duration inhalation or dermal exposure studies for humans and animals were located. The available intermediate-duration inhalation exposure study (Brown-et al. 1981) did not examine carcinogenic end points. Chronic-duration inhalation and dermal exposure studies that examine a number of end points as well as carcinogenicity would be useful in determining the targets of white phosphorus smoke toxicity as well as its carcinogenic potential.

2. HEALTH EFFECTS

Genotoxicity

White Phosphorus. No studies were located regarding *in vivo* genotoxic effects in humans or animals after inhalation, oral, or dermal (nonburn and burn) exposure. In a standard *in vitro* Ames assay, white phosphorus was not genotoxic. Studies testing the *in vitro* and *in vivo* genotoxicity of white phosphorus would be useful.

White Phosphorus Smoke. No information is available on the genotoxicity of white phosphorus smoke. Studies that examined *the in vitro* and *in* vivo genotoxicity of white phosphorus smoke would be useful.

Reproductive Toxicity

White Phosphorus. There is limited information on the reproductive toxicity of white phosphorus. Uterine hemorrhaging and spontaneous abortion were observed in a woman ingesting a lethal dose of phosphorus (Hann and Veale 1910). Intermediate-duration oral exposure studies in rats have shown no effect on reproductive performance or histological damage to reproductive organs following exposure to relatively low doses (Bio/dynamics 1991; IRDC 1985). Acute, intermediate, and chronic duration parenteral studies have shown no histological alterations in the testes (Fleming et al. 1942). Additional studies could help determine the potential of white phosphorus to induce reproductive effects at higher doses. Inhalation and dermal studies would provide information on reproductive toxicity by these routes.

White Phosphorus Smoke. No reproductive performance effects or histological lesions on reproductive tissues were observed in male and female rats exposed to white phosphorus smoke for intermediate durations (Brown et al. 1981). A limitation of this study is that the rats were exposed for a very short daily duration (15 minutes/day). Studies that involved longer daily inhalation exposures or dermal exposures would be useful to determine the potential for reproductive toxicity in humans exposed to white phosphorus smoke.

Developmental Toxicity

White Phosphorus. No information on developmental toxicity in humans was located. In two onegeneration reproduction studies, the incidence of developmental effects in rats orally exposed to white phosphorus was not significantly different from the incidence in vehicle-only controls (Bio/dynamics

1991; IRDC 1985). These studies administered relatively low doses of white phosphorus, and additional oral studies utilizing higher exposure levels could help determine the potential developmental toxicity of white phosphorus. Inhalation and dermal studies would provide information on developmental toxicity by these routes.

White Phosphorus Smoke. Decreased body weight and survival were observed in pups exposed to white phosphorus smoke *in utero* and during the lactation period (Brown et al. 1981; Starke et al. 1982). The authors suggested that these effects on the pups may be the result of impaired suckling. A study that tested this hypothesis would be useful in determining the potential of white phosphorus smoke to induce developmental effects. No dermal developmental toxicity studies were located; studies examining this route would be useful in assessing human health risk.

lmmunotoxicity

White Phosphorus. Information on the immunotoxicity of white phosphorus is limited to case reports involving decreases in total leukocyte levels or changes in differential leukocyte counts following ingestion of a single dose of white phosphorus (Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Fletcher and Galambos 1963; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968), changes in total leukocyte levels in workers exposed to white phosphorus (inhalation, oral, and dermal exposures) for chronic duration (Ward 1928), hemorrhages in the thymus in children ingesting a single dose of white phosphorus (Dwyer and Helwig 1925; Humphreys and Halpert 1931), hyperplasia of lymphoid tissue and lymph nodes in a child ingesting a single dose of white phosphorus (Humphreys and Halpert 193 l), hyperplasia of splenic lymphoid corpuscles in a child ingesting a single dose of white phosphorus (Humphreys and Halpert 193 l), and leukocytosis in individuals burned by white phosphorus (Walker et al. 1947). No information on immunotoxicity in animals was located. The human data suggest that the immune system is a target of white phosphorus toxicity; however, no information on the potential of white phosphorus to impair immune function is available. Animal studies assessing the results of a battery of immune function tests could be useful in determining the immunotoxic potential of white phosphorus. Information on different routes of exposure could be useful in assessing if effects are route specific.

White Phosphorus Smoke. No studies examining immunotoxicity following inhalation or dermal exposure to white phosphorus smoke were located. Animal studies assessing the results of a battery of

immune function tests would be useful in determining the immunotoxic potential of white phosphorus smoke following inhalation or dermal exposure.

Neurotoxicity

White Phosphorus. There is extensive information on overt neurotoxicity in humans acutely ingesting white phosphorus (Caley and Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 1931; McCarron et al. 1981; McIntosh 1927; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Talley et al. 1972; Wechsler and Wechsler 1951) and several autopsy reports on histological damage in the brain (Humphreys and Halpert 193 1; Rao and Brown 1974; Wertham 1932). Neurotoxicity has also been observed in animals exposed to white phosphorus for acute or intermediate duration (Bio/dynamics 1991; Ferraro et al. 1938; Frye and Cucuel 1969). The study conducted by Ferraro et al. (1938) demonstrated that the severity of the neurological damage was dose related. It is not known if the severity of the effects would also be duration-related; a study that examined this relation could be useful. In addition, no information on neurotoxicity following inhalation or dermal exposure in humans or animals was located. Inhalation and dermal studies would be useful in determining whether the effects are route-specific.

White Phosphorus Smoke. Information on the neurotoxicity of white phosphorus smoke is limited to an intermediate-duration study that examined the brain for histological lesions (Brown et al. 1981). Inhalation and dermal exposure studies examining a battery of neurological end points (including neurobehavioral effects) would be useful in assessing the neurotoxic potential of white phosphorus smoke.

Epidemiological and Human Dosimetry Studies

White Phosphorus. There are a great number of acute-duration human oral studies (Caley and, Kellock 1955; Dathe and Nathan 1946; Diaz-Rivera et al. 1950, 1961; Dwyer and Helwig 1925; Ehrentheil 1957; Fletcher and Galambos 1963; Greenberger et al. 1964; Hann and Veale 1910; Humphreys and Halpert 1931; Matsumoto et al. 1972; McCarron et al. 1981; Newburger et al. 1948; Pietras et al. 1968; Rao and Brown 1974; Rubitsky and Myerson 1949; Simon and Pickering 1976; Wechsler and Wechsler 1951) and several occupational exposure studies (Heimann 1946; Hughes et al. 1962; Kennon and HaIlam 1944; Legge 1920; Ward 1928). Because most individuals vomited shortly after ingestion of white phosphorus,

the amount of white phosphorus available for absorption is not known. In the occupational exposure studies, the concentration of airborne white phosphorus was not reported. White phosphorus is still used in the munitions industry and further studies of these workers may yield more useful information on doseresponse relationships and provide quantifiable data that could be used to monitor individuals living near hazardous waste sites.

White Phosphorus Smoke. There is limited information on the human toxicity of white phosphorus smoke. Respiratory effects have been observed following acute-duration exposure to white phosphorus smoke (Walker et al. 1947; White and Armstrong 1935).

Biomarkers of Exposure and Effect

White Phosphorus

Exposure. The major data insufficiency with respect to biomarkers is the lack of quantitative factors that can be measured either in-life or postmortem, and that are uniquely indicative of white phosphorus poisoning. This deficiency is related to the lack of definitive information regarding white phosphorus toxicokinetics. Because little is known about the fate of white phosphorus in the body, there are no substance-quantity or substance-presence tests that are currently available that indicate white phosphorus intoxication.

Effect. There are a number of biomarkers of exposure for white phosphorus. Most of these biomarkers are not unique for white phosphorus; however, the combination of biomarkers of effect for several targets may be specific for white phosphorus. Studies that identified unique biomarkers for exposure and effect would be useful.

White Phosphorus Smoke

Exposure. No biomarkers of exposure were identified for white phosphorus smoke. In addition, no information on the metabolism of white phosphorus smoke were located. Studies designed to assess the metabolism of white phosphorus smoke would be useful in identifying biomarkers of exposure. Biomarkers of exposure are useful in facilitating future medical surveillance that can lead to early detection and possible treatment.

2. HEALTH EFFECTS

Effect. There is limited available information on biomarkers of effect for white phosphorus smoke. Studies that assessed a number of sensitive biomarkers of respiratory irritation would be useful for the early detection of white phosphorus smoke-induced respiratory tract effects.

Absorption, Distribution, Metabolism, and Excretion

White Phosphorus. The pharmacokinetics database is inadequate. No quantitative information was located regarding absorption, distribution, metabolism, or excretion following inhalation, dermal, and dermal burn exposure to white phosphorus. Definitive quantitative data on metabolic pathways following oral exposure to white phosphorus also are lacking. Data that were located on absorption, distribution, and excretion following oral exposure were helpful. They provided some time-related data, but provided no information regarding comparisons between various dose levels.

White Phosphorus Smoke. No information on the absorption, distribution, metabolism, and excretion of white phosphorus smoke were located. Toxicokinetic studies would be useful in assessing the risk to human health following exposure to white phosphorus smoke.

Comparative Toxicokinetics

White Phosphorus. No studies were located that provided information regarding target organs following inhalation and dermal (no burn) exposure to white phosphorus. Similarities in organ-specific systemic effects between humans and animals indicate that the same organs are targeted following oral and dermal burn exposure to white phosphorus. No toxicokinetic studies have been performed on humans. Thus, the appropriateness of animals as models of white phosphorus toxicokinetics in humans is unknown. A similar tissue distribution of orally administered radiolabeled white phosphorus was observed in rats, rabbits, and mice. It seems reasonable to expect that tissue distribution in humans would be similar. No other multiple species studies were located.

White Phosphorus Smoke. Based on the limited available information on the toxicity of airborne white phosphorus smoke, it appears that humans and animals have similar targets of concern. Toxicokinetic studies in a variety of animal species would be useful in determining which animal species is an appropriate model for human toxicity to white phosphorus smoke.

2. HEALTH EFFECTS

Methods for Reducing Toxic Effects

White Phosphorus. There is limited information on the mechanisms of absorption of white phosphorus for any of the routes of exposure. Information on reducing peak absorption following acute oral exposure (Diaz-Rivera 1950), after white phosphorus-induced dermal burns (Rabinowitch 1943; Goldblatt and Oakeshott 1943; Jelenko 1974; Eldad and Simon 1991), and after acute eye exposure (Scherling and Blondis 1945) is available. No information on reducing absorption following inhalation exposure was located.

No studies were located regarding methods for reducing body burden or methods for interfering with the mechanism of action for toxic effects. Also, no definitive studies were located regarding the metabolic fate of white phosphorus after absorption. Therefore, studies elucidating metabolic pathways would be helpful as baseline data for developing methods for reducing body burden.

White Phosphorus Smoke. There are limited data for assessing methods for reducing the toxic effects of white phosphorus smoke. Studies that examine absorption would be useful in assessing methods for preventing absorption of white phosphorus smoke. Studies examining the distribution and metabolism of the white phosphorus smoke would be useful for determining methods for reducing the body burden of toxic compounds following exposure to white phosphorus smoke. Studies designed to establish methods for the mitigation of the respiratory tract effects observed in humans and animals exposed to airborne white phosphorus smoke would be useful in treating individuals exposed to white phosphorus smoke.

2.10.3 On-going Studies

White Phosphorus. No on-going research studies pertaining to white phosphorus were located.

White Phosphorus Smoke. No on-going research studies pertaining to white phosphorus smoke were located.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of white phosphorus is located in Table 3-l.

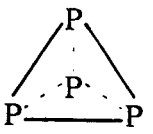
3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of white phosphorus and white phosphorus smoke is located in Table 3-2.

Elemental phosphorus exists in several allotropic forms (Van Wazer 1982). The best known and most important commercially is the a-white phosphorus whose properties are given in Table 3-2. Commercial white phosphorus is 99.9% pure, with a slight yellow color caused by traces of red phosphorus impurities. Hence, white phosphorus also is known as yellow phosphorus. When a-white phosphorus is cooled below -79.6°C, P-white phosphorus forms. Other important solid allotropes of phosphorus are red and black phosphorus (Van Wazer 1982).

The U.S. Army uses at least two phosphorus-based smoke/obscurants for training and testing activities (Shinn et al. 1985). One such agent is white phosphorus/felt (WP/F), and the other is red phosphorus/butyl rubber (Spanggord et al. 1985). WP/F consists of 75-80% white phosphorus solidified into a cellulose (felt) matrix (20-25%). When WP/F is burnt, besides unburnt white phosphorus, the smoke consists primarily of oxidation and hydrolysis products of phosphorus. For example, when white phosphorus burns in air it produces oxides of phosphorus including phosphorus pentoxide (P_4O_{10}, and phosphorus trioxide (P_40_6). These oxides react with moisture present in air to form a number of phosphorus-containing acids, such as orthophosphoric acid (H_3PO_4), pyrophosphoric acid ($H_4P_2O_7$), orthophosphorus acid (H_3PO_3), hypophosphorus acid (H_3PO_2), polyphosphoric acid of the general formula $H_{n+2}P_nO_{3n+1}$, where n=2-8, and a homologous series of linear and cyclic P_6-P_{16} polyphosphates (Spanggord et al. 1983; Tolle et al. 1988). The composition of white phosphorus smoke will change with time (Spanggord et al. 1988). In the absence of stoichiometric quantities of oxygen, phosphine (PH_3) may form in WP/F smoke from the reaction of unreacted phosphorus with moisture in air (Spanggord et al. 1983).

TABLE 3-1. Chemical Identity of White Phosphorus

Characteristic	Information	Reference
Chemical name	White phosphorus	CAS 1995
Synonym(s)	Yellow phosphorus, phosphorus tetramer	CAS 1995
Registered trade name(s)	No data	
Chemical formula	P_4	CAS 1995
Chemical structure		Spanggord et al. 1985
Identification numbers:		
CAS registry	7723-14-0	CAS 1995
NIOSH RTECS	TH3500000	RTECS 1995
EPA hazardous waste	D003	HSDB 1995
OHM/TADS	7216855	RTECS 1995
DOT/UN/NA/IMCO shipping	UN1381	RTECS 1995
HSDB	1169	HSDB 1995
NCI	No data	

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/ Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemicals Substances

TABLE 3-2. Physical and Chemical Properties of White Phosphorus

Property	Information	Reference
Molecular weight	123.895	Budavari et al. 1989
Color		
Pure form	Colorless to white	Budavari et al. 1989
Technical form	Yellow	Van Wazer 1982
Physical state	Waxy solid	Budavari et al. 1989
Melting point	44.1°C	Budavari et al. 1989
Boiling point	280°C	Budavari et al. 1989
Density:		
at 20°C	1.82 g/cm^3	Weast 1985
Odor	Garlic-like	HSDB 1993
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 15°C	3 mg/L	Weast 1985
Organic solvent(s)	Soluble in alkali, ether, chloroform, benzene, toluene	Weast 1985
Partition coefficients:		
Log K_{ow}	3.08	Spanggord et al. 1985
Log K_{oc}	3.05 (estimated)[a]	
Vapor pressure:		
at 20°C	0.025 mmHg; 0.026 mmHg	Farr 1950; HSDB 1993
Henry's law constant:		
at 20°C	2.11×10^{-3} atm·m^3/mol; 1.36×10^{-3} atm·m^3/mol[b]	Spanggord et al. 1985
Autoignition temperature	30°C (moist air); 35–46°C (dry air)	NSC 1990
Flashpoint	Spontaneous in air	Sax 1984
Flammability limits	No data	
Conversion factors	1 ppm = 5.150 mg/m^3 at 20°C	
Explosive limits	No data	

[a]Estimated from the regression equation given by Lyman (1982). The experimental values (range 2.56–2.77) of Spanggord et al. (1985) are unreliable due to the reactivity of white phosphorus.

[b]Estimated from the ratio of vapor pressure at 20°C and the water solubility at 15°C.

Reactions of white phosphorus that lead to the formation of some typical products are listed below (Cotton and Wilkinson 1980; Spanggord et al. 1985).

$P_4 + 3O_2 \rightarrow P^{+3}_4 O_6$	(phosphorus trioxide)
$P_4 + 5O_2 \rightarrow P^{+5}_4 O_{10}$	(phosphorus pentoxide)
$P_4O_{10} + 6H_2O \rightarrow 4H_3P^{+5}O_4$	(orthophosphoric acid)
$P_4O_{10} + 2H_2O \rightarrow 4HP^{+5}O_3$	(metaphosphoric acid)
$P_4O_{10} + 4H_2O \rightarrow 2H_4P^{+5}_2 O_7$	(pyrophosphoric acid)
$P_4O_6 + 2H_2O \rightarrow 4HP^{+3}O_2$	(metaphosphorus acid)
$P_4O_6 + 6H_2O \rightarrow 4H_3P^{+3}O_3$	(orthophosphorus acid)
$P_4 + 8H_2O \rightarrow 4H_3P^{+3}O_2 + 2H_2$	(hypophosphorus acid)
$4H_3PO_3 \rightarrow H_3P^{+5}O_4 + P^{-3}H_3$	(phosphine by disproportionation)
$3H_3PO_4 \rightarrow H_5P^{+5}_3 O_{10} + 2H_2O$	(triphosphoric acid)

Organic constituents that may be found in ppb levels in WP/F smoke include methane, ethylene, carbonyl sulfide, acetylene, 1,4-dicyanobenzene, 1,3-dicyanobenzene, 1,2-dicyanobenzene, acetonitrile, and acrylonitrile (Tolle et al. 1988). Since white phosphorus contains boron, silicon, calcium, aluminum, iron, and arsenic in excess of 10 ppm as impurities (Berkowitz et al. 1981), WP/F smoke also contains these elements and possibly their oxidation products. The physical properties of a few major compounds that may be important for determining the fate of WP/F smoke in the environment are given in Table 3-3.

Table 3-3. Physical Properties of Major Compounds in White Phosphorus Smoke[a]

Property	Phosphorus trioxide	Phosphorus pentoxide	Ortho-phosphorus acid	Ortho-phosphoric acid	Phosphine
Molecular formula	P_4O_6	P_4O_{10}	H_3PO_3	H_3PO_4	PH_3
Molecular weight	219.89	283.89	82.00	98.00	34.00
Color	White	White	Yellow	Colorless	Colorless
Physical state	Solid	Solid	Solid	Liquid or solid	Gas
Melting point	23.8°C	340°C[b]	73.6°C	42.35°C	-133.5°C
Boiling point	173.8°C (in N_2)	Sublimes at 360°C[b]	Decomposes at 200°C	Decomposes at 213°C	-87.4°C (auto-ignites 37.7°C[b])
Density, g/cm^3	2.135 at 21°C	2.39	1.651 at 21.2°C	1.834 at 15°C	1.529 g/L
Odor	No data	No data	No data	No data	Garlic-like[b]
Solubility:					
Water	Decomposes to H_3PO_3 at 20°C	Decomposes to H_3PO_4 at 20°C	694 g/100 mL at 40°C	548 g/100 in cold water	0.398 g/L at 17°C; 0.381 g/L at 25°C
Organic solvent(s)	Soluble in carbon dioxide, chloro-form ether	Insoluble in acetone	Soluble in ethanol	Soluble in ethanol[b]	Soluble in ethanol, ether
Partition coefficients:					
Log K_{ow}	Not relevant	Not relevant	Not relevant	Not relevant	No data
Log K_{oc}	Not relevant	Not relevant	Not relevant	Not relevant	No data
Vapor pressure	No data	No data	No data	No data	760 mm at -87.4°C
Henry's law constant at 20°C	No data	No data	No data	No data	0.09 atm·m^3/mol[c]

[a]All information obtained from Weast 1985 except where noted
[b]Hawley 1981
[c]Spanggord et al. 1985

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The domestic production capacity of elemental phosphorus in 1992 was 294,000 tons (SRI 1992). The demand for elemental phosphorus is expected to decrease (l-2%) during this decade (CMR 1991). The three companies that presently manufacture elemental phosphorus in the United States for sale or distribution are FMC Corp., Pocatello, Idaho; Monsanto Co., Soda Springs, Idaho; and Rhone-Poulenc Inc., Silver Bow, Montana (SRI 1995). The U.S. facilities that manufactured and processed white phosphorus in 1993 are given in Table 4-l (TR193 1995). White phosphorus is produced by several methods. One of the most important commercial production processes involves grinding phosphate rock, forming it into pellets, and heating them with coke or silica in an electric furnace. The elemental phosphorus vapor produced is then cleaned and collected by passing the vapor through an electrostatic precipitator and condenser (EPA 1989).

WP/F is manufactured in the Pine Bluff Arsenal in Pine Bluff, Arkansas. Molten white phosphorus stored under water is loaded in munitions shells either by the dip-fill or dry-fill methods (Berkowitz et al. 1981). In the dip-fill method, the shell canisters containing the felt wedges are passed through tubs of molten phosphorus under water. In the dry fill method, molten phosphorus is added directly to the canister under an inert atmosphere. The latter method greatly reduces phosphorus waste (phossy water) and environmental contamination (Spanggord et al. 1983).

4.2 IMPORT/EXPORT

In 1991, an estimated 5% of the production of elemental phosphorus was exported (CMR 1991). In 1982, the amount of imported elemental phosphorus from other countries to the United States was negligible (C&EN 1982) and probably remains so because the production capacity in the United States remains higher than the demand (CMR 1991).

Table 4-1. Facilities That Manufacture or Process White Phosphorus

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
ICI AMERICAS INC.	BUCKS, AL	100,000-999,999	As a reactant
ALBEMARLE CORP.	MAGNOLIA, AR	1,000-9,999	As a reactant
HALSTEAD METAL PRODS. INC.	WYNNE, AR	10,000-99,999	As a formulation component
TOWNSENDS OF ARKANSAS INC.	BATESVILLE, AR	100,000-999,999	As a formulation component
TOWNSENDS FARMS OF ARKANSAS	POCAHONTAS, AR	100,000-999,999	As a formulation component
FMC CORP.	CA	1,000,000-9,999,999	As a reactant
TOWNSENDS INC.	MILLSBORO, DE	1,000,000-9,999,999	As a formulation component
OSHKOSH TRUCK CORP.	BRADENTON, FL	1,000-9,999	As a product component
MONSANTO CO.	GA	1,000,000-9,999,999	As a reactant
TWIN STATE ENG. & CHEMICAL CO.	DURANT, IA	100,000-999,999	Import; For on-site use/processing; As a reactant
MONSANTO CO.	SODA SPRINGS, ID	1,000,000-9,999,999	Produce; For sale/distribution
FMC CORP.	POCATELLO, ID	NA	Produce; For sale/distribution
RHONE-POULENC INC.	IL	100,000-999,999	As a reactant
RHONE-POULENC INC.	IL	0-99	As a reactant
H. KRAMER & CO.	CHICAGO, IL	1,000-9,999	As a formulation component
OLIN CORP.	EAST ALTON, IL	1,000-9,999	As a formulation component
OLIN CORP.	EAST ALTON, IL	1,000-9,999	As a formulation component
MONSANTO CO.	SAUGET, IL	1,000,000-9,999,999	As a reactant
NORTH AMERICAN TRUCK PLATFORMS	ROANOKE, IN	10,000-99,999	As a formulation component; As a product component
NEW YORK BLOWER CO.	LA PORTE, IN	100,000-999,999	Produce; As a by-product
TOMKINS IND.	ALBION, IN	1,000-9,999	As a product component
FMC CORP.	KS	1,000,000-9,999,999	As a reactant
MONSANTO CO.	LULING, LA	100,000-999,999	As a reactant
SEALED POWER TECHS. L.P.	MUSKEGON HEIGHTS, MI	10,000-99,999	As a product component
GMC	SAGINAW, MI	10,000-99,999	As a formulation component
MONSANTO CO.	MI	1,000,000-9,999,999	As a reactant
MONSANTO CO.	ST. LOUIS, MO	1,000,000-9,999,999	As a reactant
MUELLER COPPER TUBE CO.	FULTON, MS	10,000-99,999	As a product component
RHONE-POULENC BASIC CHEMICALS	SILVERBOW, MT	1,000,000-9,999,999	Produce; For sale/distribution
TOWNSEND FARMS INC.	BONLEE, NC	1,000,000-9,999,999	As a formulation component

Table 4-1. Facilities That Manufacture or Process White Phosphorus (continued)

Facility	Location[a]	Range of maximum amounts on site in pounds	Activities and uses
FMC CORP.	CARTERET, NJ	1,000,000-9,999,999	As a reactant
OCCIDENTAL PETROLEUM CORP.	NY	1,000,000-9,999,999	As a reactant
MILWARD ALLOYS INC.	LOCKPORT, NY	10,000-99,999	Import; For on-site use/processing; As a product component
ELLWOOD ENGINEERED CASTINGS	HUBBARD, OH	1,000-9,999	As a product component
RHONE-POULENC INC.	PA	100,000-999,999	As a reactant
METALLURGICAL PRODS. CO.	WEST CHESTER, PA	10,000-99,999	As a formulation component
ALBRIGHT & WILSON	CHARLESTON, SC	1,000,000-9,999,999	As a reactant
RHONE-POULENC INC.	TN	1,000,000-9,999,999	As a reactant
MONSANTO CO.	COLUMBIA, TN	1,000,000-9,999,999	Produce; For sale/distribution; In repackaging only
ZENECA INC.	TN	100,000-999,999	As a reactant
RHONE-POULENC BASIC CHEMICALS	MOUNT PLEASANT, TN	1,000,000-9,999,999	In repackaging only
OCCIDENTAL CHEMICAL CORP.	COLUMBIA, TN	1,000,000-9,999,999	Produce; For on-site use/processing; For sale/distribution
NISSAN MOTOR MFG. CORP. USA	SMYRNA, TN	0-99	As a product component; As a manufacturing aid; Ancillary uses
CBI NA-CON INC.	HOUSTON, TX	1,000-9,999	As a product component
STAR ENTERPRISE	PORT ARTHUR, TX	1,000,000-9,999,999	Import; For on-site use/processing; Ancillary uses
W. R. GRACE & CO.-CONN.	DE PERE, WI	10,000-99,999	Produce; Import; For on-site use/processing; As a by-product; As a product component
BRADLEY CORP.	MENOMONEE FALLS, WI	1,000-9,999	As a product component
AKZO NOBEL CHEMICALS INC.	GALLIPOLIS FERRY, WV	1,000,000-9,999,999	As a reactant
FMC CORP.	NITRO, WV	100,000-999,999	As a reactant
L. B. FOSTER CO.	WASHINGTON, WV	1,000-9,999	As a product component
FMC CORP.	WY	1,000,000-9,999,999	As a reactant

Source: TRI93 1995

[a] Post office state abbreviations used

NA = not available

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.3 USE

In 1991, ≈83% of elemental phosphorus available in the nonmilitary market was used in the production of phosphoric acid and phosphates, 12% was used in the production of direct reaction chemicals, such as phosphorus trichloride, pentasulfide, and pentoxide and red phosphorus, and 5% was exported (CMR 1991; EPA 1989). Phosphates are generally used in the fertilizer industry, food and beverage industry, industrial and institution cleaning compounds, water and waste treatment, animal diets and in metal treatment (CMR 1991; van Wazer 1982). Small amounts of white phosphorus are used in roach and rodent poisons (van Wazer 1982). In military use, white phosphorus is used as an ammunition for mortar and artillery shells and hand and rifle grenades (EPA 1989). In the past, white phosphorus was used in the manufacture of matches. However, due to health considerations (jaw-bone necrosis), red phosphorus and tetraphosphorus trisulfide (P_4S_3) have replaced white phosphorus since the Beme Convention of 1906 (Nyunt 1983). More recently, the use of white phosphorus has been suggested for removing nitric oxide from flue gas generated during the combustion of fossil fuels in power plants (Chang and Lee 1992; Chang and Liu 1990; Liu et al. 1991).

4.4 DISPOSAL

According to the United Nation's treatment and disposal methods for wastes containing phosphorus, the two recommended methods of disposal are incineration and open burning (HSDB 1993). In the open burning method, the waste should be mixed with wet earth, allowed to dry, and ignited in a remote place. The ultimate method of disposal is controlled incineration and treatment of emitted gases by alkaline scrubbing and particle removal equipment (HSDB 1993). Landfilling phosphorus-containing wastes is not recommended by the United Nation's treatment and disposal methods (HSDB 1993). However, most of the wastes produced by U.S. manufacturers or processors of white phosphorus are disposed of in landfills (see Section 52.3). In the current disposal practice, retired or outdated army munitions are reprocessed to recover phosphorus. The munitions shells, which are still contaminated with white phosphorus, are incinerated in fluidized bed incinerators equipped with after burners and scrubbers (Berkowitz et al. 1981; Uhrmacher et al. 1985). Waste water containing phosphorus (phossy water) can be treated with ozone in a sparged stirred reactor (Campbell 1977). The resulting phosphate ions may be removed as a calcium phosphate precipitate by adding lime. Campbell (1977) claimed this process reduced the phosphorus levels in phossy water below the limit of detection (<22 μg/L).

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

Elemental phosphorus is listed as a hazardous substance and the discharge in excess of 1 pound to surface water is in violation of section 31l(b)(3) of the U.S. code of regulations (EPA 1992a). Solid waste containing elemental phosphorus is characterized as a hazardous waste when it passes the characteristic of reactivity stipulated in 40 CFR 261.23. If so characterized, the solid waste must be managed as a hazardous waste (EPA 1992b).

5. POTENTIAL FOR HUMAN EXPOSURE

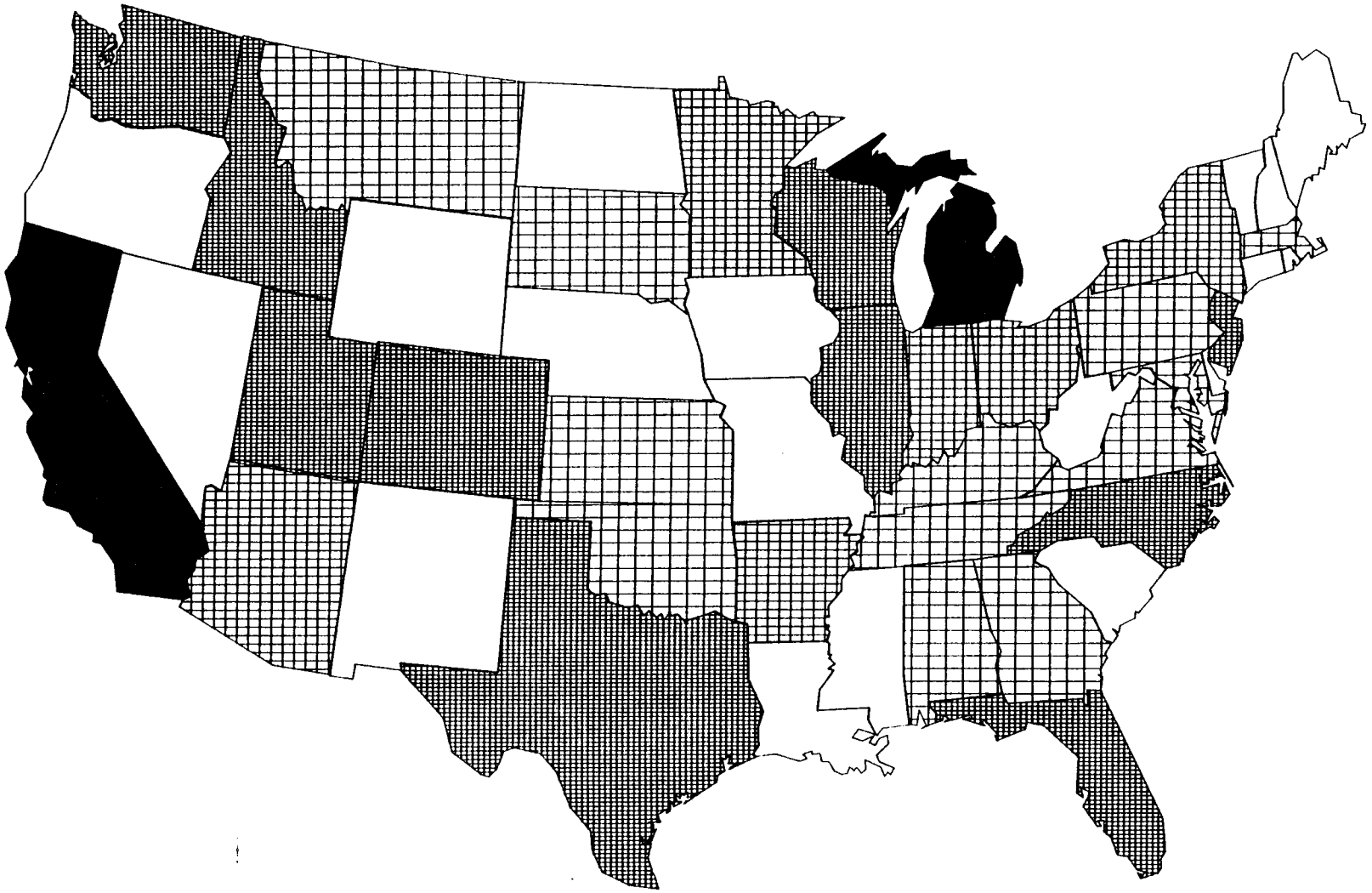
5.1 OVERVIEW

White phosphorus can enter the environment from its production, use, accidental spills during loading and unloading for shipment, and accidental spills during transport. Hazardous wastes sites containing white phosphorus can also be a source of phosphorus in the environment. White phosphorus has been found in at least 77 of the 1,430 current or former EPA National Priorities List (NPL) hazardous waste sites (HazDat 1996). However, the number of sites evaluated for white phosphorus is not known. The frequency of these sites within the United States can be seen in Figure 5-l.

The persistence of elemental phosphorus in the air is very short due to oxidation to phosphorus oxides and ultimately to phosphorus acids. However, the particulate phosphorus aerosol may be coated with a protective oxide layer that may prevent further oxidation and extend the lifetime of particulate phosphorus in air. Both wet and dry deposition remove unreacted elemental phosphorus and the degradation products from the air. Similarly, elemental phosphorus oxidizes and hydrolyzes in water and in soil. A small amount of elemental phosphorus is lost from soil and water by volatilization.

Phosphorus is used as a fumigant in the storage of grain. Because of ease of application, pellets of aluminum or magnesium phosphide are commonly used (Garry et al. 1993). Phosphine, a highly toxic gas, is generated from phosphide. The rate of formation of phosphine (permissible exposure limit [PEL], 0.4 mg/m^3) is dependent on the ambient temperature and humidity. Its release is rapid, and it is extremely fatal to the unprotected person (Garry et al. 1989). An accidental death of a pregnant woman was related to phosphine exposure from stored grain which had been fumigated with aluminum phosphide (AIP_3) pellets (Garry et al. 1993). Phosphine is also generated when phosphorus is used as a dopant in the processing of microchips, where a small amount of phosphorus is added to another substancesuch as a semi-conductor to alter its properties (Garry et al. 1989). When phosphine is formed, it decomposes to several lesser known intermediates such as P_2H_4 a potential alkylating agent, finally forming H_2PO_4 (phosphoric acid), salts, and water. In the presence of oxygen, these breakdown products are formed rapidly from phosphine (Garry et al. 1993). A small fraction of phosphine may undergo oxidation with the formation of phosphates. The half-life of elemental phosphorus in water is 2-20 hours and 3-7 days in

FIGURE 5-1. FREQUENCY OF NPL SITES WITH WHITE PHOSPHOROUS CONTAMINATION *



*Derived from HazDat 1995

soil. However, the half-life of elemental phosphorus in the anoxic zones of water, sediment, and soil can exceed 2 years and may be ≤10,000 years.

The combustion of white phosphorus felt or red phosphorus butyl rubber will produce smoke. Smoke is an aerosol comprised of oxides of phosphorus (phosphorus pentoxide and phosphorus trioxide), some of their transformation products (see Section 3.2), and a small amount of unburnt phosphorus. The aerosol components in the smoke will undergo dispersion and chemical transformation in air to form acids or phosphorus, and will ultimately deposit from air to the hydrosphere and the lithosphere. The main components of the aerosol deposited over water and soil are acids of phosphorus. Under oxidizing conditions in soil and water, phosphorus acids will be transformed to phosphate or polyphosphates. Under reducing conditions, the disproportionation reaction of phosphorus acid can produce phosphine, and the gas may be released to the atmosphere. The fate of deposited unburnt phosphorus in water and soil has already been discussed in the preceding paragraph.

Elemental phosphorus has been detected in occupational air at levels ≥0.45 mg/m^3. It has been detected in water, sediment, and aquatic animals in the vicinity of phosphorus production and user sites. Concentrations of ≤386 μg/kg were detected in freshwater drums collected from Yellow Lake in Pine Bluff, Arkansas. Elemental phosphorus was detected in dead waterfowl in the vicinity of contaminated water at a concentration of 3,501,000 μg/kg (3.5 g/kg). The fat of a dead bald eagle from Eagle River Plats, Alaska, contained 60 μg/kg elemental phosphorus. The typical intake of elemental phosphorus for the general population in the United States resulting from inhalation of air and ingestion of drinking water and food is not known. People who live near phosphorus production sites, user sites (e.g., Pine Bluff Arsenal), WP/F artillery training sites, and dumpsites that contain elemental phosphorus may be exposed to elemental phosphorus at higher levels than the control population. People who live near accidental spill sites may also be exposed to phosphorus at high doses during a spill incident. There is a lack of data providing evidence of these high exposures.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

White phosphorus can enter air from its production, use, accidental spills during loading and unloading for shipment, and accidental spills during transport. During white phosphorus production, an estimated 0.58 kg total phosphorus/ton of product is emitted into the air (EPA 1989). Part of the air emissions during production of white phosphorus from phosphate rock is expected to be in the form of phosphate. The air emission of elemental phosphorus during production of munitions at the Pine Bluff Arsenal in Arkansas was estimated at 1 mg/kg of phosphorus used (Berkowitz et al. 1981). The amount of elemental phosphorus released to air during the manufacture of phosphoric acid, phosphates, and other phosphorus chemicals is not known because the air emission factor is estimated for total phosphorus (EPA 1989). However, the emission of elemental phosphorus from the manufacture of phosphorus chemicals may be low, because the conversion rate from elemental phosphorus to compounds is high. White phosphorus is also released in air during its use as an incendiary device by the military. It will enter the atmosphere during testing, which produces phosphorus smoke in the field. At a smoke density of 0.1 mg/m^3, the estimated concentration of elemental phosphorus in the smoke was 21 ppb (EPA 1991). It has been suggested that elemental phosphorus is released into the air during manufacture and treatment of some semiconductors, such as gallium phosphide (Knizek 1978). Elemental phosphorus also enters air from accidental spills during loading and unloading at the dockside (Idler et al. 1981); but no estimate of the amount of emission from this source was located. Accidental spills during transport also emit white phosphorus to the atmosphere. In one such incident in 1986, the derailment and subsequent fire of a tanker car gradually released 12,000 gallons of white phosphorus, mostly as combustion products, in Miamisburg, Ohio (Scoville et al. 1989). According to the Toxics Release Inventory (TR193 1995), an estimated total of 30.0 thousand pounds of white phosphorus, amounting to 8.3% of the total environmental release, was discharged to the air from manufacturing and processing facilitiesin the United States in 1993 (see Table 5-l). The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list.

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process White Phosphorus

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
AL	BUCKS	ICI AMERICAS INC.	1				1		1,080
AR	BATESVILLE	TOWNSENDS OF ARKANSAS INC.	1,368				1,368		
AR	MAGNOLIA	ALBEMARLE CORP.	1,350			5	1,355		
AR	POCAHONTAS	TOWNSENDS FARMS OF ARKANSAS	445				445		
AR	WYNNE	HALSTEAD METAL PRODS. INC.		5			5		
CA	NA	FMC CORP.							
DE	MILLSBORO	TOWNSENDS INC.	2,215				2,215		
FL	BRADENTON	OSHKOSH TRUCK CORP.	5				5		13,971
GA	NA	MONSANTO CO.							
IA	DURANT	TWIN STATE ENG. & CHEMICAL CO.			5		5		
ID	POCATELLO	FMC CORP.			313,349		313,349		
ID	SODA SPRINGS	MONSANTO CO.	30		3,900		3,930		
IL	CHICAGO	H. KRAMER & CO.						250	
IL	EAST ALTON	OLIN CORP.		1,900			1,900		
IL	EAST ALTON	OLIN CORP.		250			250		820
IL	NA	RHONE-POULENC INC.							
IL	NA	RHONE-POULENC INC.							
IL	SAUGET	MONSANTO CO.	3				3		8
IN	ALBION	TOMKINS IND.							80,800
IN	LA PORTE	NEW YORK BLOWER CO.	250				250		
IN	ROANOKE	NORTH AMERICAN TRUCK PLATFORMS							250
KS	NA	FMC CORP.							

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process White Phosphorus (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
LA	LULING	MONSANTO CO.	19				19		
MI	MUSKEGON HEIGHTS	SEALED POWER TECHS. L.P.	5				5		1,685
MI	NA	MONSANTO CO.							
MI	SAGINAW	GMC	1,250				1,250	2,100	5
MO	ST. LOUIS	MONSANTO CO.							58
MS	FULTON	MUELLER COPPER TUBE CO.	15,393				15,393		
MT	SILVERBOW	RHONE-POULENC BASIC CHEMICALS	4,035				4,035		
NC	BONLEE	TOWNSEND FARMS INC.	2,560				2,560		
NJ	CARTERET	FMC CORP.							26,000
NY	LOCKPORT	MILWARD ALLOYS INC.	10				10	5	
NY	NA	OCCIDENTAL PETROLEUM CORP.							
OH	HUBBARD	ELLWOOD ENGINEERED CASTINGS	3				3		2,900
PA	NA	RHONE-POULENC INC.							
PA	WEST CHESTER	METALLURGICAL PRODS. CO.	10				10		
SC	CHARLESTON	ALBRIGHT & WILSON							250
TN	COLUMBIA	MONSANTO CO.	2				2		1
TN	COLUMBIA	OCCIDENTAL CHEMICAL CORP.	1,000	5	10,400		11,405		
TN	MOUNT PLEASANT	RHONE-POULENC BASIC CHEMICALS	300				300		
TN	NA	RHONE-POULENC INC.							

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process White Phosphorus (continued)

State[a]	City	Facility	Reported amounts released in pounds per year						
			Air	Water	Land	Underground injection	Total environment[b]	POTW transfer	Off-site waste transfer
TN	NA	ZENECA INC.							
TN	SMYRNA	NISSAN MOTOR MFG. CORP. USA	15				15		
TX	HOUSTON	CBI NA-CON INC.	5	5			10		12,000
TX	PORT ARTHUR	STAR ENTERPRISE							361
WI	DE PERE	W. R. GRACE & CO.-CONN.							10,015
WI	MENOMONEE FALLS	BRADLEY CORP.	10				10		250
WV	GALLIPOLIS FERRY	AKZO NOBEL CHEMICALS INC.							45,000
WV	NITRO	FMC CORP.							600
WV	WASHINGTON	L. B. FOSTER CO.		2,822			2,822		250
WY	NA	FMC CORP.							
		Totals	30,284	4,987	327,654	5	362,930	2,355	196,304

Source: TRI93 1995

[a] Post office state abbreviations used
[b] The sum of all releases of the chemical to air, land, water, and underground injection wells by a given facility

NA = not available; POTW = publicly owned treatment works

5.2.2 Water

The same sources that emit elemental phosphorus to air are also responsible for its emission to water. In its initial states of operation, the ERCO plant in Newfoundland, Canada, which produced white phosphorus, discharged 68-91 kg/day of colloidal white phosphorus into the Long Harbor inlet of Placentia Bay in Newfoundland. Elemental phosphorus was found in both the effluent water and the bottom sediment of Long Harbor (Davidson et al. 1987; EPA 1991). White phosphorus is also expected to be found in the effluents from user industries where it is converted into products such as phosphoric acid and phosphate, detergents, fireworks, insecticide, rat poisons, flotation agents, and red phosphorus (Idler et al. 1981). However, the concentration of elemental phosphorus in effluents from industries that produce phosphorus compounds is much lower, compared to industries that do not use chemical conversion processes for producing final products (e.g., WP/F production). White phosphorus also enters water when treated or untreated effluents are released from munitions production facilities that use white phosphorus. Before water recycling measures were implemented at the Pine Bluff Arsenal in Arkansas, the effluent water (phossy water) from the facility contained 153.4 mg/L of white phosphorus (Pearson et al. 1976). White phosphorus is usually handled in the molten state (55˚C), submerged under water or as an inert gas. Accidental spills of white phosphorus during loading, unloading, or transport can release the element into water directly or by way of washout from terrestrial surfaces. The accident in Miamisburg, Ohio, is an example of such a release (Scoville et al. 1989). Small amounts of elemental phosphorus can be released into water in leachate from sludge heaps (produced during production of phosphorus) or runoff from hazardous waste sites containing elemental phosphorus (Berkowitz et al. 1981; Idler et al. 1981). Leaching from a phosphorus-containing landfill may also transport small amounts of elemental phosphorus to groundwater (Berkowitz et al. 1981). In addition, water deposition of atmospheric phosphorus may release small amounts of phosphorus into water (since most of the phosphorus in air will oxidize with the exception of phosphorus protected from oxidation by an oxide layer) (Berkowitz et al. 1981). According to TRI93 (1995), an estimated total of 5.0 thousand pounds of white phosphorus, amounting to 1.4% of the total environmental release, was discharged to water (including public sewers) from manufacturing and processing facilities in the United States in 1993.

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5.2.3 Soil

Two important sources of elemental phosphorus in soil are the creation of slag piles during the production of white phosphorus, and the disposal of solid wastes containing elemental phosphorus in hazardous waste landfills (Berkowitz et al. 1981; Idler et al. 1981). The field use of WP/F and red phosphorus/butyl rubber smoke/obscurant releases elemental phosphorus into soil primarily as unburnt phosphorus in munitions (Berkowitz et al. 1981; Van Voris et al. 1987). During the deployment of ammunition, a significant amount of phosphorus may remain unoxidized in the form of unburnt elemental phosphorus (Spanggord et al. 1985). Elemental phosphorus is also released to soil from accidental spills during the loading, unloading, and transport of white phosphorus. Smaller amounts of particulate phosphorus present as an aerosol enter land as a result of wet and dry deposition of atmospheric phosphorus (Berkowitz et al. 1981). According to TR193 (1995), an estimated total of 328,000 pounds of white phosphorus, amounting to 90.3% of the total environmental release, was discharged to land from manufacturing and processing facilities in the United States in 1993. Additionally, a total of 196,000 pounds of white phosphorus waste (54.1% of the total environmental phosphorus release) from these facilities was transferred to other locations for disposal. Some of these wastes may have been disposed of in hazardous waste sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The persistence of white phosphorus in air is very short and may range from minutes to days (see Section 5.3.2.1). Particulate white phosphorus present as an aerosol may be coated with a protective layer of oxide and may have a longer lifetime in air (Berkowitz et al. 1981). In addition to aerosol age, phosphorus aerosol speciation is also affected by the humidity of the ambient environment (Van Voris et al. 1987). Washout and rainout processes transport both the reaction products of vapor phase phosphorus and unreacted particles of phosphorus to water and land (Berkowitz et al. 1981). Because of its lower water solubility, physical state (gas), and slower reactivity, phosphine formed during the combustion of white phosphorus or released to the atmosphere from other media persists in the atmosphere longer than other reaction products.

Phosphorus enters water mostly as phosphates; smaller amounts enter as elemental phosphorus. Phosphates in an aquatic system partition between the aquatic phase (10%) and the sediment (90%) (Berkowitz

et al. 1981). Elemental phosphorus that remains unoxidized in water can be partially deposited in the sediment after gravitational settling and also partially remains in the colloidal form in water. The rate of gravitational settling depends on the particle size of white phosphorus; larger phosphorus particles settle faster than smaller particles. Elemental phosphorus particles with diameters ranging from 0.015 to 3.0 mm were isolated from pond sediment samples of Eagle River Flats in Alaska (Bird 1991). The estimated soil sorption coefficient (K_{oc}) value of 3.05 (see Table 3-2) indicates that both the water-soluble and colloidal forms of white phosphorus in the water phase may sorb moderately to particulate matter in water (Spanggord et al. 1985; Swann et al. 1983). The particle-sorbed phosphorus is eventually transported to the sediment. Volatilization from water to air is another mode of transport of white phosphorus. The Henry's law constant (H) of 2.11×10^{-3} atm·m^3/mol (Spanggord et al. 1985) indicates that volatilization of elemental phosphorus from water is significant (Thomas 1982). The estimated volatilization half-life of white phosphorus from water is 48.5 minutes from a stream 4 feet deep, with an eddy diffusivity of 1 cm^2/second (Spanggord et al. 1985). Under turbulent conditions, the rate of volatilization is faster and may be an important fate-determining process for white phosphorus.

White phosphorus moderately bioconcentrates in aquatic organisms, but the bioconcentration factors are much lower than those for other toxic organic chemicals. The bioconcentration factors for white phosphorus in a few species of aquatic organisms are as follows: cod (*Gadus morhua*) whole body, 44, and muscle, 24; salmon (*Salvo salur*) muscle, 22 (Fletcher 1974); channel catfish (*Ictalurus punctutus*) muscle, 50-100; fathead minnow *(Pimephdes promelas)* muscle, 127 (Bentley et al. 1978); cod (G. *morhua)* muscle, l0-100 (Dyer et *al.* 1970); clams (Mya *arenaria),* 23; mussel *(Mytilus edulis),* 10; periwinkle *(Littorinu littroreu), 42;* starfish *(Asterius vulgaris),* 27; lobster *(Homurus americanus)* muscle, 23-34 (Fletcher 1971). It has been suggested that the bioconcentration factor (BCF) of elemental phosphorus in fish muscle may depend on the concentration in water. The BCF for cod muscle decreased with increasing water concentration, ranging from 34 at 4.4 ug/L to 10 at 29 µg/L (Maddock and Taylor 1976). Depuration was rapid once the contaminated fish were placed in clean water; no elemental phosphorus was observed from within hours to 7 days of exposure (Bentley et al. 1978; Fletcher 1971; Maddock and Taylor 1976).

The two processes involved in the transport of elemental phosphorus from soil are volatilization and leaching. When 35 mg of elemental phosphorus was added to two soils, one acid and the other calcareous, ≈0.004-0.6% of the applied phosphorus found at a depth of ≤ 10 cm volatilized as elemental phosphorus (not as oxides) in 3 days (Warnock 1972). The loss of a maximum amount of 0.6% phosphates was

complete in 3-7 days. The amount of phosphorus volatilized appeared to be similar from both soils. The rate of volatilization decreased by increasing the depth to which the phosphorus was applied or by increasing soil moisture content; the rate did not go to zero. The transport of elemental phosphorus from soil by leaching depends on the K_{oc} value. The estimated K_{oc} value of 3.05 (see Table 3-2) indicates that phosphorus may moderately sorb in soil. Therefore, moderate leaching of phosphorus may occur from the anaerobic soil zone where elemental phosphorus will be stable toward chemical oxidation (EPA 1989; Richardson 1992).

5.3.2 Transformation and Degradation

5.3.2.1 Air

WP/F reacted rapidly in air with an estimated half-life of ≈5 minutes (Spanggord et al. 1985). However, the deployment of the military smoke/obscurant in the field may produce an estimated 10% of unburnt phosphorus (Spanggord et al. 1985). Other sources will also emit elemental phosphorus (see Section 5.2.1). Particle size from phosphorus obscurant aerosols is determined by the age of the particles and the amount of water vapor available in the atmosphere. In wind tunnel studies particles increased in diameter by 1.3 times and increased in volume by 2.0 times at a relative humidity of 60%. Similar increases were observed with humidity levels higher than 60%. These increases are due to absorption of water vapor and to a lesser extent by coagulation of the particles. Therefore, in general particles that are smaller have been released more recently than larger particles (Van Voris et al. 1987). In air, elemental phosphorus in the vapor phase reacts rapidly with atmospheric oxygen to produce oxides of phosphorus (Spanggord et al. 1985). Since oxides of phosphorus are highly soluble in water, wet deposition removes them from air (Berkowitz et al. 1981). Particulate elemental phosphorus also reacts at most environmental pressures and at temperatures >5°C (EPA 1989). The amount of phosphorus remaining in the particles has been observed to decrease with increasing relative humidity from a phosphorus percentage of 25% at low humidities to 15% for humidities near 90% (Van Voris et al. 1987). However, if the particulate phosphorus is coated with a protective layer of oxide, further oxidation may not occur (Berkowitz et al. 1981). This may increase the lifetime of elemental phosphorus in the air. Both wet and dry deposition remove the oxide-coated elemental phosphorus from the atmosphere with the wet deposition rate increasing with increasing relative humidity.

5. POTENTIAL FOR HUMAN EXPOSURE

Hydrolysis of elemental phosphorus in the atmosphere can produce phosphine. Phosphine in the presence of oxygen is highly reactive and is rapidly oxidized to, among other things, phosphoric acid. The production of phosphine is inversely related to the oxygen concentration, and is thus favored by low oxygen pressures (Spanggord et al. 1985). Hence, the probability of phosphine formation in the atmosphere is low because the concentration of oxygen is not conducive to it. Wind tunnel studies showed levels of phosphine generated during a white phosphorus aerosol study at levels approaching the detection limit. The highest phosphine concentration observed was 70 $\mu g/m^3$, representing 0.02% of the total phosphorus in the aerosol. The higher concentrations were more prevalent at higher relative humidities (Van Voris et al. 1987). Such a reaction is more likely in water and soil (EPA 1991).

Of the several products formed during the use of WP/F obscurant/smoke, phosphine is especially important because of its toxicity (EPA 1991). Therefore, the environmental fate of phosphine is briefly discussed. The important process for the loss of phosphine in the atmosphere is most likely its reaction with hydroxyl radicals. Based on measured rates under simulated conditions, the estimated lifetime of phosphine in the troposphere due to reaction with hydroxyl radicals is <1 day (Fritz et al. 1982). The hydrogen abstraction reaction may produce [PH_2], which may react with ozone to produce H_2PO. PH_2•] is a free radical and is highly reactive, with or without ozone. Ultraviolet (UV) light can induce PH_3 (phosphine) to form [PH_2•]. H_2PO may produce hypophosphorus acid (H_2PO_2) as a result of a reaction with nitrogen dioxide in air and subsequent hydrolysis. The hypophosphorus acid is ultimately oxidized to phosphorus and phosphoric acid.

5.3.2.2 Water

White phosphorus can exist in water as dissolved phosphorus in amounts ≤3 mg/L, in the colloidal state, as large particles of elemental phosphorus at concentrations >3 mg/L, or in the particle-sorbed state (Bullock and Newlands 1969; EPA 1991). Elemental phosphorus can undergo oxidation and hydrolysis in water. The rate of reactions depends on the dissolved oxygen concentration, temperature, state. of phosphorus in water (dissolved, sorbed, colloidal, or particle form), and possibly the pH of the solution. The rate of reaction grows faster as the temperature of the water increases (Lai and Rosenblatt 1977a). At concentrations well below the solubility limit (3 mg/L), elemental phosphorus disappeared from water by a first-order process with a half-life of 2 hours at ≈10°C and 0.85 hours at 30°C (EPA 1991; Zitko et al. 1970). The rate of phosphorus disappearance in water increased with the oxygen (or air) concentration and the pH of water (Lai and Rosenblatt 1977a). However, the faster initial disappearance half-life of

3.5 hours (compared to distilled water at pH 4.2) observed in river water at 22°C and a pH of 7.6 may have been due to the catalytic effects of ions present in the river water, rather than the pH effect (Lai and Rosenblatt 1977a).

The disappearance half-life of elemental phosphorus in water also depends on the physical state of phosphorus. For example, the disappearance half-life of collodial phosphorus was 80 hours at 30°C and 240 hours at 0°C at concentrations between 10-50 mg/L (Bullock and Newlands 1969), compared to a half-life of 2 hours in solution form at 10°C (Zitko et al. 1970). The half-life of white phosphorus in solution increased from 2 to 20 hours when the phosphorus was present in the sorbed state in sediment (Zitko et al. 1970). In anoxic water, the estimated half-life of a solid chunk of white phosphorus that was protectively coated due to oxidation/hydrolysis at the oxic zone was 2.43 years (Spanggord et al. 1985).

The experiments discussed above determined the rate of disappearance and the half-life of elemental phosphorus in water in open systems. The phosphorus in these experiments disappeared due to hydrolysis/oxidation and evaporation. Spanggord et al. (1985) studied the loss of elemental phosphorus in sealed reaction flasks. In a closed reaction flask with argon-saturated water, the loss of white phosphorus can only be due to hydrolysis. The estimated half-life for hydrolysis at ambient temperatures was 84 hours (Spanggord et al. 1985). The estimated half-lives of white phosphorus at ambient temperatures due to a combination of hydrolysis and oxidation reaction were 42 hours in air-saturated water and 56 hours in nonair-saturated water (Spanggord et al. 1985). Phosphine forms both in the presence and absence of air. However, since phosphine is a gas with a low water solubility (see Table 3-3), it either oxidizes or volatizes rapidly from water (Lai and Rosenblatt 1977a). At a white phosphorus concentration of 0.205 mg/L, approximately 6-9% of initial phosphorus was released as phosphine within 2 days (Lai and Rosenblatt 1977a). Kinetic studies concluded that the rate of phosphine production is inversely proportional to the oxygen concentration, and thus is favored by low oxygen pressure (Spanggord et al. 1985). The products of hydrolysis of white phosphorus are phosphine, hypophosphorus acid, phosphorus acid, and phosphoric acid. The oxidation products are oxides of phosphorus that produce hypophosphorus acid, phosphorus acid, and phosphoric acids in the presence of water (Spanggord et al. 1985).

White phosphorus reacts rapidly with chlorine to form phosphorus trichloride, which finally hydrolyzes and oxidizes to form phosphoric acids (EPA 1991). Chlorination of water, therefore, further shortens the half-life of phosphorus in water.

5. POTENTIAL FOR HUMAN EXPOSURE

No data on the biodegradation of white phosphorus in water under aerobic conditions were located. Considering the rapidity with which phosphorus disappears from aerated water as a result of a combination of evaporative and chemical processes, it is unlikely that aerobic biodegradation can compete with these loss processes. Anaerobic biodegradation studies concluded that biotransformation of elemental phosphorus is not rapid in water (Spanggord et al. 1985).

In most natural water, phosphine is very unstable and oxidizes even under anoxic conditions. Depending upon the redox potential of water, the oxidation products are diphosphine (P_2H_4), phosphorus, hypophosphorus acid, phosphorus acid, and phosphoric acid (Kumar et al. 1985). Based on soil studies (Berck and Gunther 1970; Hilton and Robison 1972), small amounts of phosphine may also be adsorbed (reversible sorption) or chemisorbed (irreversible sorption) to suspended solid and sediments in water. However, based on the estimated Henry's law constant (H) of 0.09 atm·m^3/mol (see Table 3-3) and the expected volatility associated with various ranges of H, volatilization is expected to be the most important loss process for phosphine in water.

5.3.2.3 Sediment and Soil

The exposure of soil to phosphorus aerosols will upset the pH of the soil and create a more acidic layer of soil. This decrease in pH often can exceed the buffering capacity of the surface layer of the soil depending upon the amount of applied phosphorus. This process can be mitigated by a larger soil volume area so that phosphorus speciation on a field scale will be minimal. The interaction of metals with phosphorus condensates could lead to their leachability and possible trace metal migration from the soil (Van Vorris et al. 1987).

White phosphorus exposure to plants results in a variety of deleterious effects which are based upon the species of plant, the smoke concentration, the duration of exposure, the relative humidity, and the wind speed. These effects can include leaf tip burn, leaf curl, leaf abscission and drop, floral abortion, chlorosis, neucrotic spotting, wilting, dessication, and dieback. Other factors influencing the effects of white phosphorus upon plants are whether or not there is a post-exposure rainfall and whether the exposure is a large acute dose or several lower chronic doses (Van Voris et al. 1987).

In soils, oxidation is the predominant route of loss of white phosphorus up to a depth that allows diffusion of oxygen (Bohn et al. 1970). The oxidation of phosphorus to its oxides is usually very rapid. White

phosphorus oxidized within 2 days in soil at ambient temperatures (Rodriguez et al. 1972). A soil volatilization study found that the volatilization of elemental phosphorus stopped after 3-7 days (Warnock 1972). If the termination is attributed to oxide formation, it can be concluded that elemental phosphorus oxidized in soil within 3-7 days.

However, the rate of oxidation will be slower if white phosphorus forms a protective coating (Bohn et al. 1970). The results of anaerobic biodegradation studies with soil and sediments are inconclusive (Spanggord et al. 1985). Although white phosphorus transformed faster in some nonsterile than in sterile controls, the slower transformation in sterile soil could be attributed to a change in soil property due to autoclaving (Spanggord et al. 1985); the investigators found that the biotransformation microorganisms were difficult to grow under their test conditions. The lack of growth is an indication of lack of biodegradation. Therefore, in the absence of oxidation and biodegradation reactions in anaerobic zones of soil and sediment, the half-life of elemental phosphorus could be l0-10,000 years (Richardson 1992; Spanggord et al. 1985). It should be mentioned that although microorganisms that biodegrade elemental phosphorus under anaerobic conditions could not be grown, both linear polyphosphates and cyclic metaphosphates could be microbially hydrolyzed to simpler phosphates in water and soil under aerobic and anaerobic conditions (Spanggord et al. 1985).

In sealed tubes, phosphine completely disappeared in less than 40 days from three different types of soil with varying amounts of moisture (Hilton and Robison 1972). The disappearance was attributed to initial sorption, and the subsequent biotic and abiotic oxidation of part of the sorbed compound. The rate of adsorption increased with decreasing moisture content and increasing organic soil content (Hilton and Robison 1972). The study showed that phosphine sorption in soil can occur by both physical and chemical sorption processes, and that the chemisorption process is higher in soils with a low organic matter and high mineral content (Berck and Gunther 1970). Chemisorption irreversibly binds phosphine in soil so that it is not available for volatilization. However, since phosphine is gaseous and is only slightly soluble in water, volatilization from soil may be the most important process by whiclrphosphine is lost from soil when chemisorption is not occurring.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Phosphorus exists mostly in the phosphate form in the general environment. The levels of phosphorus determined in most environmental samples are reported as total phosphorus and do not distinguish

between elemental phosphorus and its compounds. However, elemental phosphorus is far more toxic than other oxidized phosphorus states (oxides and acids of phosphorus). This profile reports the level of elemental phosphorus and not total phosphorus in environmental samples.

5.4.1 Air

The emission of elemental phosphorus into the air from the stacks of a munitions manufacturing plant could cause an estimated exposure level of up to 0.5 mg/m^3/hour (worst-case scenario). A more likely exposure level is 0.5$\mu g/m^3$/hour (Berkowitz et al. 1981). As the elemental phosphorus undergoes dispersion and reaction in air, its level from the stack emission would continue to decrease with increased distance. During field use of a single 155 mm WP/P shell over an area of 100 m^2, the estimated maximum ambient white phosphorus and phosphine concentrations were estimated to be 7 $\mu g/m^3$ and 7 $\mu g/m^3$, respectively (Berkowitz et al. 1981). If 72 shells are used over the same area for a continuous screen, the maximum ambient white phosphorus and phosphine concentrations would be 0.12 mg/m^3 and 0.12 $\mu g/rn^3$ (Berkowitz et al. 1981). During deployment of WP/F bursting rockets and howitzers where the smoke covered a minimum ground area of 9,500-12,000 m^2, the estimated environmental concentration of smoke would be 5-25 mg/m^3 (Shinn et al. 1985). On the other hand, the deployment of white phosphorus-based mortars, guns, rockets, and howitzers covering a minimum smoke area of 100-800 m^2, may produce an environmental concentration of 1,800-3,500 mg/m^3 smoke (Shinn et al. 1985). The concentration of white phosphorus in air from the smoke would be only a small fraction of the smoke concentration.

5.4.2 Water

The concentration of elemental phosphorus in the overflow water of a settling pond of a white phosphorus filling plant in Arkansas was ≤ 84 mg/L (Pearson et al. 1976). The average concentration in the discharge was 10.6 mg/L (Pearson et al. 1976). The mean concentration of elemental phosphorus at the Yellow Lake spillway from this discharge varied from 0.14 to 2.46 mg/L at different periods during 1971-1974. The concentration of elemental phosphorus measured in 1975 at different locations in Yellow Lake ranged from 0.02 to 40.4 µg/L (Pearson et al. 1976). After recycling measures for the phossy water were implemented, the concentration of elemental phosphorus in water from Long Harbour, Placentia Bay, Newfoundland, rarely exceeded 3.0 µg/L (Addison et al. 1972a), the concentration in Yellow Lake ranged from 0.005 to 0.01 µg/L, and the level in the Arkansas River, which is connected to the lake, ranged from 0.003 to 0.004 µg/L (EPA 1989). Similarly, phossy water discharged into adjacent water from the white

phosphorus manufacturing plant in Long Harbour contained elemental phosphorus, as indicated by levels of elemental phosphorus in the sediment (see Section 5.4.3).

5.4.3 Sediment and Soil

Before the waste-water treatment facility was instituted, the concentrations of elemental phosphorus in the sediment in the vicinity of the effluent discharge pipe of the phosphorus manufacturing plant in Long Harbour, Placentia Bay, Newfoundland, ranged from 5.5 to 2,910 mg/kg (Idler 1972). After the treatment facility was installed, the overflow of a small settling pond during heavy rain continued to contaminate the adjacent waterways. The concentration of elemental phosphorus in the sediments of Yellow Lake at different locations ranged from 0.02 to 43.4 μg/kg (wet weight) (Pearson et al. 1976). For the last 10 years, the U.S. Army has used Eagle River Flats, a 1,000 hectare estuarine salt marsh near Anchorage, Alaska, for artillery training. Elemental phosphorus was detected at a concentration range of 0.0025-10.2 mg/kg in 30-47% of the sediment samples collected from the salt marsh in the fall of 1990 (Bird 1991; Racine et al. 1992b; Richardson 1992). Sediment samples from Eagle River Flats were again collected during May and August of 1991 and analyzed for elemental phosphorus (Racine et al. 1992a). Depending upon the sampling location and timing of sample collection (before and after an explosion test), elemental phosphorus was detected in 0-100% of sediment samples; the concentration ranged from undetectable (detection limit <0.0001 mg/kg) to 198 mg/kg. Samples of sediments collected before and after explosion tests indicated that the level of elemental phosphorus increased as a result of artillery training. The concentration of elemental phosphorus in soil from a phosphorus dump site at Pine Bluff Arsenal was 5,200 μg/kg (Spanggord et al. 1985). No other data on the level of elemental phosphorus in soils from artillery training sites, phosphorus manufacturing, or disposal sites or arsenal sites where the munitions are loaded into artillery were located.

5.4.4 Other Environmental Media

Elemental phosphorus has been detected in fish and birds from areas in the vicinity of elemental phosphorus production sites (ERCO of Newfoundland), an arsenal production facility (Pine Bluff Arsenal in Arkansas), and artillery training sites (Eagle River Flats, Anchorage, Alaska). The concentrations of elemental phosphorus in fish and birds collected from these sites are given in Table 5-2. The concentrations of elemental phosphorus in the gizzard content of a dead waterfowl and a dead mallard

TABLE 5-2. Concentration of Elemental Phosphorus in Fish and Birds

Sample location	Species	Year Collected	Mean P_4 Concentration (µg/kg)	Reference
Yellow Lake, Pine Bluff, AR	Channel catfish	1974	3.13–138.75[a] (207)[b]	Pearson et al. 1976
St. Croix Bay, adjacent to Long Harbor, Newfoundland	Herring mussels	1970	12.0[b]	Addison et al. 1972
Yellow Lake, Pine Bluff, AR	Freshwater drum	1974	4.50–308.85[a] (386.4)[b]	Pearson et al. 1976
ERCO[c] Wharf, Long Harbor, Newfoundland	Mackerel flash	1970	30.0[b]	Addison et al. 1972
Eagle River Flats salt marsh, AK	Gizzard contents of wild swans	1990	52,000 (207,000)[b]	Racine et al. 1992
	Fat of wild swans	1990	670 (7,000)[b]	
	Skin of wild swans	1990	60 (140)[b]	
	Gizzard contents of wild ducks	1990	304,000 (3,140,000)[b]	
	Fat of wild ducks	1990	210 (430)[b]	
	Skin of wild ducks	1990	70 (130)[b]	
	Liver of wild ducks	1990	50 (140)[b]	
Eagle River Flats salt marsh, AK	Fat of dead bald eagle	1991	60	Bird 1991
	Herring gull egg yolk		3–15[d]	
	Fat of dead ducks		190–5,900	
Clunie Lake, AK	Skin of duck	1991	5.1	Bird 1991
Gwen Lake, AK	Skin of duck	1991	34.0	Bird 1991
	Fat of duck	1991	388.0	
Eagle River Flats salt marsh, AK	Liver of wild ducks	1990	50400	Racine et al. 1992

TABLE 5-2. Concentration of Elemental Phosphorus in Fish and Birds (*continued*)

Sample location	Species	Year Collected	Mean P_4 Concentration (µg/kg)	Reference
	Gizzard contents of wild ducks	1990	14978000	Racine et al. 1992
	Heart of wild ducks	1990	66500	Racine et al. 1992
	Intestinal contents of wild ducks	1990	820000	Racine et al. 1992
	Kidney of wild ducks	1990	8250	Racine et al. 1992
	Intestines of wild ducks	1990	479667	Racine et al. 1992
	Pectoral muscle in wild ducks	1990	1600	Racine et al. 1992
	Fat in wild ducks	1990	45000	Racine et al. 1992
	Gizzard muscle in wild ducks	1990	trace	Racine et al. 1992
	Gizzard contents in tundra swans	1990	51534250	Racine et al. 1992
	Fat in tundra swans	1990	830500	Racine et al. 1992
Dartmouth Medical School	Gizzard content in mallards	1990	9890000	Racine et al. 1992

[a]The lower values are for samples collected before rain, and the higher values are for samples collected after rain.
[b]These are the maximum concentrations.
[c]ERCO = Energy Reduction Co. of Canada (Newfoundland)
[d]These are ranges in concentrations.

collected outside of the Eagle River Flats in 1991 were 3,501,000 and 103,000 µg/kg, respectively (Racine et al. 1992a). However, the levels of elemental phosphorus in different tissues of live waterfowl collected from the Eagle River Flats in 1991 ranged from undetectable to 2,700 µg/kg (Racine et al. 1992a). Elemental phosphorus at levels similar to those found in dead waterfowl at Eagle River Flats (5 µg/g) were introduced into the diets of American kestrels (*Falco sparverius*) resulting in accumulation of P_4 in the fat deposits and skin at 24 hours postdosing (Nam et al. 1994).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

No data were located indicating that detectable levels of elemental phosphorus are present in the ambient air, drinking water, or food consumed by the general population not living near sources of elemental phosphorus emission. Therefore, the general population exposure to elemental phosphorus is very low and likely to be below measurable levels. A segment of the general population that lives near sources of emissions (e.g., production sites, user sites, and disposal sites) may be exposed to elemental phosphorus at high levels. This segment of the population is discussed in Section 5.6.

The concentrations of white phosphorus levels in the atmosphere of a wet fill production iine at Pine Bluff Arsenal, Arkansas, were measured in 1975 (Berkowitz et al. 1981). The levels of white phosphorus at this location exceeded the OSHA 8-hour time-weighted average exposure limit of 0.1 mg/m^3. At one location, the concentration of elemental phosphorus was 0.45 mg/m^3 and may have been underestimated due to poor quality control (Berkowitz et al. 1981). Values well below the OSHA limit (0.7-1.2 µg/m^3) were detected during a 1977 survey at a dry fill line of the same plant (Berkowitz et al. 1981). However, the samples for these measurements were collected when the plant was not running at full capacity. Military personnel who use phosphorus-containing ammunitions may be exposed to white phosphorus smoke during warfare, training exercises, and accidents. Vapor samples were taken to measure worker exposure to H_3PO_4 PH_3 and P_4 during an Albright & Wilson acid plant decommissioning (June 9-10, 1992) (Albright and Wilson 1992a). The workers were digging out phosphorus residue from beneath storage and metering tanks. According to the decommissioning report, “Three out of three P_4 vapor samples exceeded the OSHA permissible exposure limit (PEL) of 0.1 mg/m^3 at 0.35, 0.12, and 1.11 mg/m^3. Samples for exposure to H_3PO_4 were below the OSHA PEL of 1.0 mg/m^3. Sensitivity for the PH, samples was reduced due to analytical problems. The levels of PH_4 were all reported to be below 0.5 ppm. This compares to an OSHA PEL of 0.3 ppm for PH_3 exposure. Workers were not using supplied air during their exposure (Albright & Wilson 1992a). During a phosphorus storage tank decontamination from

July 13-15, 1992, at an Albright & Wilson plant in Cincinnati, one tank P_4 vapor sample out of seven exceeded the OSHA PEL of 0.1 mg/m^3. The measured value of the sample was 0.11 mg/m^3 and occurred while a worker was using supplied air. Exposures to H_3PO_4 PH_3 and AsH_3 were all below the OSHA PELs during the tank decontamination (Albright & Wilson 1992b).

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH, an estimated 208,990 workers were exposed to white phosphorus in the workplace. The NOES database does not contain any information about the concentration levels to which these workers may have been exposed or the frequency and duration of the exposure (NOES 1991).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The general population that lives near elemental phosphorus production sites, white phosphorus user sites (e.g., Pine Bluff Arsenal in Arkansas), artillery training sites (e.g., Eagle River Flats, Anchorage, Alaska), and dumpsites that contain elemental phosphorus may be exposed to elemental phosphorus at levels higher than the control population. The exposure could occur from inhalation of contaminated air, consumption of contaminated fish or game birds, and skin exposure from bathing in contaminated water. Additionally, children living near phosphorus-containing hazardous waste sites may be exposed to elemental phosphorus by dirt ingestion and/or skin contact while playing at unrestricted dumpsites. People who live near accidental spill sites (e.g., spill in Miamisburg, Ohio) are a likely population with potentially high exposures. However, reports providing evidence of these exposures were not located. As discussed in Section 5.5, people who work in user sites and possibly production sites, waste disposal sites, and military personnel using phosphorus-containing ammunitions are likely populations with potentially high exposures.

5.7 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of white phosphorus is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of white phosphorus.

5. POTENTIAL FOR HUMAN EXPOSURE

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. Data such a log K_{ow} log K_{oc} and the Henry's law constant needed for estimating the environmental transport of elemental phosphorus are available (see Table 3-2). However, an experimentally determined and reliable log K_{oc} value for elemental phosphorus would be helpful.

Production, Import/Export, Use, Release, and Disposal. Although the current production capacity of elemental phosphorus in the United States is available (SRI 1992), the amount of elemental phosphorus actually produced is not known. The future trend for the demand of elemental phosphorus is expected to decrease by l-2% in this decade (CMR 1991). Although some fluctuation has been observed, the export of elemental phosphorus remained constant at 5% of production during the past couple of decades (CMR 1991,1985,1981,1978). The import of elemental phosphorus is expected to be low because the production capacity in the United States is higher than the demand (CMR 1991); but recent import dam were not located in the literature.

The uses of elemental phosphorus in the United States are known (CMR 1991; EPA 1991; Van Wazer 1982). There is no evidence that elemental phosphorus is used in any consumer products other than rat poisons. Fish and game birds collected from the vicinity of production and user locations may contain elemental phosphorus (Addison et al. 1972b; Pearson et al. 1976; Racine et al. 1992a, 1992b). There is evidence that significant exposures could occur in workplaces where elemental phosphorus is handled (Berkowitz et al. 1981). Monitoring data indicate that significant quantities of elemental phosphorus can be found in sediment and in certain game birds near use sites (Pearson et al. 1976; Racine et al. 1992a, 1992b; Spanggord et al. 1985). Although some of the disposal methods used for elemental phosphorus are known (Berkowitz et al. 1981; HSDB 1993; Uhrmacher et al. 1985), the efficiency of these methods for the destruction of elemental phosphorus is not known. Information about the amounts of elemental

phosphorus disposed of by each method is not known. EPA does regulate the disposal of elemental phosphorus-containing wastes in water and soil (EPA 1992a, 1992b).

According to the Emergency Planning and Community Right-to-Know Act of 1986,42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1993, became available in May of 1995. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Elemental phosphorus partitions from water to sediment (Berkowitz et al. 1981) transporting elemental phosphorus to sediment. Volatilization from water and soil transports small amounts of elemental phosphorus to air (Spanggord et al. 1985; Wamock 1972). Elemental phosphorus quickly oxidizes and hydrolyzes in air and in aerobic zones of water and soil to produce mainly oxides and acids of phosphorus, except when covered by a protective coating of phosphorus oxides (Bohn et al. 1970; Bullock and Newlands 1969; EPA 1991; Lai and Rosenblatt 1977a; Rodriguez et al. 1972; Spanggord et al. 1985; Zitko et al. 1970). However, elemental phosphorus reaching the anaerobic zones of sediment and soil may persist for periods of l0-10,000 years (Richardson 1992; Spanggord et al. 1985). Therefore, anaerobic zones of soil and sediment may act as a sink for elemental phosphorus.

Bioavailability from Environmental Media. The bioavailability of elemental phosphorus following inhalation, oral, and dermal contact is poorly understood (see Section 2.3). The estimated log K_{oc} for elemental phosphorus is 3.05 (See Table 3-2). Therefore, elemental phosphorus is moderately sorbed to aerosol particles in air, to sediment in water, and to soil. However, due to its high reactivity, elemental phosphorus may not be found in aerobic zones of soil and water, unless the element is protected from oxidation by unreactive oxide coating (Berkowitz et al. 1981). Its bioavailability in the sorbed state from inhaled air, ingested soil, and dermal contact with soil and water may be lower than the free form of the element under identical conditions.

Food Chain Bioaccumulation. Elemental phosphorus moderately bioconcentrates in aquatic organisms (Bentley et al. 1978; Fletcher 1971; Maddock and Taylor 1976). The biomagnification potential for elemental phosphorus in predators resulting from consumption of contaminated prey organisms has not been studied systematically. However, high concentrations of elemental phosphorus have been found in tissues of certain kinds of bottom-feeding waterfowls (Bird 1991; Racine et al. 1992a,

1992b). Elemental phosphorus has also been found in a dead bald eagle collected in the vicinity of Eagle River Flats (Bird 1991).

Exposure Levels in Environmental Media. With the exception of occupational air, monitoring data on the concentrations of elemental phosphorus in nonoccupational air, drinking water, and total diet were not located. The estimated value for the total human intake of elemental phosphorus from various environmental media is not available.

Reliable monitoring data for the levels of white phosphorus in contaminated media at hazardous waste sites are needed so that the information obtained on levels of white phosphorus in the environment can be used in combination with the known body burden of white phosphorus to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Data regarding the levels of elemental phosphorus in human tissues such as, blood, urine, fat, and breast milk, were not located in the literature. Such data, especially for occupationally exposed populations and populations surrounding hazardous waste sites, could be important. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for white phosphorus were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 On-going Studies

No on-going studies were located.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring white phosphorus, its metabolites, and other biomarkers of exposure and effect to white phosphorus. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

There are no standardized methods approved by federal agencies or organizations for determining elemental phosphorus in biological samples. In biological samples, phospholipids and other biogenic phosphorus-containing compounds may be present at levels that can contribute phosphorus far in excess of that arising from elemental phosphorus contamination (Idler et al. 1981). Interference also can occur from phosphine present in the sample. Therefore, the analytical methods for determining elemental phosphorus in biological samples must be able to separate these compounds before quantitation. Since elemental phosphorus can be lost from tissues stored in a cooler (3°C) or in a freezer (-40˚C), it is suggested that the stored tissues be immersed in benzene (Fletcher 1974). Table 6-l gives the methods used for determining elemental phosphorus in biological samples. The most suitable method available at the present time (in terms of sensitivity and ease of analysis) is the gas chromatographic method with phosphorus-sensitive detectors (Idler et al. 1981). Methods are also available for determining serum and urinary phosphate levels in humans and other animals (Harper 1969; Henry 1967). Although a thin layer chromatography (TLC) method was used to identify inorganic phosphates and an undefined organic phosphate as urinary metabolites in rats (Lee et al. 1975), more accurate methods for determining intermediate and final products of metabolism of white phosphorus in animal systems are lacking. It should be noted, however,

TABLE 6-1. Analytical Methods for Determining Elemental Phosphorus and Phosphine in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological tissues (phosphine, metal phosphide, and elemental phosphorus)	Pass nitrogen through ground sample to remove phosphine produced by putrefication; acidify and absorb phosphine in methanolic silver nitrate after removing hydrogen sulfide by passing through lead acetate; heat residual sample and absorb released gas in methanolic silver nitrate; the phosphine trapped as silver phosphide is oxidized to phosphine with chlorine gas	Neutron activation analysis	0.5 µg/kg in 20 g tissue	90–110	Krishnan and Gupta 1970
Biological tissues (elemental phosphorus)	Extract homogenized tissues with benzene; filter	GC-FPD	2 µg/kg in 10 g tissue	77–86	Addison and Ackman 1970; Fletcher 1974

FPD = flame photometric detector; GC = gas chromatography

that metabolite measurements for animal systems may not meet the needs of differentiating those species involved in biological effects (e.g., white phosphorus, linear and cyclic phosphorus, organicallycomplexed phosphorus).

6.2 ENVIRONMENTAL SAMPLES

Most of the analytical methods available in the literature for determining elemental phosphorus are based on older analytical techniques. Gorzny (1972) has discussed some of these methods for determining elemental phosphorus. Although a method for simultaneously determining phosphine, phosphide, and elemental phosphorus in water, soil, and sediment is not given in Table 6-2, the distillation method given by Ktishnan and Gupta (1970) can be used for this purpose. Krishnan and Gupta (1970) showed that phosphine can be removed from water or suspended solids by passing an inert gas through the sample before it is acidified. Reactions with acid liberate phosphine from metal phosphide. Elemental phosphorus, on the other hand, distills only after the sample is heated. As in biological samples, both gas chromatography with phosphorus-sensitive detectors or neutron activation analysis for determining elemental phosphorus in environmental samples are sensitive and accurate enough to meet the recommended or obligatory discharge standards (Idler et al. 1981; Lai and Rosenblatt 1977b).

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of white phosphorus is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of white phosphorus.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

TABLE 6-2. Analytical Methods for Determining Elemental Phosphorus and Phosphine in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (elemental phosphorus	Trap elemental phosphorus in impingers containing xylene	GC-FPD	0.4 μg/m^3	No data	Bohl and Kaelble 1973
Air (elemental phosphorus)	Trap elemental phosphorus in Tenax®-GC tubes and extract with xylene	GC-FPD	0.5 μg/m^3 (for 100 L sample)	94–108 (at 10–370 μg/m^3)	Dillon et al. 1978; NIOSH 1987
Water (elemental phosphorus)	Extract with organic solvent; oxidize to phosphate	Spectrophotometric	1.5 μg/L	No data	Zitko et al. 1970; Idler et al. 1981
Water (elemental phosphorus)	Extract with organic solvent (benzene or isooctane)	GC-FPD	0.002 μg/L	74–78	Addison and Achman 1970; EPA 1991
Waste water (elemental phosphorus)	Extract with organic solvent, oxidize to phosphate and back-extract in water	Neutron activation analysis	0.01 μg/L	90–110	Lai and Rosenblatt 1977b
Soil and sediment (elemental phosphorus)	Extract with organic solvent; filter	GC-FPD	0.1 mg/kg	77–90	Addison and Ackman 1970; Idler et al. 1981
Soil and sediment (elemental phosphorus)	Extract with isooctane	Capillary Column GC-NPD	0.88 μg/kg	97.2	Walsh and Taylor 1992; Racine et al. 1993

TABLE 6-2. Analytical Methods for Determining Elemental Phosphorus and Phosphine in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment (phosphine)	Trap gas in impingers containing toluene	GC-FPD, GC-NPD, or GC-MS	No data	No data	Devai et al. 1988
Water (elemental phosphorus)	Extract with isooctane or diethyl ether	GC-NPD	0.011 µg/L	107±12	Walsh 1995

FPD = flame photometric detector; GC = gas chromatography; MS = mass spectrometry; NPD = nitrogen-phosphorus detector

6. ANALYTICAL METHODS

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Elemental phosphorus, and inorganic and organic compounds containing phosphorus, are common in environmental and dietary material needed for the normal physiological functioning of living organisms. For these reasons, exposure to phosphorus is not unique. Human clinical and autopsy studies, where excess elemental phosphorus exposure has been documented, show apparent organ- and system-specific toxic effects. However, other than burn studies, there are few animal studies to quantitatively define these toxic effects, either acutely or long term. Moreover, the mechanisms of toxicity are not clearly understood. For example, elemental phosphorus is highly reactive in air and other environmental media. For this reason, its products (e.g., PH_2 phosphoric acid, and PH_3) could be significant contributors to toxicity. Minimizing formation of these reaction products may serve to prevent or alleviate the toxic effects of phosphorus.

Animal studies designed to quantitatively identify organ and system toxicity need to be carried out. Dosimetry studies to quantitatively identify levels of toxicant in blood or urine either as reaction products or elemental phosphorus need to be considered (see Section 25.1).

There are no specific effects that could be quantitatively related to phosphorus exposure (see Section 2.5.2).

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Few methods are available for the simultaneous determination of different forms of phosphorus (phosphine, elemental phosphorus, and metal phosphides) in environmental samples, and the methods are based on older technology (Gorzny 1972). It would be helpful to develop methods based on modem techniques for this purpose. It would also be useful to develop a few standard methods for analyzing different forms of phosphorus found in environmental samples.

Several methods are available for determining the degradation products of elemental phosphorus (different phosphorus acids and organic phosphorus compounds) in environmental samples (EPA 1983). A liquid chromatographic method has been developed for determining polyphosphoric acids in phosphorus smokes (Braze11 et al. 1984). It appears that there is little need to develop analytical methods that determine degradation products of elemental phosphorus in phosphorus smokes.

6. ANALYTICAL METHODS

6.3.2 On-going Studies

No on-going studies were located for determining phosphorus or its degradation products/metabolites in environmental or biological samples.

7. REGULATIONS AND ADVISORIES

International, national, and state regulations and guidelines pertinent to human exposure to white phosphorus are summarized in Table 7-1. No regulations or guidelines for white phosphorus smoke were identified.

A chronic oral reference dose (RfD) of 0.00002 mg/kg/day has been derived and verified by EPA for white phosphorus (IRIS 1993). The RfD is based on a NOAEL of 0.015 mg/kg/day for parturition mortality and forelimb hair loss in rats gavaged with 0.015 mg/kg/day in a one-generation reproduction study (Condray 1985).

TABLE 7-1. Regulations and Guidelines Applicable to White Phosphorus

Agency	Description	Information	Reference
NATIONAL			
Regulations:			
a. Air:			
EPA	Listed as Hazardous Air Pollutant	Yes	EPA 1990
OSHA	PEL TWA	0.1 mg/m^3	HSDB 1995
b. Other:			
EPA OERR	Reportable quantity	1 pound[a]	IRIS 1995
	Extremely Hazadous Substance TPQ	1/100 pounds	EPA 1992c (40 CFR 355, APP A)
EPA OPP	Intent to Cancel, Restrict or Require Reregistration of Pesticide Products Containing Phosphorus	Yes[b]	HSDB 1995
EPA OSW	Designation as Hazardous Substance	Yes	HSDB 1995
	Listing as hazardous waste: (D003)	Yes[c]	HSDB 1995
EPA OTS	Toxic Chemical Release Reporting: Community Right To Know	Yes	HSDB 1995
Guidelines:			
a. Air:			
ACGIH	TLV TWA	0.1 mg/m^3	ACGIH 1992
NIOSH	REL TWA	0.1 mg/m^3	NIOSH 1992
b. Other:			
EPA	Oral RfD	2×10^{-5} mg/kg/day	IRIS 1995
	Carcinogen classification	Group D[d]	IRIS 1995
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient concentration guidelines or standards		NATICH 1991
Connecticut		2.00 µg/m^3 8 hour	
Florida/Fort Lauderdale		1.00×10^{-3} µg/m^3 8 hour	
Florida/Pinella		1.00 µg/m^3 8 hour	
		2.40×10^{-1} µg/m^3 24 hour	
Florida/Tampa		1.00×10^{-3} mg/m^3 8 hour	
Nevada		2.00×10^{-3} mg/m^3 8 hour	
New York		3.30×10^{-1} µg/m^3 1 year	
North Dakota		1.00×10^{-3} mg/m^3 8 hour	
Oklahoma		$1.00\times10^{+1}$ µg/m^3 24 hour	
Texas		1.00 µg/m^3 30 minutes	
		1.00×10^{-1} µg/m^3 annual	
Virginia		1.70 µg/m^3 24 hour	
b. Water:			
Florida	Restriction in marine waters	≤0.1 µg/L	CELDS 1992
Ohio	Criteria for nuisance prevention and water supply use designation	*Note 1*	

TABLE 7-1. Regulations and Guidelines Applicable to White Phosphorus (*continued*)

Agency	Description	Information	Reference
STATE (Cont.)			
c. Other:			
Connecticut	Registration & use prohibited as pesticide	Yes	CELDS 1992
Hawaii	Restricted usage	Yes	
Iowa	Restricted usage	Yes	
Maine	Special provisions for waste managements	Yes	

[a]Based on aquatic toxicity
[b]List "C" reregistration status: Case #3111, Awaiting data/data in review. Reregistration is supported.
[c]A solid waste containing yellow and white phosphorus may become characterized as a hazardous waste when subjected to testing for reactivity as stipulated in 40 CFR 261.23 and, if so characterized, must be managed as a hazardous waste (40 CFR 261.23 [7/1/90]).
[d]Group D = Not classifiable as to carcinogenicity in humans

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Waste; OTS = Office of Toxic Substances; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfD = Reference Dose; TLV = Threshold Limit Value; TPQ = Threshold Planning Quantity; TWA = Time-Weighted Average

Note 1: Total phosphorus as P shall be limited to the extent necessary to prevent nuisance growth of algae, weeds, and slimes that result in a violation of the water quality criteria. Phosphorus discharges shall not exceed a daily average of **one milligram per liter** as total P, or stricter requirements imposed by Ohio Environmental Protection Agency.

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarker -- Xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during-which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentratlon$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material-in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

9. GLOSSARY

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and pg/m^3 for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

9. GLOSSARY

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A
ATSDR MINIMAL RISK LEVEL

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 994991, requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1-14 days), intermediate (15-364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified-a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEETS

Chemical Name: White Phosphorus Smoke
CAS Number: 7723-14-0
Date: September 5, 1996
Profile Status Draft 3
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 9
Species: Human

Minimal Risk Level: 0.02 [ ] mg/kg/day [X] mg/m^3

Reference: White and Armstrong 1935

Exuerimental design:(human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Four men were exposed by inhalation to an average concentration of 0.187 mg/L white phosphorus for 5 minutes in a gassing chamber. No controls were used.

Effects noted in study and corresponding doses: Throat irritation, coughing and headache were reported at 187 mg/m3 (LOAEL). One of the subjects reported pain in the eyes and lungs.
Calculations: 187 mg/m^3 X 5/60 minx l/24 hr X 1/3OUF = 0.02 mg/m^3.

Dose and endpoint used for MRL derivation: A dose of 187mg/m3 was used for respiratory effects in humans.

[ ] NOAEL [x] LOAEL

Uncertaintv Factors used in MRL derivation:

[Xl 3 for use of a minimal LOAEL
[ ] 3 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human eouivalent dose:

Other additional studies or pertinent information which lend support to this MRL: Although a 5-minute exposure duration is usually too brief to consider for MRLs and expanding over a 24-hour period would result in an exposure level of 0.6 mg/m^3, further experiments indicated that exposure for longer durations would result in more severe effects. In the field, white phosphorus smoke was generated at 0.1 mg/m^3 to protect soldiers from detection. In addition the OSHA PEL is 0.1 mg/m^3. Therefore, expanding the 5minute duration over 24 hours is reasonable.

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1° review: _____
2° review: _____

APPENDIX A

Chemical Name: White Phosphorus
CAS Number: 7723-14-0
Date: September 5, 1996
Profile Status Draft 3
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 42
Species: Rat

Minimal Risk Level: 2×10^{-4} [x] mg/kg/day [ ] mg/m^3

Reference: International Research and Development Corporation (IRDC) 1985

Experimental design: (Human study details or strain, number of animals per exposure/control groups, sex, dose administration details): A one generation reproduction study was conducted in rats. Elemental phosphorus was administered orally by gavage to Charles River COBS CD rats at dosage levels of 0.005,0.015 and 0.075 mg/kg/day, at a dose volume of 5 ml/kg. For each dosage group including control, 15 male and 30 female rats were used. Administration of the test and control materials (corn oil) to both sexes began 80 days prior to mating. The F_0 generation was mated twice to produce "a" and "b" offspring. In males, dosing continued until sacrifice. Administration to the females continued through gestation and weaning of the pups. Individual dosages were based on the most recent weekly body weights.

Effects noted in studv and corresponding doses: Elemental phosphorus administered orally by gavage at a dosage level of 0.075 mg/kg/day adversely affected parturition, decreased the mean number of viable pups at birth and increased the mean number of stillborn pups. Similar fmdings were not observed at dosage levels of 0.015 mg/kg/day (NOAEL) or less.
Calculations: 0.015 mg/kg/day X l/l00UF = 2 X $l0^{-4}$ mg/kg/day.

Dose and endpoint used for MRL derivation: A NOAEL of 0.0 15 mg/kg/day was used for the MRL derivation.

[X] NOAEL [ ] LOAEL

Uncertaintv Factors used in MRL derivation:

[] 3foruseofa minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/body weight dose?
If so, explain: No

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL: At first examination, it appeared that no intermediate oral MRL could be derived because the lowest dose indicated on Table 2-2 was 0.075 mg/kg/day, which was associated with increased mortality in pregnant rats in two reproductive studies, one by Bio/dynamics (1991) and one by IRDC (1985). However, in the IRDC study (1985), 0.075 mg/kg/day was a NOAEL for systemic endpoints (#31 in LSE Table 2-2), such that the lower doses in the study did not appear in the LSE table. No effects were seen in rats at lower doses of 0.005 and 0.015 mg/kg/day. Therefore,

the 0.015 mg/kg/day dose, which was not associated with increased mortality and produced no other effects, was the NOAEL for the intermediate database. In the Bio/dynamics (199 1) study, only the 0.075 mg/kg/day dose was used, and in addition to increased mortality, was associated with hepatic toxicity (#30 in LSE Table 2-2). Therefore, the critical endpoint is hepatic. It was noted that the EPA derived an RfD from the same NOAEL of 0.015 mg/kg/day in the same study (IRDC 1985).

Agency Contact (Chemical Manager): Patricia Richter

Agency Review Date: 1˚ review:
2˚ review:

APPENDIX B
USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1,2-2, and 2-3) and figures (2-l and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a sub-tance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1,2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects

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occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-l).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

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(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m' or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

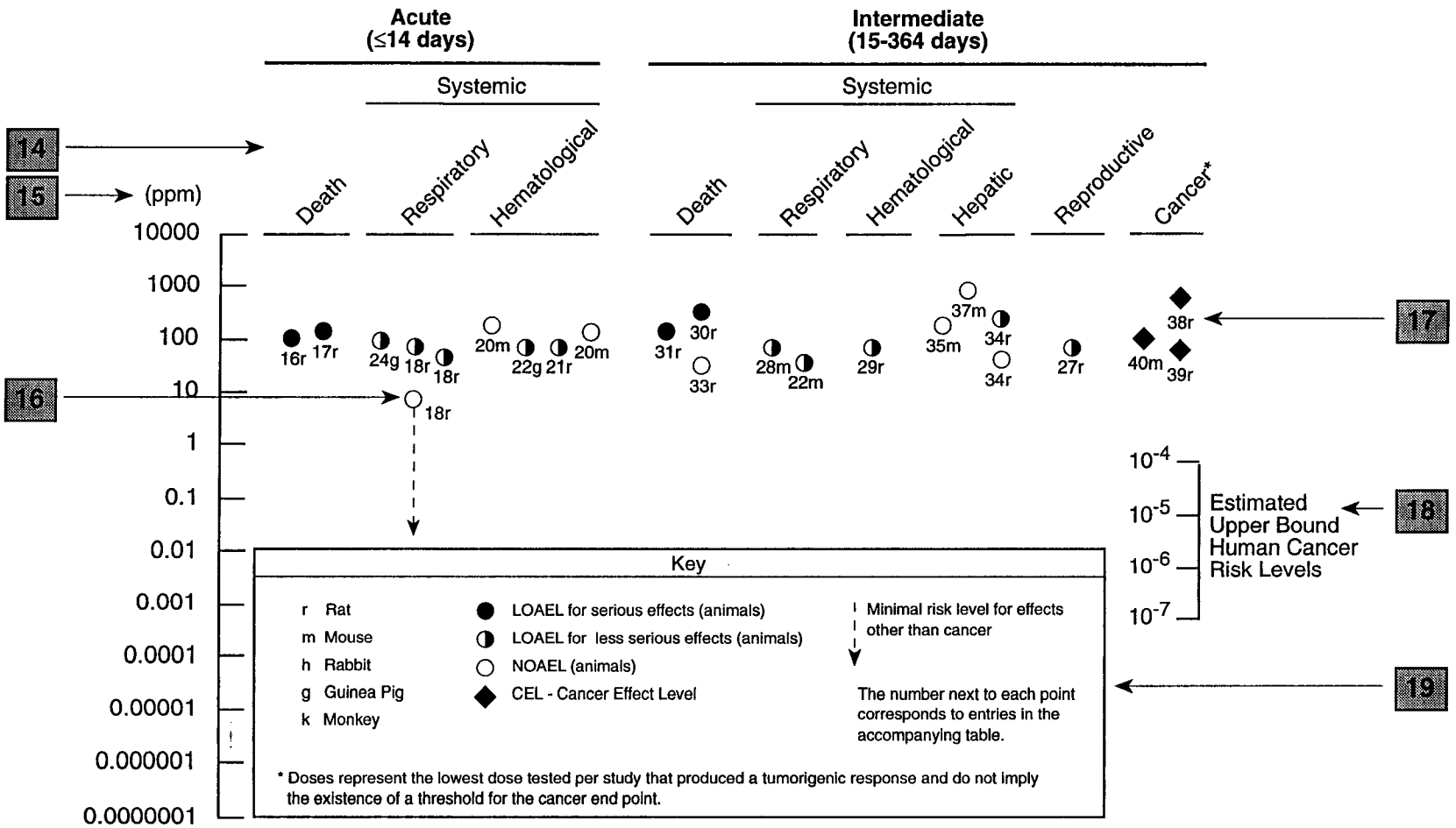
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1 . What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.7, “Interactions with Other Substances,” and 2.8, “Populations that are Unusually Susceptible” provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration, ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
GD	gavaged daily
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch

Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NCE	normochromatic erythrocytes
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion

ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram