WHITE PHOSPHORUS. AN EVALUATION OF EVIDENCE FOR THE MECHANISM OF ACTION LEADING TO A FATALITY FOLLOWING ACUTE ORAL INTOXICATION.

STAGE 1 – LITERATURE REVIEW

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BASIS OF REPORT

This report has been prepared by Expotox Pty Ltd (Expotox) with all reasonable skill, care, and diligence, taking account of the timescale and resources allocated to it by agreement with F H Treweeke Pty Ltd (the Client). The information reported herein is based on the interpretation of data collected, which has been accepted in good faith as accurate and valid.

This report is for the Client's exclusive use. No warranties or guarantees are expressed or should be inferred by any third parties. Other parties may not rely on this report without written consent from Expotox.

The Client requested an additional review of the recent case study reports on accidental and intentional poisonings arising from white phosphorus-containing products as they relate to pain and suffering. This amendment is included in the last paragraph of the Executive Summary (Revision 2.0).

Expotox disclaims any responsibility to the Client and others regarding matters outside the agreed-upon scope of the work.

EXECUTIVE SUMMARY

This report's primary purpose is to provide regulatory scientists, veterinarians, physicians, and other interested parties with an overview of the acute systemic toxicity of white phosphorus and propose mechanisms of action for key health endpoints leading to fatal outcomes.

The report describes white phosphorus's chemical and physical properties, toxicokinetics, key health end points, and mechanisms of action following acute human and animal exposures.

The literature contains reports about the health effects of acute systemic toxicity of white phosphorus in laboratory animals, in people eating rat poison or firecrackers that contain it, or from people exposed to munitions that contain it.

Systemic phosphorus poisoning may occur following oral, inhalational, and dermal exposure. The reactivity of phosphorus and differences in exposure measurements between reports make it challenging to define and quantify the absorbed dose associated with the key health effects reported in laboratory animal and human case studies.

Exposure to white phosphorus may result in multiple organ dysfunction because of its effects on the stomach, the heart, the liver (acute fatty degeneration of the liver), the kidneys, the brain, and other organs.

Systemic toxicity from acute oral exposure to white phosphorus is categorised into three stages.

Stage 1: Gastrointestinal effects can occur within minutes to eight hours; early fatalities have been reported due to cardiovascular collapse during this stage.

Stage 2: Stage 1 survivors can experience a several-day asymptomatic period, including clinical improvement and a symptom-free interval.

Stage 3: Involves a swift deterioration in condition and typically culminates in a fatality; systemic toxicity is noted across several organ systems.

Fatal outcomes in phosphorus poisoning follow distinct pathways in Stage 1 and Stage 3. Early death (Stage 1) primarily results from the direct cardiovascular toxicity, electrolyte disturbances and severe fluid loss leading to shock. Late deaths (Stage 3) stem from multi-organ failure centred around hepatotoxicity, with mechanisms including ER stress, oxidative damage, mitochondrial dysfunction, and disruption of protein synthesis.

Once ingested, the clinical course is somewhat akin to acetaminophen (paracetamol) poisoning. Pain and its severity are not well described across the case reporting literature and are unreliable indicators of prognosis. One of the strongest predictors of mortality is irreversible shock, with or without multi-organ failure. Irreversible shock may lead to a loss of consciousness, limiting pain perception before death. Patients who progress to multi-organ dysfunction following a several-day asymptomatic period often succumb within a very short duration.

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ACRONYMS AND ABBREVIATIONS

Acronym	**Definition**
ALT	Alanine aminotransferase
APVMA	Australian Pesticide and Veterinary Medicines Authority
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
ATSDR	United States Agency for Toxic Substances and Disease Registry
BUN	Blood Urea Nitrogen
CAS No	Chemical Abstracts Service Registry Number
EFSA	European Food Safety Agency
EKG/ECG	Electrocardiogram
H_3PO_2	Hypophosphoric acid (Phosphinic acid)
H_3PO_4	Phosphoric acid
HSA	United Kingdom Health Security Agency
log K_{ow}	Log octanol water partition coefficient
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
NIOSH	United States National Institute for Occupational Safety and Health
^{32}P	Phosphorus-32 is a radioactive isotope of phosphorus with a half-life of 14.3 days
P_4	Chemical structure of white phosphorus
PH_3	Phosphine
USDOE	United States Department of Energy
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation

INTRODUCTION AND BACKGROUND

White phosphorus is a highly reactive allotrope of elemental phosphorus. It exists as P_4 tetrahedra. It exists as cubic crystals (the alpha form) at room temperature (US EPA 1990a).

White phosphorus is produced commercially and does not occur naturally. The primary commercial method is the electric arc process or electric furnace method, which involves heating phosphate rock, coke, and silica. The white phosphorus vapour is condensed and stored under warm water.

Pure white phosphorus is described as a colourless-to-white waxy solid or an ivory-coloured, waxy solid. However, commercial white phosphorus is typically 99.9% pure and has a slightly yellow colour. Because of this, it is often called yellow phosphorus, a synonym used interchangeably in the literature (US EPA. 1990b). It has a characteristic garlic-like smell.

White phosphorus oxidises spontaneously in air at environmental temperatures. Due to this high reactivity, it is generally stored under water to prevent it from burning spontaneously. White phosphorus has limited solubility in water but is soluble in organic solvents and highly lipid-soluble, indicating potential for bioaccumulation and probable easy absorption into the body.

White phosphorus is generally considered a nucleophile and can also react with electrophiles, making it both a nucleophile and an electrophile depending on the reaction and reagents it is reacting with. It reacts with oxygen and water to form strong acids (H_3PO_2, H_3PO_4). Selected physical and chemical properties of white phosphorus are presented in Table 1.

Its primary military use is producing smoke munitions (such as mortar and artillery shells, as well as hand and rifle grenades) that obscure personnel movement. When these burn, they produce smoke containing various burned phosphorus products and some unburnt phosphorus (NRC 1999). It is used to make other chemicals such as phosphorus sulfides, phosphorus halides, phosphorus pentoxide, and phosphoric acid, which are utilised in fertilisers, food additives, cleaning compounds, laboratory reagents, and other products. Small amounts have been used in roach, rodent, and pest poisons, as well as fireworks. In the past, it was used to make matches, but other chemicals (red phosphorus and tetraphosphorus trisulfide) are now used due to health concerns like jaw-bone necrosis ("phossy jaw"). A specialised use is mentioned in microchip processing (US EPA 1990a; US EPA. 1990b; Davidson et al. 1987; ATSDR 1997).

HEALTH EFFECTS OF WHITE PHOSPHORUS

White phosphorus is highly toxic when inhaled, ingested, or absorbed through burned areas. Information on human exposure comes from accidental or intentional ingestion, occupational exposure (historically, especially in industries using white phosphorus, like matches and fireworks), and dermal burns.

The reported acute effects can be conflicting, but often involve severe, life-threatening organ damage. Key health effects observed from acute oral exposure and from dermal burns are summarised below (ATSDR 1997).

Gastrointestinal effects, besides vomiting, include erosion and hemorrhages in the esophagus and stomach, and necrosis and erosion of the duodenum and jejunum. Gastrointestinal hemorrhage has also been observed.

TABLE 1 PHYSICAL AND CHEMICAL PROPERTIES OF WHITE PHOSPHORUS

Adapted from (UK HSA 2025; US EPA. 1990b; Davidson et al. 1987)

CAS Number	7723-14-0 (12185-10-3)
Synonyms	α-white phosphorus, yellow phosphorus, WP
Molecular formula	P_4
Molecular weight	124.0 g/mol
State at room temperature	White-to-yellow transparent crystalline solid with a waxy appearance
Reactivity	White phosphorus spontaneously ignites on contact with air and this produces toxic fumes of phosphorus oxides. White phosphorus reacts violently with oxidants, halogens and sulphur, generating an explosive hazard. Reacts with strong bases, forming phosphine gas.
Odour	Garlic-like
Solubility Characteristics	
Water	3 mg/L (15°C); 4.1 mg/L (25°C)
Alcohol	2.5 g/L
Ether	9.8 g/L
Olive Oil	12.5 g/L
Chloroform	25 g/L
Benzene	28.5 g/L
Carbon Disulfide	1250 g/L
Log octanol water partition coefficient (log K_{ow})	3.08

Cardiovascular effects include electrocardiogram alterations (ST depression, QT elongation, microvoltage of QRS, bradycardia), tachycardia, arrhythmias, atrial fibrillation, and decreased ventricular contractility. A prominent effect is shock, manifested by marked decrease or undetectable blood pressure, vascular collapse, marked decrease in pulse, cyanotic nail beds, cold clammy skin, and cardiopulmonary arrest. Hemorrhaging in internal organs and petechial hemorrhages on the skin have also been reported.

Hepatic effects are commonly observed, including jaundice, hepatomegaly, increased serum bilirubin levels, impaired liver function tests, and increased levels of AST and ALT. Histological alterations observed include cellular fat accumulation, damage to the rough endoplasmic reticulum, a disaggregation of polyribosomes, damage to the smooth endoplasmic reticulum, and damage to the mitochondria.

Renal effects suggesting impaired function include increased blood urea nitrogen (BUN), increased urinary protein and urea nitrogen. Histological alterations observed include fatty changes in the tubules and loop of Henle, and engorged glomeruli and intratubular capillaries.

Neurological effects reported include non-specific signs such as lethargy, sleepiness, irritability, restlessness, hypoactivity, coma, toxic delirium and psychosis, hyperesthesia, coarse muscle fasciculations, marked asterixis (flapping tremor), unresponsiveness to painful stimuli, and hemiplegia. Histological damage in the brain and damage to cells of the inferior olives have been observed.

Other systemic effects include alterations in electrolyte levels, metabolic acidosis and hypoglycemia.

Systemic Toxicity Time Course

Systemic toxicity from acute oral exposure to white phosphorus is categorised into three stages.

Stage 1: Gastrointestinal effects can occur within minutes to eight hours; fatalities have been reported due to cardiovascular collapse during this stage.

Stage 2: Stage 1 survivors can experience a several-day asymptomatic period, including clinical improvement and a symptom-free interval.

Stage 3: Involves a swift deterioration in condition and typically culminates in a fatality; systemic toxicity is noted across several organ systems.

Report Objectives

The overarching objective of this report is to review relevant health-based information from the peer-reviewed and consensus literature to consider whether the mechanisms of action for acute oral phosphorus intoxication can be clarified.

Research Question

From existing literature sources, identify mechanisms of action that might contribute to the fatal outcomes observed in Stages 1 and 3 of the systemic toxicity time course following acute oral intoxication with white phosphorus.

METHODOLOGY OVERVIEW

The overall approach to reviewing the evidence is summarised below.

Guidance on the toxicity of phosphorus, white and yellow phosphorus and related chemicals was considered from Australian and international agencies including:

- World Health Organisation (WHO) (including searches of the Joint Expert Committee on Food Additives (JECFA) and the Joint Meeting on Pesticide Residues (JMPR))
- European Food Safety Agency (EFSA)
- United States Environmental Protection Agency (USEPA)
- United States Agency for Toxic Substances and Disease Registry (ATSDR)
- United States Department of Energy (USDOE)
- United States National Institute for Occupational Safety and Health (NIOSH)
- United Kingdom Health Security Agency (UKHSA)
- Australian Pesticide and Veterinary Medicines Authority (APVMA)

A search of the Internet through Google Search, Google Scholar, and PubMed used search terms such as phosphorus, white phosphorus, yellow phosphorus, and rodenticide poisoning. The searches focused on mortality and severe health outcomes in humans. Secondary searches into the mechanisms of action of shock and the relationships between phosphorus and phosphates in cardiovascular and kidney disease were conducted.

The content expert conducted data extraction, review, and interpretation. The content expert utilised NotebookLM and Perplexity Pro for document summarisation and Grammarly to enhance the report's readability.

RESULTS

TOXICOKINETICS

Adapted from (US EPA 1990a; US EPA. 1990b; Davidson et al. 1987; ATSDR 1997)

The toxicokinetics of white phosphorus are poorly understood. There are several reasons for this. First, organic and inorganic molecules containing phosphorus perform a vast and intricate web of bodily functions. 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 qualitative detection of white phosphorus in bodily fluids and tissues is equivocal.

The fate of white phosphorus following exposure is an open question. White phosphorus is an inorganic chemical poorly soluble in water, soluble in nonpolar organic solvents such as benzene, soluble in more polar organic solvents such as carbon disulfide and lipid soluble. 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 before absorption into the body. Inorganic conversion (e.g., to phosphates, phosphorus peroxide, and orthophosphates) may occur as white

phosphorus sits exposed to air, encounters moist mouth surfaces, or moves through the mammalian gut's highly acidic and basic environments. It has been postulated that the formation phosphine (PH_3) may occur under reducing conditions in the gut. However, some white phosphorus is likely absorbed by ingestion since it is lipid soluble. If white phosphorus as such is absorbed, then inorganic reactions may occur *in vivo* in the blood, interstitial fluid and intracellular fluid, although this has not been demonstrated.

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).

Absorption

There is no direct information on the pharmacokinetics of white phosphorus in humans. However, qualitative evidence of oral absorption in humans abounds in case reports of intentionally and accidentally ingested white phosphorus from rat poisons or fireworks. The toxic systemic effects observed infer that white phosphorus, or its metabolites, is absorbed from the gastrointestinal tract following oral ingestion.

The early onset of severe effects leading to death suggests that the dose of phosphorus ingested may be affected by the rate at which white phosphorus is absorbed. Death has occurred as early as 3.5 hours following ingestion. Mortality rates increase if gastric lavage is not administered within 2-3 hours after ingestion, suggesting critical absorption occurs early. Absorption may be facilitated when white phosphorus is ingested in a liquid medium, especially alcohol. The use of a vehicle correlates very well with mortality rates.

In laboratory animals (rats), absorption from the gastrointestinal tract is evident within a few minutes, with detections in the blood and liver, and is essentially complete by 24 hours. The oral administration of liquid petrolatum impeded gastrointestinal absorption in dogs, suggesting that white phosphorus preferentially dissolves in it and passes through the digestive tract without being readily absorbed.

Qualitative evidence exists of absorption in humans and animals in the form of systemic effects of white phosphorus or one of its combustion products following dermal white phosphorus burns. High mortality rates seen following white phosphorus burns can be due to absorption from the burned surface, which may result in multi-organ failure.

Distribution

Animal studies using ^{32}P-labelled white phosphorus provide the primary data on the distribution after oral exposure. In laboratory animals (mice, rats, rabbits), the radioactivity, representing white phosphorus or its metabolites, is widely distributed throughout the body. Key tissues where radioactivity was detected include the liver, kidney, bone, blood, spleen, lungs, skeletal muscle and brain, respectively. Following repeated oral dosing in rats, the accumulation of radioactivity increased in various tissues compared to a single dose, with increases noted in the brain, lungs, blood, skeletal

muscle, bone, spleen, kidney, and liver. Generally, the level of radioactivity in the blood is reported to be lower than in the liver, indicating that white phosphorus (or its breakdown products) is accumulated in tissues.

Subcellular Distribution in the Liver (Animal Studies)

In rats, the liver often showed the highest concentration or percentage of the administered dose early on (e.g., reaching 65-70% of the total dose at 2-3 hours in one study). Subcellular fractionation of homogenised liver samples 2 hours post-dosing identified that the distribution of total radioactivity was approximately 54% in the supernatant fraction, 18% in the microsomal fraction, 16% in the nuclear fraction, and 10% in the mitochondrial fraction. The radioactivity of 10% trichloroacetic acid-precipitated material was approximately 1.7% in the supernatant fraction, 5.1% in the microsomal fraction, 1.2% in the nuclear fraction and 0.3% in the mitochondrial fraction, respectively.

Subcellular/Organelle-Level Damage

While direct quantification of white phosphorus (P_4) at the subcellular level is not available, studies using radioactive tracers indicate that absorbed phosphorus atoms (likely as metabolites) are distributed throughout various subcellular fractions, particularly in the liver. Furthermore, ultrastructural and histological studies highlight damage to specific organelles like the endoplasmic reticulum, ribosomes, mitochondria, Golgi apparatus, and cell-specific changes in the liver, kidney, and brain, suggesting these are key sites affected by phosphorus toxicity across organ systems. This aligns with the normal biological role of phosphorus in forming components found throughout the cell.

METABOLISM

The metabolism of white phosphorus within the body is poorly understood. Due to its high reactivity with oxygen, it is considered probable that white phosphorus is rapidly converted to oxidation products *prior to* absorption into the body. This inorganic conversion (to phosphates, phosphorus peroxide, orthophosphates) may occur on moist surfaces of the mouth, or in the gastrointestinal tract. However, because white phosphorus is lipid-soluble, absorption of *some* white phosphorus as such is likely from ingestion.

If white phosphorus is absorbed as such, inorganic reactions *may* occur *in vivo* in body fluids, but this has not been demonstrated. No studies were found supporting or refuting enzymatic breakdown of white phosphorus.

Following its dissociation (either before absorption or in body fluids), individual phosphorus atoms are probably incorporated first into phosphates and then into a variety of biochemicals as secondary metabolites, following the normal metabolic fate of phosphorus-containing molecules in the body. Orthophosphate (H_3PO_4) is the most prevalent oxo acid of phosphorus in the blood and is a stable end-product of inorganic oxidation or hydrolysis. It is the inorganic form of phosphorus in which most excreted phosphorus appears.

Metabolism in rats, *in vivo* after acute oral dosing, appears extremely rapid, with approximately 20% of administered white phosphorus excreted as phosphate in urine within 4 hours.

Excretion

No specific information is located on the excretion of white phosphorus in humans following oral exposure.

It is highly probable that absorbed white phosphorus is rapidly converted to oxidation products, such as phosphates and organic phosphates, before or upon absorption. Therefore, studies measuring elimination track radioactive phosphorus (^{32}P), which is likely incorporated into metabolites (phosphates and organic phosphates), not white phosphorus (P_4) itself.

Animal studies indicate rapid urinary and fecal excretion of white phosphorus, metabolites, or unabsorbed inorganic breakdown products. In rats administered ^{32}P-labelled white phosphorus orally, radioactivity appeared in urine and feces. At 4 hours post-dosing, 17% of the administered dose ^{32}P dose appears in the urine and 2% in the feces. By 1 day, these percentages increased to 34.5% in the urine and 16.6% in feces. By 5 days, the percentages were 46.7% in the urine and 33.0% in feces. At least 96% of excreted phosphorus (both urine and feces) is excreted as inorganic phosphate.

It was not determined if the radioactivity in fecal material was due to direct elimination from the gastrointestinal tract or the result of biliary excretion into the small intestine.

Systemic effects

Adapted from (US EPA 1990a; US EPA. 1990b; Davidson et al. 1987; ATSDR 1997)

Gastrointestinal effects

The gastrointestinal tract is identified as a major target organ affected by white phosphorus toxicity, particularly following oral exposure. The effects observed in the gastrointestinal tract after ingestion are likely due to the local irritating properties of white phosphorus on the gastrointestinal lining (mucosa).

Vomiting is a very prominent and early symptom; however, some human case reports reported no gastrointestinal distress. It is frequently described as persistent and/or violent, and often begins shortly after ingestion, sometimes continuing for many days. Vomiting can expel much of the ingested white phosphorus from the body. The vomitus may sometimes contain blood and/or pieces of the gastric mucosa. Abdominal pain or cramps are also commonly reported and can be severe. Diarrhea may occur, sometimes described as slight.

Direct tissue damage has been observed, including necrosis and erosion of the mucosa in the esophagus, stomach, duodenum, and jejunum. Gastrointestinal hemorrhage has also been reported.

Cardiovascular effects

The cardiovascular system is identified as a major target organ damaged by white phosphorus toxicity. Cardiovascular effects can be observed shortly after exposure.

Cardiovascular effects, including damage to the heart (myocardium) and the circulatory system, have been reported following acute oral ingestion of white phosphorus. Abnormal EKGs (electrocardiogram) have been observed in rabbits burned with white phosphorus, and increased mortality in burn studies has been attributed to the systemic effects of white phosphorus or phosphorus compounds. Myocardial effects have been observed in humans burned by phosphorus. In animals, some systemic vascular effects (increased permeability of capillary walls, lesions in blood vessel walls, impaired microcirculation) were observed in the mouth of rats exposed to airborne white phosphorus from a factory.

Cardiac effects

Alterations in electrocardiograms (EKG/ECG) are frequently reported in individuals acutely ingesting white phosphorus, or rabbits burned by white phosphorus. These alterations can include altered or inverted T waves, changes in the QRS complex, prolongation of the QT interval, ST segment depression, bradycardia, and low voltage QRS complex. Other observed cardiac changes include tachycardia, arrhythmias, atrial fibrillation, and decreased ventricular contractility.

Myocardial damage has been observed. This damage has increased proportionally with the dose of white phosphorus ingested in humans.

Microscopic examination of the heart in human cases of acute oral ingestion has shown fatty degeneration, interstitial edema without cellular infiltrates, and cells with vacuolated cytoplasm. Necrosis of the myocardium has been observed in humans. Prominent cross striations in the myocardium have been reported in humans. In contrast, no histological alterations were observed in the heart in rabbits burned by white phosphorus, despite observing EKG alterations indicative of myocardial damage.

No morphological evidence of myocardial damage was observed in rats orally exposed to relatively low concentrations of white phosphorus, and no histological alterations were observed in the hearts of rats exposed to a relatively low dose (0.075 mg/kg/day) for an intermediate duration.

Vascular effects

Damage to the integrity of blood vessels has been observed in humans and animals exposed to phosphorus. Specific observations include increased permeability of capillary walls, lesions in the walls of blood vessels, and evidence of impaired microcirculation.

A prominent effect following acute human exposure, particularly ingestion, is shock. Clinical signs of vascular effects include a markedly decreased or undetectable blood pressure, vascular collapse, decreased or increased pulse, cyanotic nail beds, and cold clammy skin.

Hemorrhaging in internal organs, as well as the appearance of petechial hemorrhages on the skin and internal organs, have been reported in a number of acute human exposure cases. In addition, an increase in permeability in the 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.

In summary, the heart and vascular system is a major target of white phosphorus toxicity following oral exposures and may result in death before multi-organ failure and contribute to some of the observed renal effects. Myocardial damage increased proportionally with the dose of white phosphorus ingested in humans.

HEPATIC EFFECTS

The liver is identified as a major target organ affected by white phosphorus toxicity, particularly following oral ingestion. The hepatic effects observed are primarily systemic, likely resulting from the absorption of white phosphorus or its metabolites into the bloodstream.

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 levels of liver enzymes in the blood such as AST and ALT, decreased serum triglycerides, while hepatic triglycerides are increased and increased lactate dehydrogenase. Gross examination of the liver post-mortem often reveals a yellow appearance with areas of necrosis. Hemorrhages have been observed.

Liver damage is frequently observed in individuals exhibiting signs of neurotoxicity.

Jaundice, hepatomegaly, and increased serum bilirubin levels have been observed in humans with white phosphorus burns. Animal burn studies showed increased ALT levels, necrosis, ballooning degeneration of hepatocytes, and microthrombi in the portal veins.

A characteristic lesion observed in the liver of both laboratory animals and humans following white phosphorus intoxication is fatty degeneration. This is also referred to as steatosis. This fatty change is often marked or extensive. Histologically, the liver shows extensive fatty degeneration with vacuolisation.

Histological alterations observed include cellular fat accumulation, damage to the rough endoplasmic reticulum, a disaggregation of polyribosomes, damage to the smooth endoplasmic reticulum, and damage to the mitochondria. Liver damage can progress rapidly. In animal studies, minimal fatty changes were observed as early as 4 hours after a single dose, becoming extensive by 12 hours.

In patients who survive for more than a week after ingestion, extreme fatty changes are typically seen on many organs, and the liver is often described as yellowish with marked fatty degeneration. Fibrosis has been observed microscopically in the livers of affected humans. Animal studies with intermediate oral exposure demonstrate liver damage, including fibrosis and cirrhosis, in pigs exposed for 8 weeks and cirrhosis in rabbits and guinea pigs.

Antioxidants like glutathione and propyl gallate administered before white phosphorus prevented the elevation of hepatic triglycerides and reduced polyribosome disaggregation, helping to maintain hepatic protein synthesis.

In summary, white phosphorus is an acute hepatotoxin and acute liver failure is often observed in humans following accidental and intentional exposure to fireworks and white phosphorus-containing rodenticides.

RENAL EFFECTS

The kidney is identified as a major target organ damaged by white phosphorus toxicity, particularly following oral ingestion and dermal burns. Kidney effects are systemic effects likely resulting from absorbed white phosphorus or metabolites. Renal effects can be observed shortly after exposure and

may be associated with cardiovascular events. Some case reports, however, have reported no alteration in kidney function.

Evidence of severe renal effects has been observed in a number of individuals accidentally or intentionally ingesting a single dose of white phosphorus. Clinical signs and biomarkers suggesting severe decreased renal function include: increased blood levels of urea nitrogen, nonprotein nitrogen, creatinine, proteinuria, albuminuria, and oliguria. Histological damage observed in humans acutely exposed includes fatty changes in the tubules and loop of Henle and engorged glomeruli and intratubular capillaries. Renal insufficiency may be due to a direct toxic effect of phosphorus on the kidneys or possibly changes in the integrity of blood vessels.

Histological alterations in the kidneys have been observed in animals acutely ingesting white phosphorus. Fatty infiltrations in the nephron and subcapsular hemorrhages were observed in dogs orally exposed to an unspecified amount of white phosphorus.

Evidence of renal damage was observed in individuals burned once with white phosphorus. The severe histological alterations observed in animals acutely burned with 29-200 mg/kg/day white phosphorus support the effects observed in humans. Histological damage includes necrosis and vascular degeneration of the proximal tubule and ischemic changes in the glomerulus.

In summary, the kidney is a significant target of white phosphorus toxicity following oral and dermal burn exposure, leading to functional impairment indicated by altered blood and urine chemistry, and histological damage including fatty changes, necrosis, and vascular alterations.

Neurological Effects

Neurotoxicity has been observed following acute oral ingestion in humans and animals, dermal burns exposure in humans and animals and parenteral exposure (intravenous injection) in animals. Clinical signs include lethargy, sleeplessness, irritability, restlessness, hypoactivity, coma, toxic delirium and psychosis, hyperesthesia, coarse muscle fasciculation, marked asterixis, unresponsiveness to painful stimuli and hemiplegia. In animals: Depression, poor responsiveness to stimuli, shivering, twitching, anorexia (rabbits burned), tonoclonic convulsions, increased salivation, weakness (cat oral lethal dose), tremors (pregnant rats oral lethal dose).

Individuals acutely ingesting white phosphorus have been observed to have histological damage in the brain. The types of cellular damage observed in humans include cellular changes from ischemic damage (Purkinje cells) and direct white phosphorus-induced damage (inferior olives), fatty infiltration, and cerebral edema.

In summary, while white phosphorus can result in nervous system cellular changes, neurological effects are often observed in individuals exhibiting acute liver failure.

Other Systemic Effects

Hypoglycemia

Hypoglycemia, or low blood sugar, has been observed as a toxic effect of white phosphorus exposure in both humans and animals. Hypoglycemia was also among the symptoms observed in patients who died following acute oral ingestion.

Hypoglycemia has also been reported in workers occupationally exposed to white phosphorus for a chronic duration. In animal studies, hypoglycemia was observed in dogs acutely ingesting white phosphorus orally. Severe hypoglycemia became apparent only a few hours prior to death in some animals. However, the same study noted that some animals died without developing hypoglycemia, suggesting that severe liver damage was not the sole factor associated with death in all cases.

Electrolyte levels

White phosphorus exposure can result in changes in electrolyte levels.

Hypocalcemia, a decrease in plasma calcium, has been observed in humans acutely ingesting white phosphorus, in individuals with white phosphorus burns and in rabbits burned with white phosphorus.

Hyperphosphatemia, an increase in plasma phosphate, following ingestion in humans, might be due to the accumulation of phosphorus in tissues that is later metabolised by changes in the acid-base balance. However, serum inorganic phosphate levels are often normal or decreased rather than elevated after acute oral ingestion in most cases.

Decreased plasma potassium and/or sodium have been observed in humans acutely ingesting white phosphorus.

Metabolic acidosis in individuals ingesting a single dose of white phosphorus may be related to alterations in electrolyte levels.

DISCUSSION

Acute oral intoxication with white or yellow phosphorus follows a characteristic three-phase progression. Specific mechanisms are presented that contribute to fatal outcomes during Stage 1 (early phase) and Stage 3 (late phase) of phosphorus poisoning.

STAGE 1: EARLY FATAL MECHANISM (FIRST 24 HOURS)

While many humans survive the initial phase of phosphorus poisoning, this may be due to the dose ingested; fatal outcomes can occur before multi-organ failure through several distinct mechanisms.

DIRECT CARDIOVASCULAR TOXICITY

White and yellow phosphorus exhibit direct cardiotoxic effects that can lead to rapid death. Ingestion of large amounts can directly result in cardiovascular arrhythmia and collapse within 24 hours post-exposure.

- Phosphorus has a direct toxic action on the heart and blood vessels, leading to shock and cardiovascular collapse.
- Early electrocardiogram changes show dysrhythmias, widening QRS complexes, and depression of ST segments.

Electrolyte Disturbances

Severe electrolyte abnormalities likely trigger fatal cardiac dysrhythmias during Stage 1.

- Hypocalcemia and hyperkalemia can develop rapidly and may contribute significantly to cardiac arrhythmias (Goyal et al. 2023).
- Hypocalcemia disrupts calcium-dependent signalling in vascular smooth muscle cells and can cause systemic vasodilation and refractory hypotension (shock).
- These electrolyte derangements are particularly dangerous in conjunction with the direct cardiotoxic effects of phosphorus.

Fluid Loss and Shock

The gastrointestinal manifestation of Stage 1 can lead to fatal outcomes.

- Severe dehydration from persistent vomiting, diarrhea, and gastrointestinal losses.
- Cardiac failure secondary to fluid loss and electrolyte derangement, in addition to direct cardiac toxicity.
- Hemorrhage into the gastrointestinal tract exacerbating hypovolemia (Ravikanth, Sandeep, and Philip 2017).

Protoplasmic Poisoning

At a cellular level, phosphorus acts as a potent protoplasmic poison.

- In acute poisoning, white and yellow phosphorus function as direct protoplasmic toxins affecting multiple organ systems.
- This acute cellular toxicity can lead to widespread tissue damage even before the development of organ-specific manifestations.
- Cellular changes occur rapidly following acute exposure.

Stage 2: Latent Period (Relative Resolution)

The second stage represents a deceptive period of apparent recovery lasting 1-7 days, during which symptoms temporarily abate. A review of clinical chemistry parameters will indicate ongoing liver damage despite clinical improvement.

Stage 3: Late Fatal Mechanism (After 72 Hours)

The third stage, occurring typically 72 hours to one week after ingestion, is characterised by multi-organ failure with several distinct mechanisms contributing to mortality.

Hepatotoxicity and Acute Liver Failure

The predominant cause of death in Stage 3 is acute liver failure.

- Phosphorus causes hepatic dysfunction, disrupting carbohydrate and fat metabolism.

- Histopathology shows fat infiltration, vacuolisation and necrosis of the liver.
- The toxic effect occurs primarily in the endoplasmic reticulum and mitochondria of the hepatocytes.
- Impaired synthesis of apolipoproteins, decreased ATP production, and inhibited fatty acid oxidation lead to fat disposition and cellular damages.

Endoplasmic Reticulum Damage

The role of phosphorus in observed endoplasmic reticulum damage is complex. Phosphorus compounds localise rapidly and damages the endoplasmic reticulum through direct chemical interactions, oxidative stress, disrupting endoplasmic reticulum homeostasis and triggering apoptotic pathways.

Mitochondrial Dysfunction

Histology identifies mitochondrial swelling arising from acute phosphorus exposure. Changes in calcium homeostasis, energy metabolism and oxidative stress may contribute to this observation.

Multi-Organ Failure

Stage 3 is characterised by progressive failure of multiple organ systems, with acute liver failure being prominent.

- Hepatic encephalopathy and multi-organ dysfunction syndrome are typical terminal events.
- Renal damage can be observed.
- Cardiovascular complications may arise.

Coagulopathy and Hemorrhage

Severe bleeding complications arise from multiple mechanisms.

- Hemorrhages occur in the skin, mucous membranes, and viscera due to vascular injury and coagulation defects.
- Gastrointestinal features may progress to alimentary tract bleeding.
- Decreased synthesis of clotting factors by the damaged liver exacerbates bleeding tendencies.

Disruption of Protein Synthesis

At a molecular level, phosphorus toxicity interferes with fundamental cellular processes.

- Phosphorus affects ribosomal function, leading to defective protein synthesis.
- This disruption affects all tissues (i.e. liver, heart, kidney).

CONCLUSION

Fatal outcomes in phosphorus poisoning follow distinct pathways in Stage 1 and Stage 3. Early death (Stage 1) primarily results from the direct cardiovascular toxicity, electrolyte disturbances and severe fluid loss leading to shock. Late deaths (Stage 3) stem from multi-organ failure centred around hepatotoxicity, with mechanisms including ER stress, oxidative damage, mitochondrial dysfunction, and disruption of protein synthesis.

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