

Phosphine

Toxicological overview

Key Points

Kinetics and metabolism

- Inhaled phosphine is absorbed rapidly from the lungs and distributed round the body
- Inhaled or ingested zinc, aluminium and magnesium phosphides release phosphine into the respiratory tract and stomach; zinc phosphide can be absorbed intact from the gut
- Dermal absorption of phosphine or phosphides is not considered a significant route of exposure
- The majority of absorbed phosphine is excreted in exhaled air; minor amounts are metabolised and excreted in urine as hypophosphite and phosphate

Health effects of acute exposure

- Phosphine is acutely toxic; exposure to high levels cause immediate effects
- Early symptoms of acute phosphine or phosphide exposure are non-specific and include respiratory problems, cough, headaches, dizziness, numbness, general fatigue and gastrointestinal disturbance (pain, nausea, vomiting and diarrhoea)
- Effects of exposure to higher levels of phosphine, the onset of which may be delayed by several days or more, include pulmonary oedema, convulsions, damage to the kidney, liver and heart, and death

Health effects of chronic exposure

- Symptoms of chronic exposure include: anaemia, bronchitis, gastrointestinal disorders, speech and motor disturbances, toothache, weakness, weight loss, swelling of the jaw, mandibular necrosis and spontaneous fractures
- Phosphine is genotoxic *in vitro* but is not considered to be mutagenic *in vivo* and has not been associated with cancer
- Phosphine is unlikely to cause reproductive or developmental effects
- Repeated exposure may lead to cumulative effects

Toxicological Overview

Summary of Health Effects

Phosphine is rapidly absorbed and distributed throughout the body and is acutely toxic. The onset of symptoms is rapid following phosphine inhalation or the ingestion/inhalation of metal phosphides, which release phosphine on contact with moisture or stomach acid. Dermal absorption of phosphine or phosphides is not considered a significant route of exposure.

Exposure to low doses of phosphine causes non-specific symptoms such as headache, dizziness, numbness, general fatigue, breathing difficulties (tightness around the chest, pain in the region of the diaphragm and cough) and gastrointestinal disturbance (pain, nausea, vomiting and diarrhoea). At higher doses, subjects may experience lung irritation, persistent coughing, tremors and convulsions, leading to pulmonary oedema, myocardial injury, kidney damage and coma, and sometimes death due to cardiovascular failure, usually within the first a few hours or after a delay of up to two weeks in the case of liver failure.

Chronic exposure to phosphine is unlikely to occur in the general population but may occur in an occupational setting. Symptoms of chronic exposure may include anaemia, bronchitis, gastrointestinal disorders, speech and motor disturbances, weakness, weight loss, toothache, swelling of the jaw, mandibular necrosis, and spontaneous fractures. Some chronic effects can be confused with symptoms of acute poisoning.

Several studies indicate that phosphine is genotoxic *in vitro*, however the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) considered that since the available data on *in-vivo* mutagenicity and carcinogenicity was negative and given the very low potential exposure, this provided sufficient reassurance regarding its *in-vivo* mutagenic potential. Phosphine can be assumed to have no *in-vivo* mutagenicity. Phosphine has not been reviewed by the International Agency for Research on Cancer (IARC).

The limited data available indicate that phosphine is unlikely to cause reproductive or developmental effects, since no gross teratogenic effects have been recorded. However, a study on mice reported an increase in the number of foetal resorptions following exposure to low concentrations of phosphine, suggesting possible foetal toxicity.

Children exposed to phosphine will have the same symptoms of toxicity as adults.

Kinetics and metabolism

Although there are no formal experimental animal or human studies on the absorption, distribution and elimination of phosphine, inhaled phosphine is generally considered to be rapidly absorbed [1, 2]. Inhalation of aluminium, magnesium and zinc phosphides may result in the internal release of phosphine, and subsequent inhalation, following contact of the phosphides with the moist surfaces of the respiratory tract or, in the case of ingested zinc phosphide, gastric acid [1, 3, 4]. Inhaled zinc phosphide particles may also be absorbed and hydrolysed in surrounding tissues and may be transferred to the intestinal tract by particulate clearance mechanisms, where hydrolysis by gastric acids would release phosphine [1].

Detection of acid-hydrolysable phosphides in rat and human liver indicates that ingested zinc and aluminium phosphides can be absorbed intact from the gut [1]. Absorption of phosphine or metal phosphides through the skin is not considered a significant exposure pathway [1].

Following acute phosphine or phosphide exposure, phosphine is rapidly absorbed and distributed throughout the body leading to possible effects on the respiratory, circulatory and nervous system, liver, kidney and gastrointestinal tract [4].

The majority of absorbed phosphine is excreted in exhaled air [1]. Minor amounts are slowly and incompletely oxidised and excreted in the urine as hypophosphite and phosphate [1].

Sources and route of exposure

It is likely that the general population will be exposed to only low levels of phosphine in air, drinking water and food [3]. Phosphine and the metal phosphides have only been detected in the general environment in relation to recent localised use of metal phosphides in industrial pest control and fumigation, such as during storage of agricultural grains (cereals) and tobacco, and certain industrial activities [5]. Most reported measurements of phosphine/phosphide residues in fumigated foodstuffs are below the World Health Organisation (WHO) recommended level of 0.1 mg phosphine kg⁻¹ for raw cereals or 0.01 mg phosphine kg⁻¹ for other stored products [5].

Phosphine rarely occurs naturally although it can be formed during the breakdown of phosphorus-containing organic matter, e.g. in marsh gas, but is rapidly degraded in the environment [1, 5].

Workers involved in the production of phosphine or metal phosphides are likely to be exposed to higher levels of phosphine than the general public. The main route of occupational exposure is direct inhalation of phosphine gas or metal phosphide dust, or inhalation of phosphine released from metal phosphide dust on clothes, skin or hair in the presence of water or moisture [4]. Phosphine gas does not present a risk of secondary contamination, although solid phosphides may pose some risk. Absorption through the skin is not considered a significant route [1].

Accidental inhalation of phosphine or accidental/intentional ingestion of metal phosphides may also occur. The majority of cases of acute poisoning from metal phosphides are attempted suicides [1].

Children exposed to phosphine will have the same symptoms of toxicity as adults but may be at a greater risk of phosphine poisoning due to a higher lung surface area to body weight

ratio, an increased ventilation rate and shorter stature (phosphine gas is slightly heavier than air) [4].

In the UK, the current occupational short-term exposure limit (STEL; 15-minute reference period) is 0.42 mg m^{-3} (0.3 ppm; $1 \text{ mg m}^{-3} = 0.72 \text{ ppm}$) [6]. The Health and Safety Executive (HSE) has proposed an 8 hour time weighted exposure (TWA) limit of 0.14 mg m^{-3} (0.1 ppm), and a reduced STEL of 0.28 mg m^{-3} (0.2 ppm), in line with the European Commission occupational exposure limit. These values are awaiting formal approval by the Health and Safety Commission [7].

There are no biological indicators for exposure to phosphine [8].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Inhalation is the most common route of phosphine exposure and intoxication. Accidental or intentional (suicidal) ingestion of metal phosphides also occurs resulting in the release of phosphine on contact with moisture or gastric acid [1, 4]. Dermal absorption is not considered a significant route of exposure.

Phosphine gas is highly toxic and has a very steep concentration-response curve [9]. Symptoms usually occur within the first few hours of exposure [1, 2] and most phosphine-related deaths occur within 12-24 hours of exposure, usually as a result of cardiovascular damage resulting in collapse, cardiac arrest and heart failure [4]. Deaths after 24 hours are usually as a result of liver or renal failure [4].

Acute exposure to phosphine affects the respiratory, nervous and gastrointestinal systems, heart, liver and kidneys [9]. In *in-vitro* studies, phosphine has been found to react with haemoglobin in the presence of oxygen, and in isolated mitochondria, phosphine inhibits cytochrome c oxidase and mitochondrial oxygen uptake; however, these findings have not been confirmed in *in-vivo* studies [10].

Inhalation

Initial symptoms of phosphine inhalation are non-specific and may include headaches, dizziness, numbness, general fatigue, breathing difficulties (tightness around the chest, pain in the region of the diaphragm and cough), and gastrointestinal disturbance (pain, nausea, vomiting and diarrhoea). In cases of severe poisoning, patients may experience lung irritation, persistent coughing, tremors and convulsions, leading to pulmonary oedema, myocardial injury, liver and kidney damage, cardiovascular collapse, coma and death [1, 2, 4].

Exposure to 7-14 mg m⁻³ (5-10 ppm) of phosphine for several hours may cause serious effects [2]. The severity of the toxic effects of phosphine in humans, following inhalation of various concentrations of phosphine, are given in table 1.

Several cases of acute phosphine poisoning have been documented following accidental or occupational exposure. A review of 26 deaths resulting from phosphine poisoning reported the most common post-mortem finding as congestion of the lung with pulmonary oedema [1]. In a fatal incident, concentrations of phosphine were estimated as 1.2 mg m⁻³ (0.9 ppm) inside a house sharing a wall with a granary that was being fumigated. Symptoms were initially non-specific with subsequent effects noted at autopsy comprising congestion of all organs, pulmonary oedema with focal emphysema, and liver vacuolation [1]. Metal workers at a large shipyard in Norway were reported to experience nausea, dizziness, chest tightness, dyspepsia and disturbances of smell and taste when concentrations of phosphine were 1.4 mg m⁻³ (1 ppm) in the worker's breathing zone [1]. Installation of ventilation systems reduced phosphine to undetectable levels and relieved symptoms.

Table 1. Time taken for symptoms or death to occur following inhalation of phosphine in humans [2, 5]

Dose		Severity of Effects
ppm	mg m ⁻³	
7	10	No serious effects after 30-60 min
100-190	140-260	Serious effects after 30-60 min
290-430	400-600	Dangerous to life after 30-60 min
400-600	560-840	Death after 30-60 min
2000	2800	Death after 30-60 min

Pure phosphine is odourless, although the presence of impurities in most commercial preparations of phosphine results in an odour of garlic or decaying fish. The odour threshold for phosphine is 0.14-0.28 mg m⁻³ (0.1-0.2 ppm) [1]. However, odour is not a reliable indicator of phosphine levels [4] since impurities may be absorbed by stored products during fumigation, resulting in a loss of odour, even at toxic levels of phosphine [1].

Ingestion

Metal phosphide ingestion causes non-specific symptoms within a few hours, similar to those observed following acute phosphine inhalation [1, 4]. These include effects on the respiratory and nervous system, heart, kidney and liver. In severe poisoning, gastrointestinal haemorrhage, jaundice, cardiac arrhythmias, pulmonary oedema, liver and kidney damage, convulsions, coma and death may occur [1, 2].

The majority of documented cases of metal phosphide ingestion relate to attempted suicides, which are common in countries without restrictions on these compounds [1, 4]. The lethal dose of ingested zinc phosphide varies. Most reported fatalities have occurred following ingestion of >20 g zinc phosphide, although some deaths have been reported at doses as low as 4.5 g. Recovery generally occurs at doses below 20 g [5] although this may occur at doses above 50 g [1].

Dermal / ocular exposure

Adverse effects have not been reported following dermal exposure to phosphine gas, although skin contact with compressed, liquefied phosphine may cause frostbite [4]. Exposure to metal phosphides via broken skin can cause systemic toxicity similar to that resulting from inhalation [4].

There are no data on the effects of phosphine gas or metal phosphides on the eyes, although significant effects are not expected [1, 4].

Delayed effects following an acute exposure

Long-term effects following acute exposure to phosphine are unusual, with most non-specific symptoms occurring within several hours of exposure and in the majority of cases clearing within 30 days of exposure [11]. However, the onset of pulmonary oedema and liver damage,

resulting in jaundice, enlarged liver, elevated serum transaminases and increased blood bilirubin, may be delayed by 48-72 hours or more [4]. Most patients that survive acute phosphine poisoning do not suffer any permanent damage, although brain and heart injury due to reduced blood supply to these organs has been reported [4]. Subacute poisoning resulting from exposure to phosphine for several days, may lead to reactive airways dysfunction syndrome [4].

Animal and In-Vitro Data

Inhalation

Rats exposed to 80 mg m⁻³ (58 ppm) or 800 mg m⁻³ (575 ppm) of phosphine exhibited initial signs of respiratory irritation followed by death after 4 and 1 hours, respectively, due to pulmonary oedema; bronchiolitis and atelectasis were noted in the lungs, and all organs were hyperaemic. Fatty infiltration of the liver and cloudy swelling of kidney tubular cells were also reported [1]. In another acute inhalation study on male and female rats exposed to 28 - 56 mg m⁻³ (20-40 ppm) phosphine (1% in nitrogen) for 4 hours, no evidence of phosphine-related neuropathological changes was noted, although the acute Lowest Observed Effect Level (LOEL) of 28 mg m⁻³ (20 ppm) was based on a decrease in body temperature and motor activity in both sexes. It is not known whether other endpoints were studied. Since no systemic toxicity was reported, the No Observed Effect Level (NOEL) for systemic toxicity was 56 mg m⁻³ (40 ppm) [12]. Inhalation exposure of rabbits to 140 or 700 mg m⁻³ (100 or 500 ppm) of phosphine caused death in 2.5-3 hours and 25-30 minutes, respectively [5].

Median lethal concentrations (LC₅₀) values are given in table 2.

Table 2. Acute inhalation toxicity of phosphine in rats [1, 12, 13].

Test animal	Exposure duration	LC ₅₀ (mg m ⁻³)
Rat	35-50 min	1470
Rat	65-75 min	680
Rat	4 h	15
Rat (F)	4 h	55

An inhalation LC₅₀ of 19.6 mg L⁻¹ in rats for 10% zinc phosphide powder was reported by the US National Pest Control Association, although it was not clearly stated whether the value was for pure zinc phosphide or 10% dilution, and no indication of exposure duration was given [5].

Ingestion

In a study on the Kit fox, an oral LD₅₀ of 93 mg kg bw⁻¹ was noted for zinc phosphide, while in a study on wild Norway rats given 20-80 mg kg bw⁻¹ orally, an LD₅₀ of 40.5 ± 2.9 mg kg bw⁻¹ was recorded [1, 5]. The purity of the zinc phosphide compounds used in these studies was not given. A study on rats reported an oral LD₅₀ of 27 mg kg bw⁻¹ for 94% pure zinc phosphide [5].

Dermal / ocular exposure

An acute dermal LD₅₀ of 2000-5000 mg kg bw⁻¹ for zinc phosphide (94% purity) in rabbits was reported by the US National Pest Control Association [1].

No data are available on the effects of phosphine on the eyes.

Health Effects of Chronic / Repeated Exposure

Human Data

General Toxicity

Published data on the effects of long-term exposure to phosphine and metal phosphides are limited and are generally confined to case studies following occupational exposure.

The chronic effects of phosphine exposure can be complicated by acute poisoning but are generally distinct and may include anaemia, bronchitis, gastrointestinal disorders, speech and motor disturbances, toothache, swelling of the jaw, mandibular necrosis, weakness, weight loss and spontaneous fractures [1].

Repeated exposure to low levels of phosphine 0.11-0.42 mg m⁻³ (0.08-0.3 ppm) has been associated with mild headaches [11].

Inhalation

No long-term studies have been reported on the effects of chronic phosphine inhalation. A review of 59 poisonings suggests that the minimum lethal concentration of phosphine in air is 7-14 mg m⁻³, 2-4 h day⁻¹ for several days [13].

Ingestion

No data available.

Genotoxicity

In 1997 the COM expressed the opinion in relation to the use of phosphine in grain fumigation and rodenticides, that there was limited evidence to suggest that phosphine was an *in-vivo* mutagen. This was based on cytogenetic studies on a small group of pesticide applicators in Minnesota USA. However following a review of additional information, in 2002 the Committee noted that while it should be assumed that phosphine is genotoxic *in vitro*, the available data on *in-vivo* mutagenicity and carcinogenicity was negative and, together with the very low potential exposure arising from pesticide use, this provided sufficient reassurance regarding its *in-vivo* mutagenic potential [14].

In a follow-up study on the same population of pesticide applicators in Minnesota, no significant difference in genotoxic endpoints was noted, and the authors suggested that the use of personal protective equipment against phosphine exposure (not worn when the first study was carried out) or changes in work practices may have been responsible for the lack of observed effects [15].

Carcinogenicity

Phosphine has not been reviewed by IARC, and the EPA considers phosphine as not classifiable as to human carcinogenicity, due to inadequate animal studies and a lack of human cancer data [10].

Reproductive and developmental toxicity

No data available.

Animal and In-Vitro Data

Inhalation

Repeated exposure to phosphine causes death, with fatalities reported in several rat studies following repeated exposure to above $\sim 7 \text{ mg m}^{-3}$ (5 ppm) [9, 16]. For example, in one study on rats exposed to 14 mg m^{-3} (10 ppm) for 6 h day^{-1} , four of the ten females, but no males, died on the third day, the remaining animals were sacrificed on this day. Minor decreases in body weight gain ($\sim 7\%$ for males and 4% for females) and renal tubular necrosis were reported, and congested lungs were noted in the four females that died [10]. During the same study, rats were exposed to 0.42 , 1.4 or 4.2 mg m^{-3} (0.3, 1 or 3 ppm) phosphine for 6 h day^{-1} , 5 days week^{-1} for 13 weeks. No deaths were reported, although a significant decrease in haemoglobin, haemocrit and erythrocytes in males exposed to 4.2 mg m^{-3} (3 ppm) was reported at the end of the 13 week study period [9].

Repeat inhalation studies on rabbits and guinea pigs exposed to various concentrations of phosphine found that exposure to 28 mg m^{-3} (20 ppm) phosphine for 4 h per day, was fatal for rabbits and guinea pigs, during or after the second exposure [5]. Rabbits exposed to 14 mg m^{-3} (10 ppm) survived 7 -14 successive exposures and showed no signs of intoxication until 30 min prior to death, when animals became stuporous and showed signs of diminished reactivity and shallow respiration. Animals died during coma, and pulmonary oedema was noted at necropsy [5]. Rabbits exposed for 5 days to 7 mg m^{-3} (5 ppm) for 4 h, died when exposed to 20 mg m^{-3} (14 ppm) on the sixth day. The authors concluded that pre-treatment of animals to sub-lethal concentrations of phosphine reduces resistance to near-lethal concentrations [5]. In another study, rats were exposed to 681 mg m^{-3} (490 ppm) phosphine for 10-20 min per day for 6 days, died on the seventh day when exposed for 22 -35 min [5]. The concentration x time product for lethality after exposure for 6 days was approximately 20 mg min L^{-1} , and was one third of that of the first exposure ($48\text{-}87 \text{ mg min L}^{-1}$). It was suggested that the effects of exposure were cumulative [5].

A study on cats, guinea pigs and rats exposed to 1.4 and 3.5 mg m^{-3} (1 and 2.5 ppm) phosphine for more than 800 hours found no evidence of haemolysis of red blood cells or the formation of methemoglobin, and no signs of cumulative poisoning [13, 16].

A sub-chronic repeat dose study on rats found that exposure for 13 weeks, did not adversely affect behaviour or result in any clinical symptoms or histopathological changes in the nervous system. Changes in serum chloride concentrations were observed at the two highest doses, but the biological significance of this was considered minimal [17].

In a chronic study conducted at exposures of 0.42, 1.4 or 4.2 mg m⁻³ (0.3, 1 or 3 ppm) phosphine for 6 h day⁻¹, 5 days week⁻¹, in which rats were treated for 52 weeks or 2 years, no clinical effects and no adverse effects on body weight, food consumption, urinalysis, haematology and organ morphology were noted that related to phosphine exposure [17].

Ingestion

Data from two studies are reported here, although experimental data on chronic exposure to phosphine is generally lacking.

A rat study in which animals were fed 0, 50, 100, 200 or 500 mg kg⁻¹ zinc phosphide in the diet for 13 weeks reported reductions in both food intake and weight increase and dose-dependent depilation at all doses. At the two highest doses, 1/12 and 10/12 animals died, and the relative weights of liver, heart, brain and thyroid were increased. At 500 mg kg⁻¹ increased serum zinc and phosphatase levels were noted, and a dose-dependent reduction of haemoglobin, red blood cells and haematocrit was reported [5].

An oral study, in which rats were fed an unknown quantity of phosphine via aluminium phosphide-fumigated feed over a 2 year period, did not display any treatment-related differences in blood-glucose or urine chemistry in comparison to controls [12]. However, the study was considered of limited usefulness since toxic levels of phosphine were not achieved [10].

Genotoxicity

Phosphine has been found to be consistently negative in the Ames test with *S. typhimurium* sp. TA98, TA100, TA1535, TA1537 and *E. coli* sp. WP2UVRA, at concentrations of 0.02 - 0.5% phosphine (in helium), with and without metabolic activation [14, 18]. However, *in-vitro* studies on mammalian cells suggest that phosphine may be mutagenic. For example, human lymphocyte cells exposed to phosphine exhibited dose-related chromosomal damage (deletions, gaps and strand breaks) similar to the genotoxic effects observed in some phosphine-exposed human pesticide workers [10]. Furthermore, Chinese hamster ovary cells exposed to 2500 or 5000 ppm phosphine without S9 activation, showed increased rates of chromosomal aberration [12].

Based on the available *in-vivo* data on rodents (overall negative results in bone marrow assays for clastogenicity and negative results in a liver UDS assay in rats and a dominant lethal assay in mice), the COM concluded that there was no convincing evidence that phosphine and metal phosphides are mutagenic *in vivo*, and concluded that there was 'sufficient reassurance regarding the *in-vivo* mutagenicity of phosphine'. The Committee suggested, based on other published data that the positive results observed *in-vitro* may be due to the formation of reactive oxides, rather than direct interaction of phosphine with DNA [14].

Carcinogenicity

Rats exposed to 0.42, 1.4 or 4.2 mg m⁻³ (0.3, 1 or 3 ppm) phosphine for 6 h day⁻¹, 5 days week⁻¹, for 52 weeks or 2 years did not exhibit any treatment-related increase in the incidence of any cancer [19]. Another study, in which rats were fed an aluminium phosphide-fumigated diet found that tumour incidences were similar between control and experimental

animals, although this study was judged as insufficient for assessing the carcinogenicity of phosphine since toxic levels of phosphine were not achieved [10].

Reproductive and developmental toxicity

Only limited information is available on the reproductive and developmental toxicity of phosphine in experimental animals. This suggests that phosphine is unlikely to be a developmental toxin. Also no gross teratogenic effects from acute exposure to phosphine are known [4].

In a study on groups of pregnant Sprague-Dawley rats exposed to 0, 0.04, 0.4, 4, 7 or 10 mg m⁻³ (0, 0.03, 0.3, 3, 5 and 7 ppm) phosphine for 6 h day⁻¹, on gestational days 6-15, high maternal mortality at the highest exposure concentration, and a significant increase in foetal resorptions at the lowest exposure, suggesting foetal toxicity, were noted in comparison to controls [9]. No other differences between exposed and control animals were reported.

In a study to evaluate the effect of inhaled phosphine on male germ cells, male mice were exposed to 7 mg m⁻³ (5 ppm) phosphine for 6 h day⁻¹ for 10 days over a 12 day period, then mated to groups of untreated females. There was no effect on the percentage of females impregnated by exposed males or on percentage of resorptions or implants per female [10].

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