

Phosphine

RISK CHARACTERIZATION DOCUMENT



DRAFT

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Department of Pesticide Regulation
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I. SUMMARY

Phosphine (PH_3) is a rodenticide and insecticide used to fumigate stored agricultural products such as grain, tobacco, processed foods and animal feed. It is marketed both as a liquefied pressurized gas and in precursor products. The latter include solid aluminum phosphide and magnesium phosphide, both of which generate phosphine upon contact with moisture, and zinc phosphide, which generates phosphine upon contact with stomach acid. In addition, phosphine is used in the manufacture of flame retardants, organophosphines and as a doping agent and precursor in the semiconductor industry. Finally, it is a by-product in the illicit synthesis of methamphetamine through the hydriodic acid / red phosphorus process.

As a pure gas, phosphine is reactive, flammable, colorless and odorless. In contrast, technical phosphine has a "fishy" or "garlicky" odor due to the presence of substituted phosphines and diphosphines. An odor threshold of 0.5 ppm has been established, though odor is not a reliable indicator of the presence of phosphine.

Exposure to phosphine can be lethal. While the mechanism of phosphine's toxicity is unclear, it is probably related to its nucleophilic and reducing capabilities, which damage macromolecules and inhibit electron transport at the cytochrome oxidase step. Oxygen is an important mediator of phosphine-induced toxicity. Histological damage to kidneys, liver and brain are consistent with an anoxic state in exposed tissues. Despite the availability of several inhalation toxicity studies of varying exposure periods on phosphine gas, the USEPA and DPR have waived requirements for future studies due to the severe acute toxicity of the compound. As a consequence, gaps exist in the toxicity database.

Illness and injury reports

Between 2005 and 2009, the State of California listed 10, 0 and 27 illness/injury cases associated with aluminum phosphide, magnesium phosphide and phosphine gas, respectively. Each of these incidences was described as definitely, probably or possibly caused by phosphine in the California Pesticide Illness Query (CalPIQ). Many of these cases are described in detail in the attached exposure assessment document.

Environmental fate

Air. Phosphine reacts with hydroxide radicals (HOx) in the air. The latter result from the chemical interaction between ozone (O_3) and water. The reaction rate increases with the presence of nitroxide (NOx) impurities. The half-life of phosphine in the presence of normative concentrations of HOx is 28 hr. However, this value decreases to 5 hr under sunny conditions due to the increase in HOx concentrations. Ultimately, phosphorus oxyacids and inorganic phosphate are produced and deposited. Complete disappearance of phosphine from sealed dry tubes occurred within 40 days.

Soil and water. The presence of moisture is a major factor in slowing the disappearance of phosphine from soils. This may occur through a depressed diffusion rate into the soil matrix. Thus 18 days were required for the disappearance of 1000 ppm phosphine from dry soil in tubes, while 40 days were required for moisture-saturated soils. Soil type also plays a role in this process. The solubility of phosphine in water at normal atmospheric pressure and temperature is 0.27 (v/v at 17°C).

Wildlife and food crops. Animals poisoned by exposure to phosphine gas do not leave toxic

residues in their carcasses. Persistence of phosphine is thus considered to be low in animals. Studies in which animals were fed fumigated commodities have generally failed to establish major effects. The WHO (1988) report concluded that “it is unlikely, therefore, that the use of phosphine or phosphides results in residues that are of any toxicological significance”. However, accidental poisoning of wildlife has been known to occur.

Pharmacokinetics

No pharmacokinetics data are available for review.

Hazard identification

Acute toxicity, humans. A multiplicity of suicide and accident reports confirmed the lethality of phosphine in humans. Sublethal exposure produces epigastric distress, hypotension, cardiovascular collapse, altered sensoria, vomiting, acidosis, hypotension, cardiac arrhythmia, jaundice, pulmonary crepitation, cough, dyspnea, chest tightness, headache, giddiness, numbness / paraesthesia, lethargy, irritability, anorexia, nausea, inappetence and dry mouth. Autopsy findings from accidental death investigations show pulmonary congestion with edema, changes associated with brain anoxia and necrosis among alveolar, myocardial and liver cells.

Acute toxicity, laboratory animals - inhalation. Exposure to phosphine gas generates acute effects in animals that include lassitude, ataxia, apnea, cardiovascular collapse and renal and pulmonary histopathology. The risk from acute exposure to phosphine gas was estimated using a critical NOEL of **5 ppm** (internal dose \approx 1.7 mg/kg) based on the deaths of 4/10 female rats (0/10 males) within 3 daily exposures to 10 ppm (6 hr/day, 5 days/wk). Other effects at 10 ppm included renal tubular necrosis and increased kidney weights. No adverse effects were noted either at 5 ppm (13 consecutive days of exposure) or at 3 ppm (13 weeks of exposure). Similar observations were made in several other studies. Confidence in the critical value was reinforced by the multi-day and multi-week exposure regimens, which are more likely than strictly acute regimens to result in toxicity.

Acute toxicity, laboratory animals - dermal. No dermal studies were available for review.

Subchronic toxicity, laboratory animals - inhalation. Subchronic toxicity was evaluated with a critical NOEL of **1 ppm** based on observations of palpebral closure (sleeping behavior, wk 4), slowed respiration (wks 8 and 13) and lowered body temperatures (wk 13) in rats at 3 ppm (6 hr/day, 5 days/wk).

Chronic toxicity laboratory animals - inhalation. Only one chronic study on phosphine gas was available for analysis. The NOEL for that study, 3 ppm (0.7 mg/kg/day), was the highest dose used in that study. Consequently, phosphine's chronic toxicity was evaluated using the critical subchronic NOEL of **1 ppm**.

Reproductive toxicity. No reproductive toxicity studies on phosphine were available for analysis.

Developmental toxicity. There were no developmental effects at any sublethal dose (*i.e.*, up to 4.9 ppm, but less than the study's lethal dose of 7 ppm) in one developmental study in CD rats. A rabbit developmental study was not submitted.

Genotoxicity. Epidemiologic studies on phosphine applicators were consistent with a clastogenic role for phosphine in human populations. A study in phosphine fumigators was negative for micronucleus formation. Studies in laboratory animals were inconsistent, though there was evidence for micronucleus induction in mouse splenic lymphocytes exposed over a 13-wk period and chromosome aberrations in Chinese hamster ovary cells exposed to phosphine in roller bottles.

Oncogenicity. There was no evidence for oncogenicity in a 2-year rat study on phosphine gas. A comparable mouse study was not available for review.

Toxicity of metabolites. Toxicity studies on phosphine metabolites were not available for review.

Risk calculations and appraisal

Many acute, seasonal and annual use scenarios produced MOEs of under 100, indicating insufficient health protection for workers and bystanders under those scenarios. Moreover, some acute MOEs for occupational bystanders were as low as 17, including those adjacent to farm bins, flat storage facilities or warehouses during fumigation or aeration. In addition, residential or occupational bystanders under most occupational scenarios showed MOEs of 50. Finally, MOEs of less than 10 were common for many seasonal and annual scenarios. In light of the severity of the acute endpoint (death) and the proximity of the critical acute and subchronic / chronic NOELs, these low MOEs are cause for concern and mitigation measures should be considered.

Reference doses (RfDs)

Acute RfC = Critical acute NOEL ÷ 100 = 5 ppm ÷ 100 = **0.05 ppm**

Seasonal RfC = Critical subchronic NOEL ÷ 100 = 1 ppm ÷ 100 = **0.01 ppm**

Annual RfC = Critical chronic NOEL ÷ 100 = 1 ppm ÷ 100 = **0.01 ppm**

Many exposure estimates from the various occupational scenarios exceed these reference doses, again emphasizing the need to develop mitigation measures.

II. INTRODUCTION

A. CHEMICAL IDENTIFICATION

Phosphine (PH_3) is a rodenticide and insecticide used to fumigate stored agricultural products such as grain, tobacco, processed foods and animal feed (Pepelko *et al.*, 2004). It is marketed both as a liquefied gas under pressure and in precursor products containing solid aluminum phosphide or magnesium phosphide, from which it evolves upon contact with moisture. Another formulation, the burrow fumigant zinc phosphide, produces phosphine upon contact with stomach acid. Formulations containing zinc phosphide were not considered for this document (see following section). Phosphine is also used in the manufacture of flame retardants, organophosphines and as a doping agent and precursor in the semiconductor industry (ATSDR, 2002; Pepelko *et al.*, 2004; Wikipedia, 2006). Finally, it is a by-product in the illicit synthesis of methamphetamine through the hydriodic acid / red phosphorus process (OEHHA, 2003).

As a pure gas, phosphine is highly reactive, flammable, colorless and odorless. A fire and/or explosion hazard exists where there is contact with air, oxygen, oxidizers, metal nitrates, halogens or other substances. Flammability and explosiveness are reduced in "good" commercial formulations of aluminum phosphide by inclusion of ~40% ammonium carbonate---this occurs through release of ammonia and carbon dioxide upon contact with moisture (Gehring *et al.*, 1991).

Unlike purified phosphine, technical phosphine has a "fishy" or "garlicky" odor due to the presence of substituted phosphines and diphosphines (USEPA, 1999). While an odor threshold of 0.5 ppm has been established, OEHHA (2003) stated that "[only] 10-50% of distracted individuals perceive warning of the threshold limit value (TLV) concentration (0.3 ppm). Therefore, odor is not an adequate indicator of the presence of phosphine and does not provide reliable warning of hazardous concentrations."

Exposure to phosphine can be lethal. While the mechanism of toxicity is unclear, it is probably related to its nucleophilic and reducing capabilities. According to Garry and Lyubimov (2001), the molecule "induces a cumulative biologic oxidant cascade involving progressive alteration of a number of critical biologic endpoints". For example, phosphine blocks oxidative metabolism, probably through inhibition of electron transport at the cytochrome oxidase step, making it useful for the fumigation of metabolically dormant products such as stored grains and seeds (Wikipedia, 2006). Other macromolecular targets of phosphine-mediated oxidative damage include hemoglobin, peroxidases / lipid peroxidation, catalase, cholinesterase and DNA. Thus it appears that oxygen is an important mediator of phosphine-induced toxicity (Garry and Lyubimov, 2001). Chaudry (1997) speculated that the organ congestion and histological damage to kidneys, liver and brain noted in Klimmer's studies were consistent with an anoxic state, supporting the requirement for oxygen in the observed toxicity.

B. REGULATORY HISTORY

The US Environmental Protection Agency first registered phosphine gas in 1999 to CYTEC Industries for use as an insecticide (USEPA, 1999). The product, ECO₂FUME, had several restrictions and riders attached to it, including: (1) designation as a Restricted Use Pesticide in recognition of the acute inhalation hazard, (2) establishment of an 8-hr TWA of 0.3 ppm as the maximum allowable exposure level for workers both during and after application (including for structure reentry), (3) requirement for the availability of respiratory protection at the application site, (4) posting of "Danger" signs on entrances to fumigated areas, (5) annual provision to local officials of safety information in the form of Material Safety Data Sheets, etc. (6) protection or removal of metallic materials from the fumigation area to avoid corrosion, and (7) inspection of structures before application to ensure that they are gas-tight. Food tolerances for phosphine residues were necessitated by the following practices: post-harvest fumigation with phosphine gas or with compounds that produce phosphine gas, preharvest treatment of pest burrows in agricultural and non-agricultural areas, and fumigation of processed foods and animal feed. These tolerances are found in 40 CFR §180.225.

Aluminum phosphide (AIP) and magnesium phosphide (Mg₂P₃) received federal registrations in 1958 and 1979, respectively. Pesticide Registration Standards followed for the two compounds in 1981 and 1982. USEPA instituted a data call-in associated with the Registration Standard for AIP, resulting in PR notice 84-5, which dealt with label development for both compounds. Two separate "Amended Reregistration Standard Process" documents were issued for both compounds in 1986 as a result of the 1981 data call-in. In December 1998, the US Environmental Protection Agency issued a combined Reregistration Eligibility Decision (RED) for AIP and Mg₂P₃ (USEPA, 1998). The toxicologic details of that document are summarized in Section V.D. below. USEPA concluded that neither the toxicity nor the exposure databases indicated a unique toxicologic hazard to fetuses or newborns, obviating the need for an additional FQPA safety factor. The likelihood of toxicologically significant exposure through the diet was considered low even when zinc phosphide was also considered, though projected occupational exposure to phosphine gas resulting from use of these compounds did result in several mitigation measures. Finally, with the exception of use of AIP and Mg₂P₃ as burrow fumigants, which pose a risk to several endangered species, neither compound was considered to threaten non-target organisms.

On November 15, 1986, the California Department of Food and Agriculture determined that no health effects data specified in the Birth Defect Prevention Act of 1984 (SB950) would be required for AIP (DPR, 1994). As stated by that directive, "Because of the known high acute toxicity of phosphine gas, the EPA [*i.e.*, the USEPA] has waived the requirement for additional acute toxicity data for aluminum phosphide when used as a pesticide. By the same token, no chronic testing with aluminum phosphide is considered feasible by EPA due to the extreme high toxicity of phosphine gas". Because Mg₂P₃ was grouped with AIP for testing purposes under SB950, this compound was included in the data exemption. Zinc phosphide was specifically excluded from this grouping because, in the language of a 1994 DPR memo, "As is well known, both aluminum and magnesium phosphides react with water or atmospheric moisture to yield phosphine, but zinc phosphide does not. In fact, it requires the rather more vigorous conditions of stomach acid to cause zinc phosphide to undergo the same reaction, thus its use as a bait toxicant, rather than as a fumigant". For this reason, consideration of possible health effects stemming from zinc phosphide usage is not included in the present risk characterization document. DPR later grouped phosphine with AIP for testing under SB950 (DPR, 2000),

effectively exempting it from SB950 data requirements along with AIP and Mg_2P_3 .

Phosphine was listed by the USEPA under the Clean Air Act (1990 amendment) as a Hazardous Air Pollutant (HAP). It is also considered to be an Extremely Hazardous Substance (EHS) subject to the release reporting requirements under CERCLA section 103 and 40 CFR parts 302 and 355 when stored in amounts greater than its Threshold Planning Quantity (TPQ) of 500 lb. Notification to the National Response Center (NRC) is mandated immediately upon release of 100 lb or more. As a waste product, phosphine, including containers, inner liners, residues, contaminated soil, water or other debris, must be managed according to federal and/or state hazardous waste regulations. Phosphine and phosphine-generating pesticides are listed as Toxic Air Contaminants under Title 3 of the California Code of Regulations (Division 6, Chapter 4, Subchapter 2, Article 1-6860).

The following regulatory exposure limits are in effect for phosphine (*cf.*, Garry and Lyubimov, 2001 and DPR, 2012):

- NIOSH Recommended Exposure Level (REL): TWA 0.3 ppm (0.4 mg/m³)
- NIOSH Short Term Exposure Level (STEL): 1 ppm (1.4 mg/m³)
- NIOSH revised Immediately Dangerous to Health or Life (IDHL): 50 ppm
- OSHA Permissible Exposure Limit (PEL): TWA 0.3 ppm (0.4 mg/m³)
- 1993-1994 ACGIH Threshold Limit Value (TLV): TWA 0.3 ppm (0.42 mg/m³)
- 1993-1994 ACGIH STEL: 1 ppm (1.4 mg/m³)
- OEHHA chronic reference exposure level: 0.0006 ppm (0.0008 mg/m³)

ACGIH based both the 0.3 ppm TLV and the 1 ppm STEL on a report by Jones *et al.* (1964) which noted "symptoms such as diarrhea, nausea and vomiting, tightness of chest and cough, headache, and dizziness in a number of workers exposed intermittently to phosphine at concentrations up to 35 ppm, but averaging below 10 ppm in most cases" (ACGIH, 2001). However, O'Malley *et al.* (in press) argued that since "most of the phosphine measurements reported were area samples...it was difficult to identify the level of exposure associated with individual cases of illness and consequently difficult to identify levels of exposure that were tolerated without symptoms."

C. TECHNICAL AND PRODUCT FORMULATIONS

As of May 2008 there were 2 products containing phosphine registered in California (DPR database). In addition, there were 18 products containing aluminum phosphide and 5 products containing magnesium phosphide.

D. USAGE

Agricultural use rates for phosphine and phosphine-generating compounds in California over the 2001-2010 period are found in Table II-1. These data were gathered from the Pesticide Use Report (PUR) (<http://www.cdpr.ca.gov/docs/pur/purmain.htm>), a database maintained by the Department of Pesticide Regulation. According to the explanatory wording attached to the PUR, "...all agricultural pesticide use [in the state] must be reported monthly to the county agricultural commissioner, who in turn, reports the data to DPR. California has a broad legal definition of

"agricultural use," so the reporting requirements include pesticide applications to parks, golf courses, cemeteries, rangeland, pastures, and along roadside and railroad rights-of-way. In addition, all postharvest pesticide treatments of agricultural commodities must be reported, along with all pesticide treatments in poultry and fish production, as well as some livestock applications. The primary exceptions to the full use reporting requirements are home and garden use and most industrial and institutional uses."

Application rates for phosphine gas increased every year between 2001 and 2008. The particularly large increase in 2008 may reflect attempts to use phosphine as a replacement fumigant. Aluminum phosphide had the greatest agricultural use of all the phosphine-generating compounds throughout this period, peaking at 165,218 pounds in 2002. Magnesium phosphide use increased after 2004, reaching its highest rate in 2010 at 12,232 pounds. Zinc phosphide peaked in 2006 (3794 pounds), with the exception of 2009, when the rate rose precipitously to 20,898 pounds, falling back to 1702 lb in 2010.

These agricultural statistics do not provide a complete picture of phosphine use in California. The reason for this is that the PUR does not include home, urban-commercial, industrial and other non-agricultural use scenarios. To appreciate the extent of those usages, records for total pounds of active ingredient sold in the state over the same period are also summarized in Table II-1 ¹. Sales values include both agricultural and non-agricultural uses. As might be expected from the PUR records, aluminum phosphide dominated sales in the state over the 2001-2010 period, ranging between 166,173 and 237,785 lb/yr. Zinc phosphide sales ranged between 6429 and 17,024 lb/yr. Phosphine and magnesium phosphide sales, for which records were available only after 2002, ranged between 3212 - 36,683 and 5968 - 11,127 lb/yr, respectively.

Recognizing the possible sources of error in the sales reporting—including duplications in reporting due to sales between registrants and sales of product not completely used during that particular year—the ratio of agricultural-to-non-agricultural (*i.e.*, as defined by the PUR) other uses can be calculated (Table II-1). For aluminum phosphide, the ratio fell between 60% and 85% (thus 15% - 40% may have been used non-agriculturally through this period). The ratios for zinc phosphide and magnesium phosphide were 11% - 157% ² and 38% - 108%, respectively. 11-97% of phosphine gas was directed toward agricultural purposes, except for 2008, which showed 345% ².

¹ These records are accessible through the Department of Pesticide Regulation sales database at <http://www.cdpr.ca.gov/docs/mlassess/nopdsold.htm>.

² The reasons for the much higher amount of pesticide applied agriculturally than pesticide sold are not understood, though as noted in the text, they may reflect previous unrecorded sales within the state of California.

Table II-1. Agricultural use and total sales of phosphine-generating products in California (pounds applied^a or sold per year^b)

Compound	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Phosphine										
•ag use	44	901	1141	1664	2688	2774	5262	48,243	29,527	11,261
•lbs. sold	nr	nr	9,944	3,662	3,599	3,212	4,231	14,000	36,683	11,585
•percent	na	na	11%	45%	75%	86%	124%	345%	80%	97%
Aluminum phosphide										
•ag use	99,856	169,218	119,512	131,303	135,751	150,555	104,840	132,296	108,083	106,370
•lbs. sold	166,173	211,783	197,893	237,785	228,086	176,779	172,987	216,880	188,209	220,498
•percent	60%	80%	60%	55%	60%	85%	61%	61%	57%	48%
Magnesium phosphide										
•ag use	2492	4824	2844	2621	3156	3931	4984	10,507	8009	12,232
•lbs. sold	nr	nr	5,968	6,875	6,990	8,022	8,475	9,714	8,991	11,127
•percent	na	na	48%	38%	45%	49%	59%	108%	89%	110%
Zinc phosphide^c										
•ag use	1116	981	1253	1924	2371	3794	3215	1299	20,898	1702
•lbs. sold	6,429	9,151	8,240	17,024	12,361	13,661	11,271	10,424	13,270	22,461
•percent	17%	11%	15%	11%	19%	28%	29%	12%	157%	8%

Abbreviations: nr: not reported (either because phosphine did not achieve federal registration until 1999 or because sales figures were not available); na: not applicable

^a Data on agricultural use per year are from the Dept. of Pesticide Regulation's Pesticide Use Report: <http://www.cdpr.ca.gov/docs/pur/purmain.htm>

^b Data on quantities sold per year of from the Dept. of Pesticide Regulation's Report of Pesticide Sold: <http://www.cdpr.ca.gov/docs/mlsassess/nopdsold.htm>

^c Zinc phosphide was included in this table for informational purposes only; toxicity deriving for exposure to zinc phosphide was not considered in the risk assessment.

E. ILLNESS REPORTS

Between 2005 and 2009, 10, 0 and 27 illness/injury cases associated with aluminum phosphide, magnesium phosphide and phosphine gas, respectively, were reported to the State of California. Each of these incidences was described as definitely, probably or possibly caused by phosphine in the California Pesticide Illness Query (CalPIQ). Many of these cases are described in detail in the attached exposure assessment document (DPR, 2012).

F. PHYSICO-CHEMICAL AND ENVIRONMENTAL PROPERTIES

Table II-2. Physico-chemical and environmental properties of phosphine ³

Chemical names	Phosphane, phosphoretted hydrogen, phosphorus hydride, phosphorus trihydride, phosamine
CAS registry number	7803-51-2
Molecular weight	34.00 g/mol
Molecular formula	PH ₃
Conversion factor	1.39 mg/m ³ per ppm @ 25°C ^a
Physical state	Colorless gas
Melting point	-132.5°C ^b ; -133.8°C ^c
Boiling point	-87.5°C ^b ; -87.75°C ^c
Density	<i>absolute:</i> 1.529 g/L (0°C) ^b ; 1.390 g/L (temp. not reported) ^c <i>relative to air:</i> 1.17 @ 25°C (1 atm) ^a ; 1.184 @ 25°C (1 atm) ^d ; 1.5 @ 20°C (1 atm) ^e
Solubility in water	2.5 ml gas in 100 ml @ 20°C (3.5 mg / 100 ml) ^f
Solubility in organic solvents	soluble in alcohol, ether and cyclohexanol ^d
Vapor pressure	20 atm @ -3°C ^a ; 41.3 atm @ 20°C ^h ; 40 atm @ -129.4°C ^e
Octanol-water partition coefficient (log K_{ow})	-0.27 ^f
Henry's Law constant	123.46 atm·m ³ /mol ^g
Air half-life	5 hr (light); 28 hr (dark) ^e

^a OEHHA (2002)

^b Lewis (1996)

^c Lide (2008)

^d Omae *et al.* (1996)

^e USEPA (1999)

^f Pepelko *et al.* (2004)

^g Wilhelm *et al.* (1977)

^h Braker & Mossman (1980)

³ Physico-chemical properties of aluminum phosphide and magnesium phosphide are included in the exposure assessment document (DPR, 2012).

G. ENVIRONMENTAL FATE

The following environmental fate sections are, except where noted, summarized from a review of phosphine by the World Health Organization (WHO, 1988). References to original studies are found in that document. A more complete treatment conducted by Parakrama Gurusinge of the Department of Pesticide Regulation appears below in Appendix I.

1. Air

Phosphine reacts most importantly with hydroxide radicals (HOx) in the air. HOx are the products of the chemical reaction of ozone (O₃) and water. The reaction rate increases with the presence of nitroxide (NOx) impurities. The following reactions of phosphine with HOx are thought to occur rapidly:



The half-life of phosphine in the presence of normative concentrations of HOx is 28 hr. However, this value may decrease to 5 hr under sunny conditions due to the increase in HOx concentrations. Ultimately, phosphorus oxyacids and inorganic phosphate are produced and deposited. Complete disappearance of phosphine from sealed dry tubes occurred within 40 days.

2. Soil and water

The presence of moisture is a major factor slowing the disappearance of phosphine from soils. This probably occurs through a depressed diffusion rate into the soil matrix. Thus 18 days were required for the disappearance of 1000 ppm phosphine from dry soil in tubes, while 40 days were required for moisture-saturated soils. Soil type also plays a role in this process. According to the appended DPR report, "Environmental Fate of Phosphine" (Parakrama Gurusinge, Environmental Monitoring Branch, California Dept. of Pesticide Regulation), the solubility of phosphine in water at normal atmospheric pressure and temperature is 0.27 (v/v at 17°C).

3. Wildlife and food crops

Animals poisoned by exposure to phosphine gas do not leave toxic residues in their carcasses. Studies in which animals were fed fumigated commodities have generally failed to establish major effects. The WHO (1988) report concluded that "it is unlikely, therefore, that the use of phosphine or phosphides results in residues that are of any toxicological significance". However, accidental poisoning of wildlife has been known to occur.

III. TOXICOLOGY PROFILE

A. PHARMACOKINETICS

No guideline pharmacokinetic studies were performed with phosphine or with any of the precursor compounds (aluminum phosphide, magnesium phosphide or zinc phosphide). Consequently, there is little understanding of the absorption, distribution, metabolism or excretion of this chemical in mammals. In a review of phosphine toxicity, Gehring *et al.* (1991) stated that (1) phosphine is absorbed through the gastrointestinal tract following ingestion of aluminum phosphide or zinc phosphide, (2) the wide range of tissue effects are evidence of wide tissue distribution, (3) pulmonary excretion occurs regardless of route of absorption, and (4) the effectiveness of gas masks in preventing toxicity implies that little phosphine is absorbed through the skin.

One brief study on the fate of phosphine in insects (*Tribolium confusum*, the Confused Flour Beetle) is available (Robinson and Bond, 1970). After exposure to $^{32}\text{P}\text{H}_3$ at 0.55 mg/L (5 hr), 6.9 mg/L (0.5 hr) or 12.8 mg/L (5 hr), the beetles were homogenized and cell fractions isolated. 82-93% of the ^{32}P was localized in the "cell sap", with much smaller fractions in mitochondria (1-5%), microsomes (0.02-0.08%) and cell walls / nuclei, etc. (1-3%). The label was associated with pyrophosphate, ortho-phosphate, (hypo)phosphite and other unidentified molecules. Parent phosphine appeared to be completely degraded. There was no attempt to follow the organ distribution or excretion patterns in this species.

B. ACUTE TOXICITY

1. Overview

Because of the USEPA data waiver and DPR concurrence (see section II.B above), requirements for toxicity studies on phosphine, aluminum phosphide and magnesium phosphide were waived. Nonetheless, several recent inhalation toxicity studies on phosphine, including acute, subchronic and chronic studies, were available. These, along with several older studies from the open literature, provided information on phosphine's toxicity. Summaries of the original reviews conducted by the Medical Toxicology Branch of the Department of Pesticide Regulation appear below in Appendix II.

The following section reviews what is known of phosphine's acute toxicity to humans, both from accidental and deliberate exposures. Section 3 provides detailed summaries of the laboratory animal studies on phosphine

2. Human exposures (accidental, occupational and suicidal)

In view of phosphine's lethality, it is to be expected that no laboratory studies were conducted on humans. Nonetheless, information on the consequences of phosphine exposure was forthcoming from investigations of suicides and suicide attempts using oral aluminum phosphide and from investigations of accidental inhalation exposures to phosphine gas under both occupational and non-occupational scenarios.

Bajaj and Wasir (1989) commented that suicide by AIP ingestion was "the single most frequent suicidal method in northern India", perhaps surpassing the number of deaths that occurred in the Bhopal methylisocyanate tragedy. The rise in Indian AIP-mediated suicide attempts was attributed to a combination of poor economic prospects and easy access to the compound (Siwach *et al.*, 1988). Examination by Chugh *et al.* (1991) of a single hospital cohort in Rohtak, India, revealed a precipitous rise in AIP-mediated illness during the 1980s, from 0.06 per 1000 admissions in 1981 to 5.1 per 1000 admissions in 1987; 70.6% of those admissions were considered suicidal, 77.2% were fatal. The lethality of even a single 3-gram tablet of Celphos® containing 56% AIP, which liberates 1 gram of phosphine gas, was attested to by the reported estimated lethal dose of 0.1 g AIP per 70-kg person, equivalent to about 1.4 mg/kg (Chugh *et al.*, 1991⁴). For comparison, two oral studies of aluminum phosphide toxicity in rats and rabbits analyzed for this document identified LD₅₀s between 8 and 15 mg/kg (Batra *et al.*, 1994; Okolie *et al.*, 2004).

A review by Garry and Lyubimov (2001) described toxic signs in humans resulting from phosphine exposures as follows: "Rapid onset of epigastric distress, hypotension, cardiovascular collapse, and death are a recurrent pattern. In those who reach a hospital, altered sensoria, vomiting, severe acidosis, hypotension, cardiac arrhythmia, jaundice, and pulmonary crepitation were common occurrences." They cited autopsy findings from accidental death investigations which show "microscopic pulmonary congestion with edema and alveolar cell necrosis, individual myocardial cell and liver cell necrosis, and anoxic changes in the brain."

In contrast to AIP oral exposures, where the internal dose of phosphine was inferred from the

⁴ The value of 0.1 g AIP per 70-kg person should be viewed with caution, as its origin was unclear in Chugh's report.

number of tablets ingested and where effects were partly due to gastrointestinal absorption, it was difficult to discern from epidemiologic studies or incident reports the precise air concentrations of phosphine gas that threaten humans. Time of exposure, a critical factor in the acute toxicity of phosphine, is also difficult to characterize. A review by Childs and Coates (1971) quoted a 1937 reference from the German literature that listed environmental phosphine as "rapidly fatal" to humans after exposure to 2000 ppm (2800 mg/m³), with death occurring within 1/2 - 1 hr of exposure to 400 - 600 ppm (560 - 840 mg/m³). The gas was considered "dangerous to life" after 1/2 - 1 hr at 290 - 400 ppm (400 - 600 mg/m³), but not causing "serious effects" at 100-190 ppm. Finally, they claimed phosphine can cause serious adverse effects after several hours at 7 ppm (10 mg/m³), a level not appreciably different from the effect levels noted in several rodent studies reviewed for this document.

Two incidents resulting in the deaths of children after phosphine gas exposure are summarized here: (1) Thirty-two of 35 people aboard a Greek freighter were sickened and a 2-yr-old child killed in 1978 when phosphine gas evolving from AIP applied to grain in a cargo hold leaked into human-frequented areas of the ship (Wilson *et al.*, 1980). Air analysis conducted six days after the application by NIOSH, the US Coast Guard, the USDA and AIP manufacturers found phosphine concentrations in the 20-30 ppm range in a "void space of the main deck adjacent to the air intake system for ventilation amidships. In addition, substantial phosphine leakage (7.5 - 10 ppm) was noted around hatch No. 3 on the forward deck and at an air intake ventilator aft of the main house (12 ppm). Levels of 0.5 ppm of phosphine gas were measured in some of the living quarters amidships." There was no discussion of the elapsed exposure time, though illness was evident in about half the crew within two days of the beginning of fumigation. (2) Heyndrickx *et al.* (1976) investigated the deaths of two children, ages two and four years, who succumbed within 18 hours of playing on top of a load of wheat on a river transport vessel. The wheat had been treated with aluminum phosphide, pyrethrum and malathion, though causative roles for the latter two chemicals were ruled out. Phosphine was implicated mainly on the evidence of measurements carried out two days after the incident which established a concentration of 1 ppm at several places over the surface of the wheat. The concentration of phosphine at the time the children were playing was unknown.

In an early occupational exposure study, Jones *et al.* (1964) documented phosphine-induced symptomatology among 67 workers at a wheat storage terminal in Australia where aluminum phosphide was used as a fumigant (no demographic characteristics were reported for this cohort). Air concentrations of phosphine ranged between non-detectable and 35 ppm. Employees were provided with respirators, though most wore them only when there was a strong odor. No ameliorating effect of the respirators was observed. Symptoms, which occurred either immediately upon exposure or up to two days later, included diarrhea (82% incidence), nausea (73%), epigastric pain (65%), vomiting (29%), chest tightness (52%), breathlessness (34%), chest pain (29%), palpitations (27%), severe retrosternal pain (6%), headache (83%), dizziness (35%) and staggered gait (12%).

Misra *et al.* (1988) investigated phosphine-induced toxicity in workers at an Indian facility where stacks of bagged grain were treated with aluminum phosphide tablets. Upon completion of the 20-30-min distribution task, the workers (n=22; no personal protective equipment; age range 24-60 yr; mean duration of exposure 11.1 yr; 68% smokers, 50% alcohol consumers) were subjected to clinical exams. Neurological tests for motor and sensory conduction were carried out the following morning. Exposure monitoring in the breathing zone was carried out during tablet placement, as well as when the grain stacks were covered with plastic and when those

covers were sealed. The following symptoms were detected: cough (18.2% incidence), dyspnea (31.8%), tightness around chest (27.3%), headache (31.8%), giddiness (13.6%), numbness / paraesthesia (13.6%), lethargy (13.6%), irritability (9.1%), anorexia (18.2%), epigastric pain (18.2%), nausea (9.1%) and dry mouth (13.6%). Other symptoms included a bad taste in the mouth and loss of appetite. Neurological testing did not reveal remarkable or clearly phosphine-generated signs. Breathing zone phosphine concentrations ranged between 0.17 and 2.11 ppm, though no attempt to correlate symptoms with exposure dose was reported.

3. Laboratory animal studies

a. Inhalation toxicity

Garry and Lyubimov (2001) cited O.R. Klimmer's work published in German documenting lassitude, ataxia, apnea and cardiovascular collapse in laboratory animals exposed to phosphine. Death occurred within 0.5 hr at high air concentrations (>360 ppm) and at 12-15 hours at concentrations of 10 ppm and slightly below. Contemporary studies summarized below indicate that the threshold for lethality occurred at or above 5 ppm and was time dependent.

Waritz and Brown (1975) exposed male CD rats to phosphine gas, phenylphosphine gas or nebulized triphenylphosphine in 18-L glass chambers. Exposures were acute (4 hours) and subacute (4 hours daily for up to 12 days). Subacute animals were also exposed to control atmospheres during a 2-wk recovery period. Six animals per exposure condition were used in both the acute and subacute phases. The individual acute doses were analyzed by colorimetric phosphate determination after H₂SO₄ scrubbing and perchloric acid digestion (phosphine); by gas chromatography and phosphorus detection by flame ionization (phenylphosphine); and by direct colorimetry (triphenylphosphine). Gross pathology was performed on all rats after acute exposure. Histopathology was performed on two rats in each of the following acute scenarios: 14 days after exposure to 0.8 µM/L (20 ppm) phosphine; one, two and seven days after exposure to 0.78 µM/L (19 ppm) phenylphosphine; 14 days after exposure to 0.8 µM/L (44 ppm) phenylphosphine; one, two and seven days after exposure to 19.1 µM/L (5 mg/L) triphenylphosphine; 14 days after exposure to 6.5 µM/L (1.7 mg/L - units of ppm were not used for the latter compound because it was not a gas) triphenylphosphine. In addition, two rats dying after exposure to 1.31 µM/L (32 ppm) phenylphosphine were also subjected to histopathology. Gross pathology and histopathology were performed on three test and three control animals both immediately after the final subacute exposure and 14 days after that exposure.

Acute toxicity. The acute 4-hr LC₅₀ for phosphine was 11 (95% confidence limits: 8.1-15) ppm, equivalent to 15 µg/L or 0.44 µM/L; for phenylphosphine this value was 38 (31-47) ppm, equivalent to 171 µg/L or 1.56 µM/L; for triphenylphosphine this value was 12.5x10³ (8.6-18.2) µg/L, equivalent to 47.8 µM/L. Clinical signs for all three compounds were similar at dose levels of "comparable toxicity" and were considered by the authors to be "typical of respiratory irritation - red ears, salivation, lacrimation, facepawing and dyspnea". Gross and histopathologic examinations were negative for all three compounds.

Subacute toxicity. The mean subacute exposure concentration for phosphine was 0.163 µM/L (~4.0 ppm), or about one-third of the acute LC₅₀. The mean subacute concentrations for phenylphosphine and triphenylphosphine were 0.31 µM/L (~7.6 ppm) and 9.32 µM/L, respectively, both about one-fifth of their respective acute LC₅₀s. Clinical signs for all three compounds "were again those typical of mild respiratory irritation - lacrimation, salivation, dyspnea, red ears." Piloerection was observed during and after the fourth phosphine exposure, dermatitis around the mouth and feet after the final phenylphosphine exposure, and brownish

discolored fur during the second week of triphenylphosphine exposures. After 12 days of phosphine exposure, the test animals weighed about 67% of controls (data were portrayed graphically; precise bodyweight values were not provided), with the 2-wk recovery period not appreciatively changing the slowed weight gain rate of the exposed animals compared to controls. Weight gains were more severely impacted by the phenylphosphine exposure---after the 12-day exposure, the exposed animals weighed approximately 26% of controls, though they resumed a normal-appearing weight gain rate by 15 days. Triphenylphosphine-exposed animals were less affected, with body weights registering at about 75% of controls at the end of the exposure period, reinstating gains at control rates thereafter. As with the acute exposures, gross and histopathologic exams did not reveal abnormalities in the phosphine or triphenylphosphine exposed animals. Foci of RBC formation were noted in the spleens of phenylphosphine-treated animals even after the 2-wk recovery period, though no effects on bone marrow were observed. In addition, there was a mild depression of spermatogenesis in these animals. On the basis of the pathologic analyses and the severe curtailment of weight gain rate, the authors considered that only phenylphosphine induced cumulative effects. Thus the order of acute toxicity---phosphine > phenylphosphine > triphenylphosphine---may not be a good indicator of cumulative toxicity.

Neither an acute NOEL nor acute LOEL was determined for phosphine in this study due to a lack of dose-related information. A subacute LOEL of 4.0 ppm for phosphine based on clinical signs and body weight gain decrements was established. Because it was the only dose tested, a subacute NOEL was not determined⁵. This study was considered supplemental⁶.

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Shimizu *et al.* (1982) exposed CD rats, 10/sex/dose, to phosphine gas using whole body

⁵ Since the critical inhalation endpoint values in this document are expressed as air concentrations (ppm), internal doses were not calculated for most studies. Nonetheless, such doses can be estimated. For this study, such an estimation would be based on the following assumptions: (1) a default absorption factor of 1, and (2) a default rat breathing rate of 40 L/kg/hr (DPR / Medical Toxicology Risk Assessment Handbook). The internal dose LOEL of 0.9 mg/kg/day resulted from the following calculation:

$$\begin{aligned} & \textit{To convert ppm to mg/L:} \\ & \text{MW [=34 g/M]} \div \text{molar volume [=24.4 L @ 25°C]} = 1.4 \text{ g/L} \\ & 1.4 \text{ g/L} \times (4 \text{ ppm} \times 10^{-6}) = 0.0056 \text{ mg/L} \end{aligned}$$

$$\begin{aligned} & \textit{To convert mg/L to mg/kg:} \\ & 0.0056 \text{ mg/L} \times \text{absorption factor [=1]} \times 40 \text{ L/kg/hr} \times 4 \text{ hr} = 0.9 \text{ mg/kg/day} \end{aligned}$$

⁶ This risk characterization document contains technical references to the acceptability, non-acceptability or supplemental quality of the studies used to gauge risk. These designations refer to each study's status with regard to guidelines established through the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). In this context, a "supplemental" designation indicates that the work was not done using those guidelines. It should be emphasized that DPR does not necessarily base its judgement of the usefulness of a study for risk assessment purposes on the FIFRA designation. More to the point, a supplemental or unacceptable study can play an important or even critical role in the ultimate risk characterization.

inhalation chambers. The gas was generated by addition of water to magnesium phosphide (Mg_2P_3 purity, 89%) inside the chamber. Phosphine levels were determined using Kitagawa gas detector tubes and Dräger-Kag detector tubes. Dose levels, which were based on a pilot study, were 0, 150, 165, 182, 200, 220 and 242 ppm. Exposure was for 1 hour. Observations were made during the exposure period and daily thereafter for 14 days. Bodyweights were determined immediately before and immediately after exposure, and on post exposure days 1-7, 9, 11, and 14. Gross necropsies were performed after death or terminal sacrifice at two weeks.

Mortality at increasing phosphine concentrations was 0/10, 0/10, 0/10, 1/10, 4/10, 8/10 and 10/10 in males (1-hr LC_{50} = 204 [195-213] ppm) and 0/10, 0/10, 3/10, 6/10, 10/10, 8/10 and 10/10 in females (1-hr LC_{50} = 179 [170-188] ppm). All deaths occurred from just prior to the end of exposure through 7 hours following the end of exposure. Common observations included tonic convulsions, sudden running about and death in a prone position. Food consumption in both sexes was diminished for the first day, but returned to normal by day 2. Mean bodyweights were reduced in the 220 ppm group on day 1, returning to normal gain rates thereafter (no 242 ppm animals survived to the day 1 bodyweight determination). Necropsies did not reveal abnormalities.

A NOEL was not determined in this study as the observations were not presented in sufficient detail. The study was considered unacceptable due to a lack of information regarding the gas sampling methodology.

Newton (1989) administered phosphine gas in whole body inhalation chambers to Fischer 344 rats, 15/sex/dose, at analytical doses of 0 (room air controls), 2.4, 4.9 and 11 ppm. Chamber atmospheres were supplied from a tank containing 1.06% phosphine in nitrogen. The exposure period was 6 hours. In-life observations were performed immediately prior to exposure, at 15-min intervals during exposure and on days 7 and 14 following exposure. Body weights were determined on test days 1, 8 and 15. Complete post mortem exams were carried out following terminal sacrifice on day 15. Histopathology was performed only on brain, heart, kidney, liver and lungs, and only on 5/sex on the day of exposure.

There were neither deaths nor definitive clinical signs throughout the study. Some animals in all treatment groups evidenced red or mucoid nasal discharge, though dose response was not apparent and most had no abnormalities. Bodyweights were not affected. Gross pathology and histopathology also failed to reveal treatment-related findings.

Based on the lack of definitive effects at all doses, a NOEL of 11 ppm was assigned. The study was considered to be supplemental.

Newton (1991) exposed Sprague-Dawley rats to phosphine gas in whole-body chambers in two studies. Study 1: 5 rats/sex/group were exposed for 6 hr to analytically determined phosphine concentrations of 0, 1.3, 6.0 or 28 ppm (0, 0.002, 0.008 or 0.039 mg/L at ambient temperature and pressure). Study 2: 10 males/group were exposed for 6 hr to analytically determined concentrations of 0, 3.1, 10 or 18 ppm (0, 0.004, 0.014 or 0.025 mg/L). Chamber atmospheres were supplied from a tank containing 1% phosphine in nitrogen. Body weights and clinical signs were recorded in both studies. Blood was drawn from the orbital sinuses at the end of exposure in study 2 and analyzed for hemoglobin, hematocrit, RBC count and Heinz bodies. All surviving animals were sacrificed on day 2, one day after the exposure.

Mortalities were reported only at the high dose - 28 ppm / 0.039 mg/L - in the first study: 3/5 males and 2/5 females (there were no mortalities in study 2). Clinical signs at that dose included hunched appearance, coarse tremors, decreased activity and coldness to touch. Dry

rales were noted at 18 ppm in study 2. Mean body weights decreased over the 24-hr post exposure period in both sexes at 28 ppm (♂: from 249±8 to 246±5 g; ♀: from 199±6 to 180±7 g) and in males at 10 ppm (from 229±7 to 227±11 g) and 18 ppm (from 230±7 to 219±8 g) (females were not tested at the latter two doses). The mean hemoglobin concentration, hematocrit and RBC count increased in a dose responsive and statistically significant manner at 10 and 18 ppm (blood parameters were not analyzed at 28 ppm). Heinz bodies⁷ were not detected at any exposure concentration. The toxicologic significance of the blood observations was not known.

Because the LD₅₀ of 0.039 mg/L was lower than 0.05 mg/L, phosphine qualifies as a Toxicity Category I inhalation hazard. An acute NOEL of 6 ppm was set in this study based on the body weight decreases at 10, 18 and 28 ppm. This study was considered to be supplemental.

Morgan *et al.* (1995) studied the responses of Fischer 344 rats and B6C3F1 mice to phosphine gas in two separate studies. The first, a 4-day study, is summarized in the following paragraphs. The second, a 14-day study, is summarized in section III.C.2 (Subchronic Toxicity).

The mean chamber concentrations for the 4-day study were 0, 1.05, 4.98 and 10.05 ppm phosphine (nominal: 0, 1, 5 and 10 ppm). Chamber concentrations were determined by gas chromatography. Exposures were for 6 hr/day, utilizing 5 male rats/dose and 10 male mice/dose. An additional 10 mice were exposed at the high dose because of the expected mortality. Multiple animals were present in each exposure chamber.

Responses were limited to the 10 ppm dose group, as follows. All rats died after 2-3 exposures; all mice were in moribund condition by the end of the fourth exposure. No clear cause of death was established. Hematologic indices were not statistically altered in 1- and 5-ppm rats; mortality precluded clinical pathology measurements in high dose rats. At 10 ppm, mice were anemic (reduced RBC, WBC, platelet, lymphocyte, monocyte and eosinophil counts, as well as reduced hemoglobin and hematocrit). Clinical chemistry findings included large increases in alanine amino transferase (23-fold over air-exposed controls; p<0.05; consistent with liver damage), sorbitol dehydrogenase (15-fold; p<0.05; consistent with kidney damage), and blood urea nitrogen (19-fold; p<0.05). Hemoglobin banding patterns were unaffected in the 10 ppm mice. Methemoglobin levels also did not show statistically significant effects in rats or mice. The 10 ppm mice had "minimal to mild degeneration and necrosis of the renal tubular epithelium... limited to tubules in the renal cortex and outer medulla". Mice with mild kidney lesions showed tubular necrosis along with "minimal to mild subcapsular foci of hemorrhage and necrosis in the liver." The mildness of the kidney and liver lesions suggested that they were not the cause of the observed mortalities. Finally, the moribund mice exhibited "myocardial degeneration and focal mineralization of cardiac muscle fibers." Assays of blood, kidney, liver and lungs of 10 ppm mice failed to detect acid-labile phosphine.

These data were consistent with a 4-day inhalation NOEL of 4.98 ppm for both rats and mice. In rats this was based on mortality at a LOEL of 10.05 ppm. In mice this was based on mortality, anemia, clinical chemistry findings, renal tubular necrosis, hepatic hemorrhage / necrosis and myocardial degeneration at a LOEL of 10.05 ppm.

It was concluded that (1) only exposures approaching the acutely lethal range elicited

⁷ Heinz bodies: "coccoid inclusion bodies resulting from oxidative injury to and precipitation of hemoglobin, seen in the presence of certain abnormal hemoglobins and erythrocytes with enzyme deficiencies" (Dorland's Illustrated Medical Dictionary, 1985, 26th edition, page 180).

toxic responses, and (2) no specific target organ could be identified. The authors speculated based on previous metabolic studies that phosphine may act as an inhibitor of oxidative phosphorylation. This study was considered to be supplemental.

Omae *et al.* (1996) studied acute and subacute responses to phosphine gas in male ICR mice in whole-body chambers. The acute aspects of this study are summarized here. The subacute aspects are summarized below in section III.C.2a. Phosphine concentrations were determined by gas chromatography in samples drawn every 12 minutes. In 1-hr and 4-hr LC₅₀ studies, the animals were observed for two weeks following exposure. In other acute studies, animals were anaesthetized three days after exposure and blood drawn for biochemical and hematologic determinations. In addition, the major organs were removed, weighed, fixed and examined histologically. The sciatic nerve, skull and femoral bone were also removed for histology. The right testis was fixed and stained, while the left testis was frozen in liquid nitrogen for sperm enumeration.

The mortality curve for the 1-hr LC₅₀ study was: 17.2±1.3 ppm (0/10), 25.1±0.9 ppm (0/10), 31.7±1.4 ppm (0/10), 41.6±1.4 ppm (0/10) and 59.2±2.0 ppm (0/10), resulting in a 1-hr LC₅₀ of >59.2 ppm. The mortality curve for the 4-hr LC₅₀ study was: 22.5±3.8 ppm (0/10), 26.5±2.4 ppm (0/10), 33.4±2.6 ppm (10/10), 45.5±4.0 (10/10) and 66.9±5.0 ppm (10/10), resulting in an LC₅₀ between 26.5 and 33.4 ppm. All mice in the 4-hr study died within 12 hours of exposure at 66.9 ppm, within 2 days at 45.5 ppm and within 3 days at 33.4 ppm. The slope of the 4-hr mortality curve was extremely steep.

Behavioral changes observed both in the 1-hr and 4-hr studies included face washing movements and high physical activity during the exposure period at all doses. However, no effects were noted following the exposure period in the 1-hr study. The 4-hr study also included the following additional observations: at 45.5 ppm and above there was complete loss of spontaneous motor activity, ocular cloudiness and moribundity after exposure; at 33.4 ppm and above the mice reacted more slowly to tapping the exposure chamber wall after 3 hours of exposure, while after completion of the exposure period there was piloerection and mild loss of spontaneous motor activity; at 22.5 ppm and above, slight tremor and piloerection were noted after exposure.

In addition to the studies described above, animals were exposed at 23.9-24.9 ppm for time periods of 1, 2, 4 or 8 hr. All animals exposed for 1, 2 or 4 hours survived, while all those exposed for 8 hours died (4/10 before the completion of exposure, 6/10 between the completion of exposure and day 3). The cause of death was not discerned, though the authors speculated that myocardial damage leading to decreased cardiac function and pulmonary and hepatic congestion were involved. The 1-hr animals experienced initial decrements in bodyweight gain, but recovered. Bodyweight losses were observed in the 2, 4 and 8-hr animals. Absolute organ weights were statistically lowered in the kidney (1 & 4 hours), testes (4 hours) and heart (2 and 4 hours), though the biological significance of these observations was unclear. The following histologic observations were considered possibly or definitely due to phosphine exposure: lung congestion (at 0, 1, 2, 4 and 8 hours: 0/10, 2/10, 1/10, 3/10 and 10/10), lung inflammation (0/10, 0/10, 0/10, 0/10 and 2/10), microvacuoles in hepatic cells (0/10, 0/10, 0/10, 0/10 and 7/10), liver congestion (0/10, 0/10, 0/10, 0/10 and 9/10), nasal cavity exudate (0/10, 0/10, 1/10, 10/10 and 5/10), necrotic nasal epithelial cells and cell infiltration (0/10, 0/10, 3/10, 10/10 and 3/10), heart edema (0/10, 0/10, 0/10, 0/10 and 1/10) and heart papillary muscle necrosis (0/10, 0/10, 0/10, 0/10 and 1/10). A statistically significant ~5% decrease in RBC concentration was noted in the 4-hr group that was attributed to exposure (hematology was not conducted on the 8-hr animals due to mortality). Some statistically significant differences were detected in various types of

white blood cell counts, though it was unclear if these were treatment-related.

An acute NOEL was not determined in this study, as effects, including slight tremor and piloerection, were noted in the 4-hr exposures at the lowest 4-hr concentration tested, 22.5 ppm (which is thus the acute LOEL). In addition, lung congestion and nasal cavity exudate were evident at 23.9-24.9 ppm at 4 and 8 hr, and necrotic nasal epithelial cells and cell infiltration at 2, 4 and 8 hr. This study was considered supplemental.

Roy (2003) exposed 5 Wistar rats/sex/dose nose-only to 0, 43 or 83 ppm phosphine for 4 hours. The phosphine was generated from QuickPHlo-R Granules (aluminum phosphide: 78%). One female in the 43 ppm group and one male and four females in the 83 ppm group died within 24 hours post exposure. Clinical signs included nasal discharge, abdominal breathing and lethargy during exposure. All signs resolved in the survivors by 24 hours post exposure. Necropsy revealed moderate to severe lung congestion and mild to moderate liver pallor in animals dying during the study. The reported LC₅₀ (M/F) was 83 ppm (0.117 mg/L). A NOEL was not determined in this study.

This study was considered unacceptable by FIFRA guidelines, though it was possibly upgradeable with submission of data and documentation used to determine the analytical chamber concentration.

b. Oral toxicity

Batra *et al.* (1994) investigated the oral toxicity of aluminum phosphide in male Wistar rats. The test article, referred to as "Celphos", contained 56% aluminum phosphide along with ammonium compounds, binding and lubricating agents, fillers, etc. It was administered by gavage to 6 "partially starved" animals per dose after having been ground to a powder and suspended in refined peanut oil. The doses were 0 (vehicle control: 0.5 ml/100 g bodyweight), 10.2, 12.8, 16.0 and 20.0 mg/kg. The animals were observed for 15 days following treatment.

The mortality curve at ascending doses was: 0/6, 1/6, 2/6, 4/6 and 5/6. Most deaths occurred within 3-5 hours of exposure. Clinical signs included crouching, breathing incoordination, restlessness, paralysis of hindlimbs, listlessness, anorexia and lack of desire for food for at least 24 hours (despite a virtually normal water intake). Coma and convulsions were observed prior to death. Necropsies of dead animals revealed enlarged stomachs with dark brown contents (which the authors speculate as due to phosphine gas release and consequent capillary rupture) and white lesions in the liver (possibly due to interactions between phosphine gas and red blood cells).

Three statistical methods were employed to calculate the LD₅₀ values - Litchfield, probit and Weil - which were between 13.9 and 14.8 mg/kg. In view of the dearth of reported information, acute NOELs and LOELs were not established. This study was considered supplemental.

Okolie *et al.* (2004) investigated the effects in New England White rabbits (sex not stated) of daily gavage over a 2-wk period with aluminum phosphide (AIP). The test article was referred to as "phostoxin", but not further described. Doses were 0 (vehicle control) and 0.84 mg/kg, which represented one-tenth of the acute LD₅₀ of 8.4 mg/kg established in a preliminary study. Vegetable oil was used as the vehicle in an attempt to delay the release of phosphine gas until the AIP reached the gastrointestinal tract. Following the exposure period the animals were weighed, their blood sampled, and sacrificed for pathologic exams and enzyme activity determinations in kidney, liver and heart.

Mean food intake and body weight gain were severely suppressed in the AIP-exposed animals - food intake: 52±9 g/rabbit/day in controls vs. 38±5 in experimentals (p<0.05); weight gain: 128±11 vs. 35±9 g/rabbit (p<0.05). This resulted in a marked decrease in food efficiency, from 2.5 to 0.9 g weight gain/g feed. Total protein per gram of tissue was statistically reduced in kidney, liver and heart, while the relative organ weights were statistically elevated in liver and heart. Na⁺-K⁺-ATPase activity was statistically reduced in all three tissues, while Ca²⁺-ATPase and Mg²⁺-ATPase activities were statistically reduced in liver only. Hematologic analyses revealed significant reductions in hematocrit, platelet count, and RBC and hemoglobin concentrations in treated animals. Histology revealed “massive liver necrosis with clinical equivalent of massive liver failure”, “swollen heart muscles with severe interstitial oedema”, and “severe [renal] tubular necrosis of the proximal convoluted tubules.” The authors attributed the histopathology to the changes in ion pump enzyme activities, though this is speculative.

An oral LOEL of 0.84 mg/kg was assigned, based on weight gain decrements and severe histopathology in liver, kidney and heart tissues. A NOEL was not established, as only one dose was tested. Note that, with the exception of the aluminum phosphide concentration, the composition of the test article was undefined. This study was considered to be supplemental.

d. Dermal toxicity

No acute dermal toxicity studies on phosphine were available for review.

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Table III-1a. The acute / short term toxicity of phosphine

Species	Tox. Cat.	LD ₅₀ or LC ₅₀	NOEL / LOEL, ppm NOEL, mg/kg*	Effects at LOEL
Oral LD₅₀	no studies available			
Dermal LD₅₀	no studies available			
Inhalation LC₅₀	no studies available			
rat (CD) - 1 hr ^a	na	M: 204 (195-213) ppm F: 179 (170-188) ppm	nd	na
rat (unspec. strain) - 4 hr, 12 days ^b	I	M: 11 (8.1-15) ppm	nd ^b	na
mouse (ICR) - 1 hr ^c	na	M: >59.2 ppm	nd	na
mouse (ICR) - 4 hr ^c	I	betw. 26.5 and 33.4 ppm	no NOEL / 22.5 ppm	tremors & piloerection
rat (Fischer 344) ^d 6 hr/day, 4 days	I	M: <10.05 ppm	4.95 / 10.05 ppm	mortality
mouse (B6C3F1) ^d 6 hr/day, 4 days	I	M: <10.05 ppm	4.95 / 10.05 ppm	mortality, anemia, clinical chemistry, histopathology
rat (Fischer 344)-6 h ^e	na	M/F: >11 ppm (hdt)	11 ppm (NOEL, hdt)	na
rat (Fischer 344) 6 hr/day, 13 days^f	na	nd	5 / 10 ppm^f	mortality, kidney & lung pathology
rat (Sprague-Dawley) - 6 h ^g	I	M: <28 ppm	6 / 10 ppm	body weight decrements
rat ntx (CD) - 4 hr ^h	na	M/F: >40 ppm (hdt)	no NOEL / 21 ppm	reduction in measures of motor activity, etc.
Eye irritation	no studies available			
Dermal irritation	no studies available			
Dermal sensitization	no studies available			

Abbreviations: Tox. cat., toxicity category; nd, not determined; na, not applicable; ldt, lowest dose tested; hdt, highest dose tested; ntx, neurotoxicity

**Note:* The critical inhalation study of Newton (1990) is highlighted.

^a Shimizu *et al.* (1982) - This study was considered unacceptable by DPR due to limited information on gas sampling methodology.

^b Waritz and Brown (1975) - A "subacute" LOEL of 4 ppm (0.9 mg/kg/day) was established in this study. As it was determined after a 12-day exposure, it was considered with the subchronic NOELs. As an open literature study, it was considered to be "supplemental".

^c Omae *et al.* (1996) - as an open literature study, this was considered to be "supplemental".

^d Morgan *et al.* (1995) - as an open literature study, this was considered to be "supplemental".

^e Newton (1989) - this study was considered to be "supplemental".

^f Newton (1990); despite the longer course of this study (13 days), the histopathology and death noted at 10 ppm occurred

within 3 days of exposure. The NOEL of 5 ppm was therefore considered a "short term" NOEL. This study was considered acceptable according to FIFRA standards.

^g Newton (1991) - this study was considered to be "supplemental".

^h Schaefer (1998a) - Mortalities were recorded at 47 ppm in a preliminary dosing study. This study was acceptable by FIFRA standards.

ⁱ Assumed a LOEL-to-NOEL uncertainty factor of 10.

Table III-1b The acute toxicity of aluminum phosphide formulations

Species	Tox. Cat.	LD ₅₀	NOEL / LOEL	Effects at LOEL
Oral LD₅₀ rat (Wistar) ^a	I	M: 13.9-14.8 mg/kg	nd	na
rabbit (NZW) ^b	I	8.4 mg/kg	0.84 mg/kg (LOEL, ldt)	↓ weight gain, liver-kidney-heart histopathology
Inhalation LC₅₀ rat (Wistar) - 4 hr ^c	II	M/F: 83 ppm	nd	na

Abbreviations: NZW, New Zealand White; ldt, lowest dose tested.

^a Batra *et al.* (1994). The exact composition of the test article, referred to as "Celphos", was not stated.

^b Okolie *et al.* (2004); the LD₅₀ was reported from a preliminary study. The exact composition of the test article, referred to as "phostox", was not stated.

^c Roy (2003) - note: this study was considered unacceptable by DPR due to inadequate information provided on chamber concentration analysis. The test article, QuickPHlo-R Granules (aluminum phosphide: 78%), was also not completely defined.

C. SUBCHRONIC TOXICITY

1. Overview

Newton (1990) observed slight hematologic and serum chemical changes in Fischer 344 rats at and above 3 ppm, and decreases in liver weights at and above 0.3 ppm in a 13-wk inhalation study (mortality and kidney and lung histopathology were also noted at 10 ppm within three exposure days, indicating a severe acute or subacute effect). Schaefer (1998b) recorded an increased incidence of sleeping behavior and its correlate, complete palpebral closure, at 1.01 ppm and perhaps as low as 0.3 ppm by 4 weeks in a 13-wk inhalation neurotoxicity study in CD rats (see section III.H.2). Omae *et al.* (1996) documented pulmonary congestion, hepatocytic microvacuoles, accumulation of cells in the liver sinusoid, nasal cavity exudates and necrotic nasal epithelial cells and cell infiltration in ICR mice exposed for 4 weeks to 4.9 ppm phosphine. Finally, Barbosa *et al.* (1994) observed body weight gain decrements and micronucleus formation in spleen and bone marrow in Balb-c mice exposed to phosphine gas on a daily basis for 13 weeks at 4.5 ppm.

2. Laboratory animal studies (inhalation)

Newton (1990) subjected 30 Fischer 344 rats/sex/group to whole body inhalation at 0, 0.3, 1 or 3 ppm phosphine gas (1.04% a.i. in nitrogen) for 13 weeks (6 hr/day, 5 days/wk). Ten rats/sex/group were allocated for interim sacrifice after 4 weeks, 10 at the end of 13 weeks and 10 after 13 weeks plus 4 weeks of recovery. Due to the meager treatment response in this dose range, two additional groups of 10/sex were dosed either with (1) 10 ppm (four female deaths forced removal of this dose group from the exposure regimen after 3 exposure days; the surviving animals were allotted an additional 4-wk recovery period before recovery sacrifice), or (2) 5 ppm (removed from the exposure regimen after 13 days, at which time 5/sex were sacrificed and 5/sex allowed an additional 4 weeks before recovery sacrifice). Six control rats/sex were run in parallel with each of these groups. The mean analytical concentrations, determined 4x/chamber/day using gas chromatography, were 0, 0.37, 1.0, 3.1, 5.1 and 10 ppm. Mass median aerodynamic diameters ranged between 3.0 and 5.1 microns, not showing appreciable differences between the control and treatment groups. This was interpreted by the authors as evidence for the absence of aerosolized test substance (which would be expected, as phosphine is a gas). Basic subchronic toxicologic study parameters were evaluated.

Clinical observations and ophthalmoscopic exams were negative throughout the study. Statistically significant bodyweight gain decrements were apparent in males during the last three weeks of exposure at all doses, while in females they were apparent only during the first four weeks at the high dose and, more variably, through the first three weeks at the other doses. However, there was considerable variation in bodyweight gain between doses throughout the study, making these possible effects insufficiently robust to define a LOEL. At any rate, the authors asserted that the bodyweight gain decrements were related to decreased food consumption in both sexes (a claim that was not entirely clear from the data).

Four of the ten females later placed on study at 10 ppm died after 3 days of dosing. The concentration x time (C x T) product which produced death was 180 ppm • hr (*i.e.*, 10 ppm x 18 hr). However, there was a threshold for death, as no 5 ppm animals had died, even by termination of that group at 13 days (using Haber's Law, the 5 ppm animals should have died after 6 exposures). There were no deaths in the other dose groups.

Hematologic analyses in 4-week interim sacrifices showed a statistically significant increase in platelets in males at 3 ppm (6.51×10^5 vs. 6.21×10^5 / μl in controls; $p < 0.05$). Also in males, terminal sacrifices showed statistically significant reductions in hemoglobin (16.4 vs.

17.3 g/dl; $p < 0.01$), hematocrit (43% vs. 45%; $p < 0.01$) and red blood cells (6.85×10^6 vs. 7.18×10^6 / μ l; $p < 0.01$). Females were negative for these responses. The occurrence of these changes at the high dose (for groups carried through 13 weeks), combined with the appearance of similar RBC effects in the satellite 10 ppm group sacrificed after 3 exposure days, suggested that they may be treatment-related, though their toxicologic significance was unclear.

Clinical chemistry revealed statistically elevated blood urea nitrogen (BUN) in 3 ppm males after 4 weeks (at ascending doses, mg/dL: 17.0, 17.5, 16.9 and 19.3**; ** $p < 0.01$), but no effect in parallel females. Similarly, BUN was elevated in 5.1 ppm males after 2 weeks (30.1** mg/dL vs. 22.8 in controls), without an effect on females, and in 10 ppm males after 3 days (19.1* mg/dL vs. 15.5; * $p < 0.05$). Parallel 10 ppm females may have shown elevated BUN after 3 days (26.8 mg/dL vs. 17.7), but only one female was tested. These effects may reflect an impact of phosphine on the kidney, correlating with the histopathologic changes noted below. Alkaline phosphatase was slightly, but statistically, increased in the male 10 ppm early sacrifices (218* IU/L vs. 183 in controls; * $p < 0.05$). Serum glutamic pyruvic transaminase activities were decreased in both sexes at 3 ppm after 13 weeks (σ , IU/L: 79, 72, 60 and 49*; ρ : 45, 42, 44 and 36*; * $p < 0.05$). Effects on the latter two enzymes suggested an effect on the liver.

Male kidney weights showed statistically significant increases at 10 ppm with the 3-day early terminal sacrifices (absolute wts: 1.50 g* vs. 1.34 g in controls, * $p < 0.05$; relative to bodyweights $\times 1000$: 9.83* vs. 8.68, * $p < 0.05$). These correlated with changes seen with histopathology (see below). No conclusion can be drawn regarding females, as only one female was sacrificed at that point. Terminal sacrifices at 13 weeks also revealed statistically significant decreases in absolute and relative liver weights in males at 0.3, 1 and 3 ppm, though a strict dose response was not observed (absolute weights in grams at ascending doses: 7.481, 6.791*, 6.309**, 6.662*; relative to bodyweight: 2.59, 2.41**, 2.36**, 2.37**; *, ** $p < 0.05$, 0.01). Early terminal sacrifices at 10 ppm (*i.e.*, after 3 days of exposure) did not show such an effect in males (again, females at 10 ppm were represented by only one individual), nor was a liver weight effect observed at the 5.1 ppm early terminal sacrifice after 13 days of exposure.

Gross pathology and histopathology on interim sacrifices did not show treatment effects. The incidence of "small seminal vesicles" increased at 1 and 3 ppm in terminal males (6/10 and 5/10, respectively, vs. 1/10 in controls), though the lack of a histopathologic correlate rendered this finding of uncertain toxicologic significance. Histopathology did reveal treatment-related renal tubular necrosis in the outer cortex of both sexes at 10 ppm (5/5 in both sexes, vs. 0/10 in both controls in terminal sacrifices), with females exhibiting the more severe characteristics. In addition, pelvic mineralization was observed in 3 ppm males (3/10 vs. 0/10 in controls), as was tubular mineralization (10/10 vs. 5/10 in controls). It was unclear if this represented a treatment response. Renal lesions were not noted at 5 ppm. Histopathologic data were not provided for 0.3 and 1 ppm animals. Pulmonary congestion (4/5 vs. 0/10 controls) and edema (2/5 vs. 0/10 controls) also occurred in 10 ppm females. 28-day recovery animals did not display treatment-related lesions.

Neither a subchronic NOEL nor LOEL were defined for this study, due to the lack of histopathologic reports at the intermediate doses. It is noted, however, that death occurred within three days at 10 ppm, but was not observed even after 13 days of exposure at 5 ppm. In addition, there were clear kidney lesions and pulmonary congestion at 10 ppm, with possible histologic effects in the kidney (pelvic and tubular mineralization) noted even at 3 ppm, though the toxicologic significance of the latter was not clear. These effects were likely acute or near acute in nature, as they may have been elicited after a single exposure (and were obviously present after three exposures). Despite the lack of a subchronic NOEL, enough data were present to establish a "short-term" NOEL of 5 ppm, based on the severe effects, including mortality, within 3 days at 10 ppm. This study was considered to be acceptable.

Morgan *et al.* (1995) studied the responses of Fischer 344 rats and B6C3F1 mice to phosphine from a commercial pressurized cylinder both over a 4-day period, summarized above in section III.B.3 (Acute Toxicity), and over a separate 14-day period, summarized in the following paragraphs. Chamber concentrations were determined by gas chromatography

In the 14-day study (6 hr/day, 5 days/wk) there were at least 6 rats or mice per sex per time point. The mean chamber concentrations were 0, 1.19, 2.25 and 5.14 ppm (nominal: 0, 1.25, 2.5 and 5 ppm). Male rats and mice were killed after 1, 5 or 10 exposures. Female rats and mice were killed after day 10 only. There were no deaths. After 14 days there were statistically significant decreases in lung weights in high dose male rats and mice, significant increases in heart weights in high dose female rats and mice, and increases in BUN in high dose male mice. Histopathology did not reveal clear effects of treatment. Acid-labile phosphine was not detected in high dose mouse or rat tissues. These results supported a NOEL determination of 2.25 ppm for this short-term exposure. This study was considered to be supplemental.

Omae *et al.* (1996) studied acute and subacute responses to phosphine gas in male ICR mice in whole-body chambers. The subacute aspects of this study are summarized here while the acute aspects appear above in section III.B.3 (Acute Toxicity). Phosphine concentrations were determined by gas chromatography using samples taken every 12 minutes. Animals, 9-10/dose and exposure time, were exposed for 6 hr/day, 5 days/wk for 2 or 4 weeks at a mean phosphine concentrations of 0 or 4.9 ppm. Blood was drawn 1 day after the termination of the two exposure periods for biochemical and hematologic determinations. In addition, the major organs were removed, weighed, fixed and examined histologically. The sciatic nerve, skull and femoral bone were also removed for histology. The right testis was fixed and stained, while the left testis was frozen in liquid nitrogen for sperm enumeration.

Except for one animal dying at day 12 with right ventricular dilatation and pulmonary congestion, all animals survived 2 and 4 weeks of exposure at 4.9 ppm phosphine. Face washing movements and high cage activity were noted soon after the start of the daily exposure periods. Mild piloerection was also noted. After 1 hour, however, spontaneous motor activity diminished and the animals gathered in the corners of their cages. Bodyweight gain was significantly inhibited between days 2 and 16 in the 4-wk group (data not provided) - it is unclear why a similar effect was not observed in the 2-wk group, as those animals were exposed to the same phosphine concentration. Absolute organ weights were statistically diminished for liver, spleen and thymus in the 2-wk animals, and for kidney in the 4-wk animals. Whether or not there was biological significance associated with these apparent effects was unclear. Histologic analyses did not reveal effects in the 2-wk animals. However, the 4-wk animals showed evidence of pulmonary congestion (0/10 in controls vs. 1/10 in exposed), microvacuoles in hepatocytes (2/10 vs. 8/10), accumulation of cells in the liver sinusoid (0/10 vs. 4/10), nasal cavity exudate (0/10 vs. 2/10) and necrotic nasal epithelial cells and cell infiltration (0/10 vs. 2/10). Eosinophilic neutrophils were statistically elevated in the 4-wk group (0.1% vs. 1.3%*; *p<0.05; expressed as a percentage of WBCs). A small but statistically significant increase in alanine aminotransferase was also noted in this group (22.3 vs. 27.4* IU/L; *p<0.05).

A subacute / subchronic NOEL was not determined, as there was a series of clinical observations noted at the only dose tested. Thus the LOEL for this study was 4.9 ppm. This study was considered supplemental.

Barbosa *et al.* (1994) exposed Balb-c mice to phosphine gas (supplied in nitrogen at 1400 ppm) in two exposure regimens, subchronic and "short-term". 1) Subchronic regimen: 13 weeks, 5 days/wk, 6 hr/day, 12 animals/sex/dose at 0, 0.3±0.1, 1.0±0.2 and 4.5±0.8 ppm. Dose levels were based on the TLV of 0.3 ppm set by the ACGIH. Endpoints monitored included bodyweight, organ weights, micronucleus incidence in bone marrow polychromatic erythrocytes (PCE) and in cultured spleen lymphocytes, and point mutations using the HPRT / thioguanine assay in spleen lymphocytes. 2) "Short-term" regimen: 2 weeks, 5 days/wk, 6 hr/day at 0 (4/sex) and 5.5±0.67 (6/sex) ppm. The dose level in the short-term study was based on an estimation of the maximum tolerated dose. Endpoints monitored included weight gain and micronucleus incidence in cultured skin keratinocytes and in PCE from whole blood. The exposure chambers for both regimens had dimensions of 50x30x30 cm. Chamber gas was controlled by two flowmeters. Phosphine concentrations were monitored by gas chromatography.

In the subchronic regimen, high dose mice of both sexes showed signs of itching during exposure (face, tail, feet) and were less active than other dose groups at the end of each exposure period. There were no other cageside observations. Weight gains were decreased at increasing doses, showing high statistical significance in a regression analysis ($p < 0.0001$ for both sexes), though individual group comparisons were not reported (Table III-2). Females appeared to be the more sensitive gender, exhibiting a weight gain decrement of 9.1% at the high dose over the 13-wk period, compared to a 4.1% decrement in males at the same dose. Relative organ weights were also affected by phosphine exposure, though here, too, there were sex differences. Where statistically significant differences were noted compared to controls, female organ weights generally increased (liver at the mid dose excepted), whereas male weights decreased (Table III-2). However, the statistical effect in males, which was apparent at 0.3 ppm, lacked dose responsiveness - thus the effect, if real, was of questionable toxicologic significance. The statistical effect in females was present at the high dose in all organs except brain (which also showed higher weights at the high dose, though not statistically significant), and in two cases - lung and heart - was present at the low dose of 0.3 ppm. Absolute organ weights, which are not summarized here, showed statistically significant changes in high dose female kidneys and spleen.

The mean frequency of micronuclei in splenic lymphocytes, expressed as a function of binucleated cells (BN), showed statistically significant increases in both sexes at the high dose (the mid and low doses were not analyzed): 3.3±1.0 micronuclei / 1000 BN in control males vs. 6.3±1.6 @ 4.5 ppm, and 3.4±1.3 in control females vs. 7.5±1.3 @ 4.5 ppm. No statistically significant increase in micronuclei / 1000 PCE was detected in bone marrow in either sex. However, when the data for both sexes were combined, there was a statistically significant increase at the high dose (3.63 / 1000 BN in controls vs. 5.59 @ 4.5 ppm; $p < 0.001$). No effect was observed for mutation frequency at the HPRT locus. Micronucleus assays were not conducted for mid and low dose animals.

In the 2-wk "short-term" regimen, control males and females sustained 9.5% and 9.0% body weight gains over the course of the study, respectively. Animals exposed to 5.5 ppm phosphine sustained gains of 8.4% and 4.8%, respectively. The effect did not achieve statistical significance in either sex, though the larger apparent effect in females resembled the effect observed in the subchronic study. Micronucleus frequencies in peripheral blood and in skin keratinocytes appeared unaffected.

A subchronic NOEL of 1.0 ppm was established in this study, based on the following effects at 4.5 ppm: 1) decrements in body weight over the 13-wk period in both sexes; and 2) increases in micronucleus frequencies. Possible body weight gain decrements at the low and

mid doses were insufficiently robust to support LOEL determinations. It is also noted that females sustained statistically significant decreases in relative organ weights, sometimes at the low dose. However, the toxicologic significance of these effects was not clear, particularly as histopathology was not conducted. This study, which came from the open literature, was considered to be supplemental.

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Table III-2. The effect of daily phosphine gas exposure over 13 weeks on bodyweight change and relative organ weights in Balb-c mice (Barbosa et al. [1994])

PH ₃ , ppm	% Δ Body wt. ^a		% Kidney wt. ^a		% Lung wt. ^a		% Liver wt. ^a		% Heart wt. ^a		% Brain wt. ^a		% Spleen wt. ^a	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0	17.0 ^b (1.4)	20.1 ^b (3.1)	1.59 (0.17)	1.19 (0.09)	0.65 (0.04)	0.64 (0.05)	4.77 (0.47)	4.88 (0.46)	0.78 (0.11)	0.53 (0.04)	1.57 (0.14)	2.01 (0.31)	0.30 (0.03)	0.36 (0.03)
0.3	15.1 (2.5)	18.1 (2.6)	1.45 ^d (0.10)	1.25 (0.17)	0.60 ^c (0.07)	0.72 ^d (0.08)	4.73 (0.51)	4.76 (0.29)	0.63 ^d (0.05)	0.61 ^c (0.07)	1.41 ^d (0.10)	1.93 (0.18)	0.26 (0.03)	0.37 (0.04)
1.0	14.1 (2.5)	17.2 (2.5)	1.55 (0.15)	1.24 (0.08)	0.62 (0.10)	0.69 ^d (0.03)	4.41 (0.47)	4.55 ^c (0.31)	0.76 (0.15)	0.62 ^d (0.07)	1.46 (0.18)	1.98 (0.09)	0.30 (0.05)	0.41 ^d (0.03)
4.5	12.9 (2.6)	11.0 (1.7)	1.53 (0.24)	1.30 ^c (0.01)	0.63 (0.07)	0.74 ^d (0.09)	4.86 (0.49)	5.40 ^c (0.46)	0.67 ^c (0.10)	0.65 ^d (0.07)	1.62 (0.34)	2.16 (0.36)	0.28 (0.02)	0.45 ^d (0.06)

^a Terminal body weight change, mean ± standard deviation; organ weights are expressed as percent of whole body weights; standard deviations are in parentheses; n = 10.

^b p < 0.0001 (trend)

^c 0.01 < p < 0.05

^d p < 0.001

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D. CHRONIC TOXICITY AND ONCOGENICITY

1. Overview

In the only chronic inhalation study available for analysis, Newton (1998) detected no treatment effects through a high dose of 3 ppm after 2 years of daily exposure at 6 hr/day, 5 days/wk.

2. Laboratory animal studies (inhalation)

Newton (1998) evaluated the potential for chronic toxicity and oncogenicity in Fischer CDF (F-344)/CrI/BR VAF/Plus rats, 60/sex/dose, exposed to phosphine gas in whole body inhalation chambers for 104 consecutive weeks (6 hr/day, generally 5 days/wk). The target doses were 0, 0.3, 1 and 3 ppm; the analytically determined mean doses for the first 52 weeks were 0, 0.30, 1.01 and 3.01 ppm; for the second 52 weeks the analytical mean doses were 0, 0.30, 1.00 and 3.01 ppm. Analytical determinations were made hourly using gas chromatography. Dosing was based on previous studies that showed lethality at concentrations greater than 5 ppm.

Animals were observed for mortality, morbidity and injury twice each exposure day (before and after exposure) and non-exposure day. Bodyweights were determined weekly. Food consumption was recorded weekly during the first 13 weeks, then approximately monthly for the remainder of the study. Clinical laboratory studies (hematology, clinical chemistry and urology) were conducted on 10 randomly selected rats/sex/dose after 26, 52, 78 and 104 weeks. Ophthalmoscopy was conducted on each rat after 52 and 104 weeks. Interim sacrifices were conducted on 10/sex/dose after 52 weeks; as with the terminal sacrifices, each interim was subjected to a complete *postmortem* examination. Organ weights were determined. Representative tissues examined in the control and high dose groups, with potential target organ tissues examined also at the intermediate doses.

There were 99 unscheduled deaths (0 ppm: 7 σ / 14 φ ; 0.3 ppm: 16 σ / 15 φ ; 1 ppm: 14 σ / 9 φ ; 3 ppm: 12 σ / 12 φ), none of which appeared to be phosphine related. There were no clinical signs or palpable masses that could be related to treatment. Neither bodyweight nor food consumption were impacted by exposure. No clear treatment-related effects were seen with clinical laboratory studies (hematology, clinical chemistry and urology) and ophthalmoscopy. Gross pathology, organ weights, histopathology and tumor incidence all appeared to be unaffected by exposure.

No effects of treatment were seen in this study. Consequently, the NOEL was set at 3 ppm and the LOEL at >3 ppm. This study was considered to be acceptable.

Table III-3. NOEL and LOEL values for subchronic and chronic toxicity studies on phosphine

Species, strain	Study type & exposure regimen	Effects at LOEL	NOEL, ppm NOEL, mg/kg/day	LOEL, ppm	Reference / comment
rat, CD	12-days (4 hr/day) inhalation	mild respiratory irritation, ↓ body wt. gain	nd	4.0 ppm (ldt)	Waritz & Brown (1975) / supplemental
rat, Fischer 344	14-days (6 hr/day, 5 days/wk) inhalation	↓ lung wt., ↑ heart wt.	2.25 ppm	5.14 ppm	Morgan <i>et al.</i> (1995) / supplemental
mouse, B63CF1	14-days (6 hr/day, 5 days/wk) inhalation	↓ lung wt., ↑ heart wt., ↑ BUN	2.25 ppm	5.14 ppm	Morgan <i>et al.</i> (1995) / supplemental
rat, Fischer 344	13-wk (6 hr/day, 5 days/wk) inhalation	na	na ^a	na ^a	Newton (1990) / acceptable
rat, CD	13-wk (6 hr/day, 5 days/wk) inhalation (neurotoxicity)	sleeping behavior / palpebral closure, ↓ respiration rate, ↓ body temperature	1 ppm	2.99 ppm	Schaefer (1998b)^b / acceptable
mouse, Balb-c	13-wk (6 hr/day, 5 days/wk) inhalation	↓ body wt. gain, ↑ micronucleus frequency	1 ppm	4.5 ppm	Barbosa <i>et al.</i> (1994) / supplemental
mouse, ICR	4-wk (4 hr/day, 5 days/wk) inhalation	clinical & histopath. effects, ↓ body wt. gain	nd	4.9 ppm (ldt)	Omae <i>et al.</i> (1996) / supplemental
rat, Fischer 344	2-yr (6 hr/day, 5 days/wk) inhalation	no effects noted	3 ppm (hdt)	>3 ppm (hdt)	Newton (1998) / acceptable

Abbreviations: na, not applicable; nd, not determined; ldt, lowest dose tested; hdt, highest dose tested.

Note: The critical subchronic study of Schaefer (1998b) is highlighted. The endpoint value in this study was also used to evaluate chronic risk.

^a The subchronic inhalation study of Newton (1990) established neither a NOEL nor LOEL (the latter because of inadequate histopathology). Death occurred within three exposure periods at 10 ppm, but was not observed even after 13 days of exposure at 5 ppm (when the animals in that dose group were terminated) or after 13 weeks of exposure at 3 ppm. In addition, there were clear kidney lesions and pulmonary congestion at 10 ppm, effects likely to be acute or near acute, as they were elicited by, at most, three exposures.

^b This study is reviewed below in section III.H.2. (Neurotoxicity).

^c Assumes an estimated NOEL (ENEL) of 0.4 ppm, using a LOEL-to-NOEL uncertainty factor of 10.

E. GENOTOXICITY

1. Overview

Studies of phosphine applicators indicated a potential genotoxic impact of phosphine in human populations. Garry *et al.* (1989) documented a tripling of various types of chromosome aberration in applicators, including a 5-fold increase in deletions. In a follow-up investigation, Garry *et al.* (1992) demonstrated a tripling of chromosome rearrangements in applicators, resulting mostly from chromosome or chromatid breaks. Breakpoint distribution analysis of the combined 298-break sample revealed four bands in which there were statistically elevated specific breaks among the applicators but none among controls. The authors state that three of the four pesticide-sensitive bands “bear a known and accepted relationship to non-Hodgkin’s lymphoma [NHL]”, prompting them to speculate about possible relationships between phosphine exposure and disease. In contrast to the studies of Garry *et al.*, Barbosa and Bonin (1994) failed to detect an effect on micronucleus formation in peripheral lymphocytes from phosphine fumigators, nor did they see an increase in the mutagenicity of fumigator urine samples.

Laboratory animal and *in vitro* studies gave equivocal results. While all gene mutation and DNA damage studies were negative, four structural chromosome aberration studies, including one *in vivo* rat study, were positive. However, two further *in vivo* studies in mice showed no increases in chromosome aberrations, sister chromatid exchanges, micronucleus formation or dominant lethal effects, nor were there changes in cell cycle kinetics.

While it is not clear why inconsistent results were forthcoming from the laboratory studies, phosphine will be regarded as potentially clastogenic for the purposes of this risk assessment.

2. Studies from human populations

Garry *et al.* (1989) investigated the incidence of chromosome abnormalities in fumigant applicators who used phosphine-generating products. From a group of 40 such individuals, 24 males were selected based on criteria that excluded those with chronic disease, long-term medication use or recent x-rays. The groups were matched for age and smoking status. Among the 24 individuals were 9 exposed to phosphine alone, 11 to phosphine and other pesticides, and 4 to other pesticides and fumigants. There were two control groups: 1) “community” controls, *i.e.*, 24 workers with no known contact with mutagens; and 2) agricultural industry controls, *i.e.*, 15 workers involved in the inspection and processing of grain (so-called “state grain workers”). These controls may sustain incidental exposure to phosphine or other pesticides, though it is not expected to be as great as with the phosphine applicators.

Lymphocytes were isolated and cultured by standard techniques. Blood was sampled at least twice from the phosphine-exposed group within a 24-hr period during peak fumigation times, as well as at 6 weeks and 3 months after the end of peak fumigation. Control specimens were taken within 3 days of the exposed group specimens. “Non-banded” 48-hr cultures, which reportedly capture first division metaphase cells containing both stable and unstable aberrations, were prepared for karyotype analysis of the peak time subjects. “Banded” analysis of non-synchronized 72-hr cultures, which reportedly captures second division cells with increased proportions of stable aberrations, was undertaken in addition to the non-banded analysis in the 6-wk and 3-month post-fumigation subjects.

In vitro exposure of G₀-stage human lymphocytes to phosphine (range: 0 - 4.5 µg/L [~3.2 ppm]) was also undertaken. After a 20-minute exposure and a 96-hr post-exposure period (*Note*: the cells were harvested later than is usually practiced in assays of this nature due to phosphine-induced mitotic delay), the cells were analyzed for chromosome aberrations. The data from 5 separate experiments were combined to generate the reported aberration

frequencies.

Using personal monitoring techniques, phosphine concentrations were measured among applicators working in closed spaces (2.97 [0.5-5.8] mg/m³; n=10) and in open spaces (range=0.1-0.9 mg/m³ [mean not provided]; n=4). These measurements indicated that phosphine levels can rise above the accepted national permissible exposure limit (PEL) of 0.4 mg/m³. The authors note that “worker protection is highly variable, and exposure without appropriate respiratory protection was common among applicator groups”.

The incidence of various chromosomal aberrations evident in non-banded analysis of lymphocytes sampled during peak fumigation times in the *in vivo* epidemiologic study is shown in Table III-4. Total aberrations (excluding gaps) increased more than 3-fold in the phosphine-only group when compared to community controls. All non-gap aberration types (deletions, breaks and rings-dicentrics-quadriradials-acentric) contributed to this result. Both gaps and deletions showed statistically higher incidence than agricultural controls.

Lymphocytes from blood samples taken 6 weeks and 3 months after the fumigant application season were also examined from chromosome aberrations. Non-banded 48-hr cultures reportedly showed no differences between exposed and non-exposed groups (these data were not shown), suggesting that the effects seen in the peak period measurements may have been transient. On the other hand, “banded” analysis of non-synchronized 72-hr cultures did show an effect. Eleven of 12 phosphine applicators showed rearrangements in one or more of the 100 cells analyzed per subject, compared to only 2 of 10 control subjects. Analysis of 1200 cells from the exposed group vs. 1000 cells from the controls showed that such rearrangements occurred at a 6-fold greater frequency in the former group (p<0.05). The latter results suggest that phosphine may induce stable chromosomal aberrations.

The incidence of chromosomal aberrations in the *in vitro* study also showed statistically significant dose-dependent increases in gaps, deletions and total aberrations (excluding gaps). For example, deletions increased from 0.05 per 100 cells in controls to 10.4 per 100 cells at 4.50 µg/L, while gaps increased from 3.5 per 100 cells to 8.8 per 100 cells, and total aberrations (excluding gaps) increased from 0.15 per 100 cells to 16.0 per 100 cells. However, sister chromatid exchange did not show statistically significant differences between groups in either the *in vitro* or *in vivo* phases of this study (these data were not presented in the report).

These results demonstrate the potential for chromosomal toxicity, both of a temporal and possibly a more stable nature, resulting from phosphine exposure in an occupational population. This study was considered to be supplemental.

Table III-4. Chromosomal aberrations in phosphine workers (Garry *et al.*, 1989)

	Mitotic cells counted	Gaps	Deletions	Breaks	Rings, dicentrics, etc. ^a	Total (excl. gaps)
Phosphine alone (n=9)	2400	5.92±1.00*, ^γ	2.52±0.53***, ^γ	1.64±0.28	0.46±0.28	4.62±0.74***
Phosphine & other pesticides (n=11)	3600	2.86±0.54	1.45±0.48*	1.67±0.34*	0.55±0.16	3.67±0.79
Other pesticides & fumigants (n=4)	800	1.25±0.52	1.62±1.01	1.25±0.32	0.88±0.24	3.75±0.83
Agricultural controls (n=15)	1500	2.33±0.51	1.20±0.45	0.87±0.32	0.07±0.07	2.14±0.65
Community controls (n=24)	2400	3.3±0.51	0.54±0.20	0.71±0.21	0.13±0.09	1.38±0.31

Data are expressed as the average rate per 100 cells

*, ***, p<0.05, 0.001; statistical comparisons are to community controls.

^γp<0.05; statistical comparisons are to agricultural controls.

^a Includes rings, dicentrics, quadriradial figures and acentric fragments.

In a follow-up to the study summarized above, Garry *et al.* (1992) examined chromosome rearrangements in cultured whole blood lymphocytes from fumigant applicators. The study laid special emphasis on those individuals applying phosphine-generating products. Four exposure groups were examined: (1) applicators who used phosphine generators almost exclusively in their work - testing for these individuals was conducted during the peak application season (n=6); (2) five of the six tested in group 1 discontinued use of phosphine during the 2-yr study period - these individuals were tested ~8-12 months later to determine the stability of any changes noted in group 1 (n=5); (3) applicators whose primary exposure was probably to pesticides other than phosphine, but who did occasionally use phosphine generators (n=12); (4) controls who had no known contact with mutagens (n=26). Individuals with chronic disease, used medications chronically, or who had x-rays taken within the previous 3 months were excluded from the study. All subjects were male. One hundred G-banded metaphase cells per subject were examined.

There were no significant differences in the incidence of breaks between the groups. However, the incidence of rearrangements (most of which result from chromosome or chromatid breaks) was increased by statistically significant amounts in groups 1 (phosphine applicators: 1.7±0.5 per subject, 700 mitoses examined) and 3 (mixed exposure: 1.4±0.4 per subject, 2205 mitoses examined) compared to the controls (0.5±0.1 per subject, 2533 mitoses examined). Furthermore, no rearrangements were observed in group 2 (500 mitoses examined).

Breakpoint distribution analysis of the combined 298-break sample revealed four bands with elevated break numbers in both the exposed and the control groups and four bands in which there were statistically elevated breaks among the applicators but none among controls (the authors used a statistical procedure to determine if the number of breaks at each chromosomal band was proportional to the relative band length). The former four bands were

taken as evidence for spontaneously susceptible break sites, whereas the latter bands were probably examples of sites susceptible under pesticide stress.

In repeat samples taken over a 1-yr period in 13 of the 18 exposed subjects (presumably from groups 1 and 3), one rearrangement, t(6:7), recurred in the same individual, suggesting an effect on a progenitor cell which generated a clonal lymphocyte population. The authors state that three of the four pesticide-sensitive bands "bear a known and accepted relationship to non-Hodgkin's lymphoma [NHL]", prompting them to speculate about possible relationships between exposure and disease, particularly in light of reports of high NHL incidence in grain industry workers. However, as presented, the rearrangement data did not allow the reader to discriminate between the phosphine and mixed exposure groups (groups 1 and 3, respectively). This report was considered supplemental.

Barbosa and Bonin (1994) examined the incidence of micronuclei in peripheral lymphocytes from phosphine fumigators employed by the Australian government. They also examined urine mutagenicity, multiple hematologic and blood chemistry parameters, whole blood organochlorines, and serum and whole blood cholinesterase levels. Thirty-one fumigators with the New South Wales Grain Corp., with a mean work period of 11.6 years (range: 1.5-32 years), were compared to 21 non-fumigators (eg., grain handlers, mechanics and clerks) working at the same sites. Blood and urine samples were collected over a 3-month period in 1992 (Note: the report did not explicitly state that this was a peak fumigation period). Subjects with a history of x-rays or medication use were monitored separately to ensure that they did not act as confounders (they did not). Micronuclei were measured in 72-hr cultured lymphocytes, two cultures/subject, after cytochalasin treatment at 44 hours and modified Wright staining. Urine mutagenicity was determined using two strains of *Salmonella typhimurium* (TA100 and TA98), \pm S9 microsomes, after XAD-2 resin chromatography, elution of a putative mutant fraction into acetone, freeze-drying and reconstitution in dimethylsulfoxide. Phosphine levels were monitored in the breathing zone of the fumigators using both collar badges and phosphine tubes attached to a gas detector pump.

No significant differences in micronucleus incidence were noted between fumigators and controls (6.9 \pm 4.5 vs. 7.1 \pm 4.0 micronuclei per 1000 binucleated cells, respectively) or between smokers and non-smokers (7.2 \pm 3.9 vs. 6.8 \pm 3.4 micronuclei per 1000 binucleated cells, respectively). A statistically significant difference ($p < 0.01$) was observed when the cohort was divided between those under 35 years and those over 35 years (4.5 \pm 3.4 vs. 8.1 \pm 4.0 micronuclei per 1000 binucleated cells, respectively). No robust effects of fumigation were seen on the other parameters measured, though some mild effects might have been present. For example, with respect to liver function tests, 55.5% of the fumigators had γ -glutamyl transpeptidase activities above the normal range vs. 17.6% of the controls, 25.8% of the fumigators had raised alanine aminotransferase activities vs. 11.7% of controls, and 17% of the fumigators had one or more raised liver function variables vs. 35.3% of controls. The authors speculated that higher alcohol consumption in the fumigators might explain part of this effect, especially with respect to the γ -glutamyl transpeptidase activities, but could not exclude phosphine-induced liver damage. In contrast to these results, smoking did raise the mutagenicity of urine, both in terms of severity and of incidence. Thus 100% of the fumigators who smoked exhibited mutagenic urine (with 50% of these having tripled the background *Salmonella* mutation frequency) vs. 29% of the non-smoking fumigators (with none showing more than a doubling of background frequency). Among non-fumigators, 83% of the smokers showed mutagenic urine (with 100% of these showing a tripled mutation frequency) vs. 38% of the controls (80% of these had only a 1.5-fold increase in mutation frequency).

In the monitoring phase of the study, phosphine levels were not found to rise above 2.4 ppm over a 1-hr period; these levels were apparently lower than those reported in previous studies. Such low levels may explain the lack of clear measured effects of phosphine.

This study was deemed supplemental.

3. Gene mutation

Sutou *et al.* (1982) tested the ability of phosphine gas to (1) induce reversion to histidine independence in five tester strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and (2) induce reversion to tryptophan independence in *E. coli* WP2 Hcr⁻. The source of the phosphine was magnesium phosphide (89% Mg₃P₂ + 11% paraffin), which was weighed and added to a glass container placed at the bottom of a dessicator. The bacterial agar plates were exposed for 1 hour to the evolving phosphine by inverting them over the glass container. The post exposure incubation period was 2 days for the *Salmonella* and 3 days for the *E. coli*. Positive controls were included. The phosphine concentrations were 0, 640, 1280, 2560, 6400, 12800 and 25600 ppm. These were calculated concentrations based on the amount of phosphine theoretically released from a known amount of magnesium phosphide. They were compared to a previously determined rat 1-hr LC₅₀ value of 200 ppm. It should be noted that such concentrations in the atmosphere above the agar were unlikely to resemble those in the agar in contact with the bacterial cells. These were estimated to range between 7 and 134 ppm based on a method published by Liss and Slater (1974) (Eric Kwok, DPR - personal communication). In addition, the presence of metals in the agar may have lowered the effective phosphine concentration by forming metal-phosphine complexes.

Phosphine gas was not considered to be mutagenic under the conditions assayed in this study, either in the presence or absence of S9. However, the study was considered to be unacceptable due to a lack of repeated trials and insufficient cytotoxicity data.

Stankowski (1990) tested the ability of phosphine gas to induce reversion to histidine independence in six tester strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100 and TA102). Exposure to analytically-determined air levels of phosphine gas was for 48 hours using triplicate cultures at each dose. The doses ranged between 4.52 ppm and 4340 ppm in five separate assays, which were run both in the presence and absence of an exogenous metabolic activation system (S9). Appropriate positive controls were run to ensure that the system was operative. Toxicity in the form of inhibited growth was observed at and above 488 ppm, ±S9. The observation of toxicity at those doses was the only indication that the bacterial cells were actually exposed to the gas. As in the study by Sutou (1982), the phosphine concentration above the agar was probably on the order of 200-fold higher than that *in* the agar, which would thus have ranged between 2.3 ppb and 22 ppm. The possibility that metal-phosphine complexes would have further lowered the effective phosphine concentrations should also be noted.

Some increases in numbers of revertant colonies in four tester strains were observed in the first three assays. However, they were never independently confirmed and thus were considered to be artifactual. Phosphine gas was not considered to be mutagenic under the conditions assayed in this study, either in the presence or absence of S9.

This study was considered to be acceptable.

4. Chromosomal aberrations

SanSebastian (1990) evaluated the ability of phosphine gas to produce structural chromosome aberrations in Chinese hamster ovary (CHO) cells cultured in roller bottles. An initial cytotoxicity

assay was conducted at analytically determined doses ranging between 0.167 and 8775 ppm, in the presence and absence of an S9 metabolic activation system. Cell proliferation kinetics were not affected following the 5-hr exposure period. This resulted in the establishment of the dose range for the aberration test: 426 - 4957 ppm, \pm S9. Cells were analyzed following 8, 18 and 26 hours of post exposure incubation and colcemid-induced mitotic arrest, cell harvest, slide preparation and staining. One hundred fifty metaphases were examined from each duplicate culture.

Statistically significant increases in total aberrations were noted in the 8-hr post incubation cultures at 2733 and 4957 ppm phosphine gas, \pm S9. Thus at 0 (untreated control), 0 (air control), 436, 2733 and 4957 ppm, -S9, the total aberration numbers were 23, 16, 22, 37* and 29* ($p \leq 0.05$). For the +S9 cultures, the 8-hr numbers were 5, 6, 8, 22* and 14*. Such increases were not observed in the 18- or 26-hr cultures. Of the two positive controls (-S9: MNNG, assayed only at 8 and 18 hr; +S9: 1,3-butadiene, also assayed only at 8 and 18 hr) only MNNG was functional at both time points; BD (1,3-butadiene) failed to elicit aberrations at 18 hr and had only a minimal effect at 8 hr. The authors speculated that "this lack of a true positive response for BD indicates that the S9 activation system was not functioning biologically or perhaps the BD was not tested at the appropriate dose to induce structural chromosomal aberrations". If indeed the S9 system was dysfunctional, it is possible that the +S9 results may have over- or underestimated the apparent effect seen at the 8-hr post-incubation time point.

The results of this study are consistent with an ability of phosphine to induce chromosome aberrations *in vitro*, both with and without S9. This study was considered to be acceptable.

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Barbosa *et al.* (1994) detected an increase in micronucleus frequency in the spleen and bone marrow of Balb-c mice exposed for 13 weeks to 4.5 ppm phosphine (5 days/wk, 6 hr/day). However, no increase in point mutations at the HPRT locus was detected. A complete summary of this study appears above in section III.C.2.

Kligerman *et al.* (1994a) investigated the cytogenetic effects of phosphine inhalation after a 6-hr exposure in male CD-1 mice. Atmospheres in the whole-body chambers were controlled through a mass flow controller and monitored by both infrared spectroscopy and colorimetric detection tubes. Mean chamber concentrations were 0, 5.24 ± 0.69 , 9.94 ± 0.69 and 16.00 ± 1.15 ppm. Samples for analysis were taken 20 hours after exposure. The following parameters were analyzed in cultured splenocytes: chromosome aberrations, sister chromatid exchanges, cell cycle kinetics and micronuclei. Polychromatic erythrocytes from bone smears were also scored for micronuclei.

There were no deaths. Lethargy and shallow breathing were noted at the high dose of 16 ppm. No statistically significant cytogenetic effects were observed, though a dose-dependent slowing of the cell cycle occurred (replicative index at increasing doses: 1.87 ± 0.12 , $1.67 \pm 0.09^*$, $1.61 \pm 0.18^*$ and $1.56 \pm 0.10^*$; * $p < 0.05$).

This study was considered to be supplemental.

Kligerman *et al.* (1994b) examined the cytogenetic effects of subacute exposure to phosphine gas in male B6C3F1 mice and F344/N rats (~5 animals/dose). Based on preliminary studies that showed "that 5 ppm was the highest PH3 concentration that could be administered over a 12-day period without significant loss of animals", exposure was conducted in whole-body chambers at target concentrations (measured concentrations were determined but not reported)

of 0, 1.25, 2.5 and 5 ppm for 6 hr/day, 9 days over an 11-day period, for analysis of sister chromatid exchange and chromosome aberrations in cultured peripheral lymphocytes (rats and mice), micronuclei in cytochalasin B-induced binucleated lymphocytes (mice), and micronuclei in polychromatic and normochromatic erythrocytes from bone marrow smears (rats) and peripheral blood smears (mice). In addition, dominant lethal assays in which male mice were exposed to 5 ppm phosphine for 6 hr/day, 10 days over a 12-day period and then mated to non-exposed females in 6 consecutive 4-day mating periods to cover the gamut of sperm morphologic development, were performed.

None of the above assays showed positive results after subchronic exposure to phosphine. The only statistically significant observation was a slight decrease in implants per female mouse in the dominant lethal assay, from 10.2 ± 2.0 in controls to $9.6 \pm 2.2^*$ at 5 ppm; $*p < 0.05$. The authors state that these values were “well within the historical control range as well as the control range of the present study”. The authors could not explain the disparity between their study and those of Garry *et al.* (1989, 1992), who noted chromosomal aberrations in fumigators, and of Barbosa *et al.* (1994), who noted an increase in micronucleus frequency in mice after 13 weeks of daily exposure to 4.5 ppm phosphine. They speculate that the apparent lack of effect in the current study compared to other studies may be due to 1) unique human sensitivities, 2) undocumented chemicals in the environment of fumigators, or 3) the greater total exposure sustained in the Barbosa study (4.5 ppm for 13 weeks).

This study was considered to be supplemental.

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Al-Hakkak (1988) investigated phosphine's potential to produce toxicity and sex-linked recessive lethal mutations in *Drosophila melanogaster* (Oregon-k strain). Exposures were carried out in sex-segregated 10-ml glass vials, with the phosphine administered through the stopper using a gas-tight syringe. The final concentration was calculated to be 0.8 mg/L (~575 ppm), far above the lethal dose in mammals. Exposure times were 10, 30 and 60 minutes, with 100 females and 100-130 males at each time interval. Male survivors were tested for recessive lethal mutations by mating them individually to 3 virgin females (Muller-5 Basc strain). The resulting heterozygous females were mated to Muller-5 males and the number of sterile and lethal cultures enumerated.

The percentage of female flies dying within 2 hours at 0, 10, 30 and 60 minutes of exposure to 0.8 mg/L phosphine was 0, 18, 38 and 59, while for males the percentage was 0, 22.6, 60.1 and 79.2. It was noted that the wings of survivors were permanently raised up, suggesting neuromuscular toxicity. The percentage of recessive lethal mutations was 0.25, 0.76, 1.62 and 2.19*, while the percentage of sterile insects was 0.50, 1.01, 2.48* and 3.52** (*, **: $p < 0.05$, 0.01).

These findings were considered to support a genotoxic potential for phosphine. However, it should be noted that the concentration of phosphine was calculated from the amount predicted to result from the decomposition of an aluminum phosphide pellet allowed to stand in a 25-ml stoppered bottle for 48 hours before administration of a 1 ml of the gas to the 10-ml exposure tubes. Thus the actual phosphine levels were not measured, nor was the possibility that other decomposition products were present considered. This study was considered to be supplemental.

5. DNA damage

McKeon (1993) tested for unscheduled DNA synthesis (UDS) in primary hepatocytes cultured at two timepoints (2-3 hr and 12-14 hr) following a 6-hr whole-body exposure of adult male Fischer 344 rats to phosphine gas. Dose levels were 0, 4.8, 13, 18 and 23 ppm. Positive controls

received intraperitoneal dimethylnitrosamine at 10 or 15 mg/kg for the short and long post-exposure groups, respectively. Hepatocytes were obtained by collagenase treatment, and were allowed to form monolayers on plastic slides within dishes, each containing $\sim 5 \times 10^5$ viable cells. After ~ 2 hours incubation to establish monolayers, unattached cells were removed and medium was added containing 10 $\mu\text{Ci/ml}$ of ^3H -thymidine. After 4 hours, labeled medium was replaced with fresh medium containing 0.25 mM thymidine and incubation continued for ~ 18 hours. Slides were removed, dried and nuclei were swollen. Slides were then fixed, dried, dipped and exposed to emulsion and stained. Typically, 3 slides per rat providing 150 readable cells were evaluated for UDS.

There were no deaths, though labored breathing was noted immediately post-exposure in the 18 and 23 ppm groups and a 5-7% body weight decrease occurred in the 13, 18 and 23 ppm groups. The results of the UDS analyses were uniformly negative, while the positive controls were functional.

This study was considered to be acceptable.

6. Genotoxicity and carcinogenicity of phosphine metabolites or degradates

No data are available on the genotoxicity or carcinogenicity of phosphine metabolites or degradates.

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Table III-5. Genotoxic effects of phosphine (excluding human epidemiology)

Test type / system	Species / strain / culture	Dose range	S9	Result	Reference / comment
Gene mutation:					
<i>E. coli</i> and Ames / <i>Salmonella</i>	<i>E. coli</i> B/r WP2 TRP ⁻ HCR ⁻ ; <i>S. typhimurium</i> (6 tester strains);	640 - 25600 ppm ^a	±	negative	Sutou (1972) ^a / <i>unacceptable</i>
Ames / <i>Salmonella</i>	<i>S. typhimurium</i> (6 tester strains)	4.52 - 4340 ppm	±	negative	Stankowski (1990) ^c / <i>unacceptable</i>
Ames / <i>Salmonella</i>	Urine from phosphine applicators tested in <i>S. typhimurium</i> (2 tester strains)	<2.4 ppm over a 1-hr period	na	negative	Barbosa and Bonin (1994) / <i>supplemental</i>
HPRT / thioguanine resistance	Balb-c mice, 13-wk daily exposure	0.3 - 4.5 ppm	na	negative (possible slight positivity when combined with smoking)	Barbosa <i>et al.</i> (1994) / <i>supplemental</i>
Structural chromosome aberration:					
Chromosome aberration	Phosphine applicators, G ₀ stage lymphocytes	0-4.5 µg/L (0-3.2 ppm)	-	positive	Garry <i>et al.</i> (1989) / <i>supplemental</i>
Chromosome rearrangements	Phosphine applicators, lymphocytes	unknown	-	positive	Garry <i>et al.</i> (1992) / <i>supplemental</i>
Chromosome aberration	Chinese hamster ovary cells	426 - 4957 ppm	±	positive ^b	SanSebastian (1990) / <i>acceptable</i>
Micronucleus formation	Phosphine applicators	<2.4 ppm over a 1-hr period	na	negative	Barbosa and Bonin (1994) / <i>supplemental</i>
Micronucleus formation	Balb-c mice, 13-wk, 6-hr daily exposures	0.3 - 4.5 ppm	na	positive	Barbosa <i>et al.</i> (1994) / <i>supplemental</i>
Chromosome aberrations, sister chromatid exchanges, cell cycle kinetics and micronuclei	male CD-1 mice, 6-hr acute exposure	5.24 - 16.00 ppm	na	negative	Kligerman <i>et al.</i> (1994a) / <i>supplemental</i>
Chromosome aberrations, sister chromatid exchanges and micronuclei	male B6C3F1 mice & F344/N rats, 6-hr daily exposures, 11 days	1.25 - 5 ppm	na	negative	Kligerman <i>et al.</i> (1994b) / <i>supplemental</i>
Dominant lethal effects	male B6C3F1 mice	5 ppm	na	negative	Kligerman <i>et al.</i> (1994b) / <i>supplemental</i>
Recessive lethal effects	<i>Drosophila melanogaster</i>	575 ppm	na	positive	Al-Hakkak (1988) / <i>supplemental</i>
DNA damage:					
Unscheduled DNA synthesis	Fischer 344 rat	4.8 - 23 ppm	na	negative	McKeon (1993) / <i>acceptable</i>

Abbreviations: na, not applicable.

^a The actual phosphine concentrations in the agar were recalculated by Eric Kwok (DPR, personal communication) to range between 7 and 134 ppm based on a study by Liss and Slater (1974). This study was considered to be unacceptable according to FIFRA guidelines.

^b Positive results were seen only at the 8-hr post-incubation time point, \pm S9, not at the 18- or 26-hr points. There was also some question as to the functionality of the S9 system in that assay (see summary).

^c The actual phosphine concentrations in the agar were likely to be about 200-fold lower than the concentration measured in the atmosphere above the agar--- *i.e.*, between 2.3 ppb and 22 ppm--- as was the case in the Sutou (1982) study (see footnote "a").

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F. REPRODUCTIVE TOXICITY

A reproductive toxicity study on phosphine was not available for analysis.

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G. DEVELOPMENTAL TOXICITY

1. Overview

One epidemiologic study from the open literature suggests that children born to couples where the father is a phosphine applicator have a somewhat higher likelihood of birth defects, showing an odds ratio of 2.48 (Garry *et al.*, 2002). However, in the only laboratory developmental toxicity study available for analysis, Schroeder (1989) failed to detect developmental effects in CD rats at phosphine inhalation doses through 4.9 ppm.

2. Laboratory animal studies (inhalation)

a. Rats

Schroeder (1989) studied the effects on fetal development of whole-body inhalation exposure of pregnant CD rats, 24/dose, to phosphine gas (1% in nitrogen). Treatment was for 6 hr/day, during gestation days (gd) 6-15 inclusive. The target doses were 0, 0.03, 0.3, 3, 5 and 7.5 ppm. The mean analytical concentrations were 0, 0.034, 0.33, 2.8, 4.9 and 7.0 ppm. The 7.0 ppm group was terminated when 14 dams died within 3-10 days of treatment. Observations for clinical signs and mortality were made twice daily. Detailed physical examinations on each female occurred on gd 0, 6-15 and 20. Bodyweights were determined on gd 0, 6, 10, 12, 16 and 20, with food consumption recorded for gd 0-6, 6-10, 10-16 and 16-20. Survivors were sacrificed on gd 20 and subjected to necropsy. Uteri were removed, weighed and evaluated for fetuses and resorption sites, the ovaries dissected and the corpora lutea counted. Fetal gender, weight and external malformations / variations were noted, after which one half of the fetuses from each litter was examined for visceral effects while the remainder were evaluated for skeletal effects.

Except for the 7.0 ppm group (see above), there were no maternal deaths during the study. Other than those high dose mortalities, neither clinical nor toxicologic signs were observed in this study. There were no treatment effects on maternal weight gain or on gravid uterine weights, through 5 ppm. Food consumption appeared unaffected. Reproductive and pregnancy parameters (number of corpora lutea, number of implantation sites, preimplantation loss, number of viable fetuses, number of dead fetuses, number of resorptions, resorptions / implants, number of litters with resorptions, mean viable fetus bodyweights, gender ratio of viable fetuses) were not clearly different than controls. Maternal postmortem examinations were normal, except for reddening of the lungs and livers of the 7.5 ppm animals that died, which was attributed to the lack of exsanguination prior to exam in those individuals. Neither treatment related malformations nor variations were detected.

The maternal NOEL was set at 4.9 ppm, based on mortalities at 7.0 ppm. The developmental NOEL was set at 4.9 ppm, based on the absence of any treatment effects through that dose. This study was considered to be acceptable by FIFRA standards.

b. Rabbits

A rabbit developmental toxicity study was not available for analysis.

Table III-6. NOEL and LOEL values for studies on the developmental toxicity of phosphine

Species, strain	Study type & exposure regimen	Effects at LOEL	NOEL (ppm)	LOEL (ppm)	Reference / Comment
rat, CD	6 hr/day, gestation days 6-15	maternal: death developmental: none	4.9 4.9	7.0 >4.9 ^a	Schroeder (1989) / <i>acceptable</i>

^a This was the highest non-lethal dose.

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H. NEUROTOXICITY (ACUTE AND SUBCHRONIC)

1. Overview

In separate studies, Schaefer examined the toxicologic effects of acute and subchronic phosphine exposures in rats (Schaefer, 1998a and 1998b, respectively). A single 4-hr exposure to phosphine at as low as 21 ppm resulted in decrements in motor activity counts and stereotypic time immediately post-exposure (reversed by the next measurement at 7 days). FOB parameters were less affected by acute phosphine exposure, though other indicators, including decreased body temperature, arousal, palpebral closure and slowed or labored respiration, were impacted by acute exposure. Subchronic exposure led to an increased incidence in sleeping behavior and its correlate, complete palpebral closure, by 4 weeks, slowed respiration at weeks 8 and 13, and decreased body temperature at week 13, all at the high dose of 3 ppm.

2. Laboratory animal studies (inhalation)

Schaefer (1998a) examined the effects of acute exposure to phosphine gas on Sprague-Dawley derived-Crl:CD BR VAF/Plus[®] rats. Eleven rats/sex/dose were exposed for 4 hours in whole-body chambers to 0, 21, 28 or 38 ppm phosphine (analytical concentrations determined by gas chromatography), after which they were observed for 14 days. Bodyweights were determined pre-exposure and at 7 and 14 days. Functional observational batteries (FOBs) were executed within 8 hours of exposure and again at 7 and 14 days. Motor activity assessments were carried out using a Digiscan[®] Activity Monitor. Six rats/sex/dose were subjected to neuropathology exams, while complete postmortem exams were carried out on the remaining 5 rats/sex/dose.

No animals died as a result of phosphine exposure, though one high-dose male was found to be emaciated. Except for that animal, which showed weight loss at day 8, no effects on bodyweight were detected in the study. Though occasional differences between dose groups were noted in the FOB tests, it was difficult to relate them unambiguously to phosphine exposure, with the possible exception of the following:

- 1) Body temperature, day 1, both sexes (at increasing doses, °C, σ : 38.9±0.4, 37.4±0.3**, 37.1±0.4**, 36.0±0.6; ♀ : 39.1±0.3, 37.3±0.5**, 37.1±0.4**, 35.8±0.8; **p<0.01).
- 2) Arousal, day 1, "slightly low" and "low" combined, females (2/11, 5/11, 5/11, 11/11).
- 3) Palpebral closure, day 1, "completely shut", both sexes (σ : 0/11, 4/11, 0/11, 6/11; ♀ : 1/11, 4/11, 6/11, 7/11). This was interpreted as a sign of sleeping behavior.
- 4) Slowed or labored respiration, day 1, both sexes (σ : 1/11, 5/11, 5/11, 7/11; ♀ : 0/11, 3/11, 3/11, 8/11).

On the other hand, day 1 measurements of motor activity and the amount of time spent in stereotypy (defined as the total time spent in repetitive movements) showed strong dose-dependent effects, particularly during the 0-10 minute and 10-20 minute test periods (Table III-7). After 20 minutes, these measures were reduced in all dose groups as the animals habituated to the motor observation arena, though some treatment effects were still evident during the 20-30-min interval. Such changes were not apparent after 7 days of recovery.

Adrenal gland weights (mean absolute weight and mean weight relative to bodyweight and brain weight) were statistically increased in 38 ppm males, with a similar increase noted at 21 ppm. Such an effect was absent in 28 ppm males and in all females, which led the authors to speculate that it was not due to phosphine exposure. Neither gross nor neurohistopathologic changes were evident.

The neurotoxicity LOEL for acute inhalation exposure to phosphine was set at the low dose of 21 ppm, based on the various measures of decreased motor activity and stereotypic time, and on altered FOB parameters (body temperature, arousal, palpebral closure and slowed / labored respiration) at that dose. This study was acceptable by FIFRA standards.

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Table III-7. The effect of phosphine exposure on motor activity and stereotypic time counts, day 1 (Schaefer, 1998a)

	Phosphine ^a				LED ₁₀ / ED ₁₀ ^b
	0 ppm	21 ppm	28 ppm	38 ppm	
Horizontal activity ♂					
0-10 min	3188±1123.3	751±227.2**	901±383.1**	518±201.4**	1.94 / 2.52
10-20 min	1073±717.6	240±182.2**	123±125.2**	22±23.7**	2.99 / 4.32
20-30 min	621±910.3	66±67.3	115±142.8	58±72.0	4.76 / 9.00
Horizontal activity ♀					
0-10 min	4217±1190.8	1212±481.4**	2191±1092.9**	694±354.7**	3.08 / 4.38
10-20 min	1552±1408.6	220±187.5*	391±376.1	161±233.9*	3.70 / 5.74
20-30 min	259±261.4	119±162.8	91±198.3	80±207.6	6.60 / 16.87
Vertical activity ♂					
0-10 min	1019±315.3	412±171.1**	256±150.9**	343±144.9**	2.08 / 2.75
10-20 min	484±326.9	74±66.2**	14±22.4**	26±56.5**	2.58 / 3.57
20-30 min	209±326.4	29±54.1	8±18.4	38±59.5	4.60 / 8.53
Vertical activity ♀					
0-10 min	850±264.6	497±174.1**	406±194.6**	247±121.1**	4.16 / 6.70
10-20 min	351±300.8	121±157.9	45±75.5*	31±48.7*	4.30 / 7.25
20-30 min	51±81.5	37±76.0	1±1.6	23±71.4	8.14 / -9999
Total distance ♂					
0-10 min	2066±879.3	417±101.0**	586±256.1**	309±108.6	2.16 / 2.82
10-20 min	679±651.3	66±100.6*	36±50.5*	4±9.8*	3.34 / 5.04
20-30 min	406±714.6	21±28.2	25±47.4	23±31.0	4.92 / 9.57
Total distance ♀					
0-10 min	2906±1073.2	573±216.5**	1434±738.7**	410±282.7**	2.99 / 4.44
10-20 min	945±1094.9	71±93.8	144±196.2	32±61.3	3.98 / 6.54
20-30 min	96±135.1	32±67.3	6±11.0	24±76.1	5.46 / 11.51
Stereotypic time ♂					
0-10 min	104±35.8	43±17.3**	33±15.4**	26±14.4**	2.53 / 3.48
10-20 min	34±16.4	11±10.0**	6±5.8**	1±1.4**	3.07 / 4.45
20-30 min	24±34.4	2±3.9	7±9.2	2±2.6	4.99 / 9.78
Stereotypic time ♀					
0-10 min	126±30.8	65±32.0**	75±36.6**	31±15.5**	4.79 / 8.20
10-20 min	65±55.7	12±10.2*	21±16.3	9±16.7	3.92 / 6.37
20-30 min	17±15.0	7±10.6	6±13.7	5±12.1	6.15 / 14.40

*, **: p<0.05, 0.01, respectively.

^a n = 11 for all determinations except for the 20-30 min interval at 38 ppm (♂, n=8; ♀, n=10)

^b Benchmark dose analysis, polynomial algorithm, implicit dichotomization @ 0.61 (≈ 10% response). Values are expressed in ppm units.

Schaefer (1998b) administered phosphine gas by the inhalation route to CD rats, 16/sex/dose. Exposures were carried out in whole-body chambers for 13 weeks, 5 days/wk, 6 hr/day. The analytically determined doses were 0, 0.3, 1.01 and 2.99 ppm (nominal: 0, 0.3, 1 and 3 ppm); hourly samples were analyzed by gas chromatography. Additional groups of 6/sex exposed to 0 or 3 ppm were allowed an additional 2-wk recovery period before sacrifice. Observations for mortality and toxic signs were made twice daily. Detailed clinical exams and bodyweight determinations were carried out weekly. Hematologic, serum chemical, ophthalmologic, urine, necropsy and histopathologic evaluations were conducted at termination. Neuropathologic exams were carried out on six randomly selected rats/sex/dose. Functional observational batteries (FOBs) were executed pretest and during weeks 4, 8, 13 and post-2-wk recovery period. Motor activities were evaluated at those time points with a Digiscan® Activity Monitor.

There were 3 mortalities during the study: one male each at 0.3 and 3 ppm, and one female at 3 ppm. None of these was considered to be due to phosphine exposure (the high dose male death was incidental to bleeding). Observations of clinical signs, body weights, urine composition and serum chemistry did not reveal a treatment effect. High dose females showed elevated lymphocyte counts at study termination ($7.4, 6.0^*, 8.6$ and $9.2^* \times 10^3/\text{mm}^3$; $*p < 0.05$), though this was not considered of toxicologic significance (for one thing, it was within historical control limits).

Complete palpebral closure (also recorded as sleeping behavior) was noted at the high dose, though statistical significance was achieved only at week 4 in males (Table III-8). There was a possibility that this parameter was increased at lower doses, but the high incidence in pre-test controls made it virtually impossible to assign a treatment level below the high dose. Some high dose males experienced slowed respiration at weeks 8 and 13, though statistical significance was not achieved (wk 8: 1/17, 1/11, 1/11, 4/17; wk 13: 1/17, 0/11, 0/11, 3/17). Body temperatures were statistically lower in high dose males at week 13 ($^{\circ}\text{C}$: 38.3, 38.2, 38.0, 37.7**; $p < 0.01$). Statistically significant differences between treated groups and controls arose in the motor activity determinations (horizontal activity, vertical activity and total distance). However, these differences were both non-systematic and present in pre-test animals, making it difficult to assign toxicologic significance to the motor activity observations.

Necropsies of non-neural tissues did not reveal abnormalities, nor did organ weight determinations. Neurohistopathologic analyses conducted on control and high-dose animals also did not reveal clear abnormalities, though degeneration of the sciatic nerve was noted in 0/6 control and 3/6 treated males (right sciatic nerve) and in 1/6 control and 4/6 treated females (left sciatic nerve). It was not clear that these were phosphine-related effects, however, as in each case data from the opposing nerve did not show a similar tendency.

A NOEL for this study was set at 1 ppm based on the following observations in high dose (2.99 ppm) males: statistically significant palpebral closure (sleeping behavior) at week 4, slowed respiration at weeks 8 and 13 and statistically significant lowered body temperatures at week 13.

This study was acceptable by FIFRA standards.

Table III-8. Incidence of palpebral closure / sleeping behavior after subchronic exposure to phosphine gas. (Schaefer, 1998b)

	Males				Females			
	0 ppm	0.3	1.01	2.99	0 ppm	0.3	1.01	2.99
Exposure period n =	(17)	(11)	(11)	(17)	(17)	(11)	(11)	(17)
Pre-test								
Total palpebral closure (sleeping)	0	4	1	0	2	2	3	6
►Incidence (%) ^a	0	36	9	0	12	18	27	35
Week 4								
Total palpebral closure (sleeping)	0	1	3	8*	0	2	1	6
►Incidence (%)	0	9	27	47	0	18	9	35
Week 8								
Total palpebral closure (sleeping)	0	2	4	5	1	0	0	2
►Incidence (%)	0	18	36	29	9	0	0	12
Week 13								
Total palpebral closure (sleeping)	0	1	3	6	0	0	0	2
►Incidence (%)	0	9	27	35	0	0	0	12
Recovery period n =	(6)	(0)	(0)	(6)	(6)	(0)	(0)	(6)
Recovery								
Total palpebral closure (sleeping)	0	-	-	1	0	-	-	0
►Incidence (%)	0	-	-	6	0	-	-	0

*p<0.05

^a Incidence is calculated as the percentage of animals exhibiting this character.

I. TOXICITY OF PHOSPHINE DEGRADATES AND METABOLITES

Waritz and Brown (1974) examined the acute and subacute toxicity of phosphine, phenylphosphine and triphenylphosphine. This work is summarized above in section III.B.3.

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IV. RISK ASSESSMENT

A. HAZARD IDENTIFICATION

1. Non-oncogenic effects

a. Acute toxicity

The risk from acute exposure to phosphine gas was estimated using a critical NOEL of 5 ppm established by Newton (1990). Newton observed no adverse effects in Fischer 344 rats exposed by the inhalation route to 5 ppm for 13 days (6 hr/day, 5 days/wk), while 4/10 females (0/10 males) died within 3 days of exposure to 10 ppm (a single exposure at that dose was not sufficient for lethality). Other effects included renal tubular necrosis of the outer cortex in both sexes at 10 ppm, as well as statistically significantly increased male kidney weights (female data at 10 ppm were unreliable because only one animal was available for analysis). The proximity of the no-effect and lethal levels is important to note. A parallel group exposed to 3 ppm phosphine did not show clear adverse effects even after 13 weeks of daily exposure, supporting the critical acute NOEL designation. However, functional observational batteries were not carried out in the Newton (1990) study, increasing the possibility that subtle neurologic effects were overlooked.

For acute, subchronic and chronic toxicity, absolute air concentrations, not internal doses, were used to calculate margins of exposure. This course of action was based primarily on the observation that death occurred at approximately the same concentration regardless of laboratory species (Pepelko *et al.*, 2004; see further discussion in section V. below), suggesting that absorption, metabolism and distribution played secondary roles in mediating the toxicity of phosphine. In addition, many of the clinical signs of phosphine intoxication were consistent with a direct toxic interaction between gas and tissue (particularly lung).

Support for the 5 ppm critical acute value came from several studies:

1. Morgan *et al.* (1995) noted mortality and moribundity in Fischer 344 rats and B6C3F1 mice within four daily 6-hr exposures at 10 ppm, similar to Newton (1990). Anemia, clinical chemistry findings, renal tubular necrosis, hepatic hemorrhage / necrosis and myocardial degeneration were also noted in mice at that dose. No such observations were made at the 4-day NOEL dose of 4.98 ppm, precisely that determined by Newton *et al.* (1990) in the same strain of rat for a 13-day exposure.
2. Schroeder (1989) observed the deaths of 14 / 24 pregnant CD rats within 3-10 days of exposure to 7 ppm phosphine. Neither deaths nor toxic signs were observed at the NOEL dose of 4.9 ppm, equivalent to that observed by Newton (1990).
3. Omae *et al.* (1996) noted face washing movements, high physical activity, tremors, piloerection, lung congestion, nasal cavity exudate and necrotic nasal epithelial cells / cell infiltration in ICR mice after a single 4-hr exposure to 22.5 ppm phosphine. Death was observed in 8-hr exposures to virtually the same air concentration, emphasizing the seriousness of the endpoint and corroborating the observations of lethality at 10 ppm within 3 days in the Newton (1990) study.

As 22.5 ppm was the only dose tested in the acute part of that study, a NOEL was not designated.

b. Subchronic toxicity

The potential for subchronic toxicity due to phosphine exposure was evaluated using a critical NOEL of **1 ppm**) from the study of Schaefer (1998b). This selection was based on observations of statistically significant total palpebral closure (sleeping behavior) at week 4, slowed respiration at weeks 8 and 13, and statistically significant lowered body temperatures at week 13 with exposure to 3 ppm phosphine gas (6 hr/day, 5 days/wk).

Support for the critical subchronic LED₁₀ determination was forthcoming in three studies:

1. Omae *et al.* (1996) noted bodyweight gain decrements and histopathologic changes (pulmonary congestion, hepatocytic vacuolization, accumulation of cells in the liver sinusoid, nasal cavity exudate and necrotic epithelial cells and cell infiltration) in male ICR mice at 4.9 ppm resulting from daily 6-hr exposures over a 4-wk period. This was the only dose employed in the subchronic part of Omae's study.
2. Waritz and Brown (1975) noted bodyweight gain decrements in CD rats during and after 12 daily 4-hr exposures to 4.1 ppm phosphine. The clinical signs at this dose---the only dose utilized in the study---were reported to be "typical of mild respiratory irritation, including lacrimation, salivation, dyspnea, [and] red ears", with piloerection appearing after the fourth exposure. In addition to these relatively mild symptoms, there was a weight gain decrement of ~33% over the 12 days.
3. A NOEL of 1 ppm (0.45 mg/kg/day) was established by Barbosa *et al.* (1994) in Balb-c mice. This was based on a statistically significant increase in micronuclei in binucleated splenic lymphocytes, as well as decrements in body weight gain, particularly in females, at the LOEL dose of 4.5 ppm after 13 weeks of daily inhalation exposure.

c. Chronic toxicity

Only one chronic study on phosphine gas, that of Newton (1998) in Fischer 344 rats, was available for analysis. The NOEL for that study, 3 ppm, was the highest dose used in that study. In view of the proximity of that value to a lethal dose (>5 ppm), it is remarkable that Newton observed no adverse effects, though the experimental design did not include detailed measurements of neurotoxicity (as observed by Schaefer, 1998a and 1998b) or genetic toxicity (as observed by Barbosa *et al.*, 1994).

Phosphine's chronic toxicity will be evaluated using the critical subchronic NOEL of **1 ppm**.

d. Reproductive toxicity

No reproductive toxicity studies on phosphine were available for analysis.

e. Developmental toxicity

Schroeder (1989) saw no developmental effects at any sublethal dose (*i.e.*, up to 4.9 ppm, but less than the study's lethal dose of 7 ppm) in CD rats. A rabbit developmental study was not

available for review.

f. Genotoxicity

Epidemiologic studies on phosphine applicators were consistent with a clastogenic role for phosphine in human populations (Garry *et al.*, 1989 and 1992). A study in phosphine fumigators showed no effect on micronucleus formation (Barbosa and Bonin, 1994). Phosphine did not induce mutations in two FIFRA-acceptable *in vitro* studies (Stankowski, 1990; Barbosa *et al.*, 1994) and in one unacceptable *in vitro* study (Sutou, 1972), nor did it cause DNA damage in one *in vivo* unscheduled DNA synthesis study in Fischer 344 rats (McKeon, 1993). However, 13 weeks of daily 6-hr exposures to Balb-c mice led to statistically elevated micronucleus formation in splenic lymphocytes (Barbosa *et al.*, 1994). SanSebastian (1990) reported a statistically significant increase in chromosome aberrations at the 8-hr point, but not at the 18 or 26-hr points, in cultured Chinese hamster ovary cells. Cytogenetic effects were not observed in male mice or male rats subjected to acute or subacute (11-12 days) phosphine exposure (Kligerman *et al.*, 1994a and 1994b). The reasons for these discrepancies were not clear.

2. Oncogenicity

There was no evidence for oncogenicity in the 2-year Fischer 344 rat study on phosphine gas (Newton, 1998). A comparable mouse study was not available for review.

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B. EXPOSURE ASSESSMENT

1. Introduction

Estimates of exposure to phosphine resulting from various occupational and bystander scenarios were developed by the Worker Health and Safety Branch (WH&S) of DPR. These, along with all of the calculations and assumptions that underlay those estimates, are contained in a companion report to this document entitled Estimation of Exposure to Persons in California to Phosphine (DPR, 2013). Exposure estimates from that report are summarized in the following sections.

2. Occupational exposure (including occupational and residential bystander exposures)

A range of occupational exposure scenarios were considered. These included fumigation operations in grain elevators, farm bins, flat storage facilities, warehouses, rail cars (bulk and box cars), ship holds and shipping containers. Spot fumigation and burrowing pest fumigation were also examined. Occupational categories under these tasks included applicators, aerators and spent fumigant retrievers. In addition, exposures to occupational and residential bystanders were estimated. The use of personal protective gear was assumed based on label instructions.

Exposures were estimated for short-term, seasonal and annual durations. As noted in the accompanying exposure assessment document (DPR, 2012), many of these estimates were derived from two studies - a registrant task force study and a study by the National Institute for Occupational Safety and Health. The exposure values for applicators, aerators, and occupational bystanders associated with commodity fumigation in ship holds and shipping containers were surrogate estimates. One study provided the data for estimating exposure from burrowing pest fumigation. Detailed descriptions of, and references to, these studies can be found in the exposure assessment document.

Short-term estimates represent acute exposures as well as exposures of up to a week in duration. Depending on the scenario, these were generated using 8-hr, 12-hr or 24-hr time weighted averages (TWA). As noted in the exposure assessment, the highest TWA work shift breathing-zone phosphine air concentration, normalized to the maximum product label application rate and corrected for sample recovery, was used to estimate short-term exposure for the workers. For residential bystanders, when data were lacking, short term exposure was assumed to be the 24-hr equivalent of the 8-hr TWA permissible exposure limit of 0.3 ppm on the product labels. Worker seasonal exposure estimates were calculated from the arithmetic mean of the work shift breathing-zone phosphine air concentrations, which were normalized to the estimated seasonal application rate and corrected for recovery. However, if only one replicate (*i.e.*, one work shift TWA exposure value for one worker) was available, the seasonal exposure was derived from the short-term exposure estimate. For the residential bystander, seasonal exposure was derived from that replicate. Depending upon the scenario, seasonal exposures were 6 or 8 months in length. Annual exposure estimates were calculated by multiplying the seasonal estimate by the ratio of the length of the season in months to the number of months in the year (*e.g.*, 8 months/12 months).

Occupational and bystander exposure estimates appear in Table IV-1.

3. Ambient exposure

Significant ambient exposure (*i.e.*, exposure to the general public distal to, and not associated

with, specific applications) was not anticipated.

4. Dietary exposure

Though tolerances for phosphine exist for ~50 food crops, it is unlikely that residues would remain at the time of consumption. The USDA's Pesticide Data Program, the primary source of food residue data intended for risk assessment, does not assay for phosphine. This is probably due to the low possibility of residue detection. USEPA appeared to concur in their 1998 RED: "For all data submitted to the Agency for establishment of food tolerances, residues of phosphine gas have been typically reported as non-detectable." (USEPA, 1998; p. 62). In its DEEM[®]-based acute and chronic exposure calculations, USEPA set the phosphine residue values at the highest limit of detection, 0.006 ppm, for all commodities carrying tolerances. Even with this conservative approach, the predicted exposures did not indicate a level of concern, as no subpopulation exceeded 30% of the reference dose for acute exposure (USEPA NOEL = 5 ppm) or 9% for chronic exposure (USEPA NOEL = 3 ppm). Consequently, DPR does not consider an independent dietary risk analysis to be necessary at this time.

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Table IV-1. Estimates of occupational and bystander exposure to phosphine gas

Exposure scenario	Short-term exposure (ppm)	Seasonal exposure (ppm)	Annual exposure (ppm)
Commodity fumigation in upright concrete grain elevator bins (DPR, 2012: Table 13)			
Occupational bystander (inside and outside of grain-elevator)	0.02	0.2	0.13
Residential bystander	0.1	0.1	0.07
Occupational bystander (inside and outside of grain-elevator), post application	0.01	0.14	0.09
Residential bystander, post application	0.1	0.1	0.07
Occupational bystander (outside of grain-elevator), post aeration	0.005	0.07	0.05
Residential bystander, post aeration	0.1	0.1	0.07
Commodity fumigation in farm bins (DPR, 2012: Table 14)			
Applicator	0.05	0.007	0.005
Aerator	0.01	0.3	0.2
Occupational bystander (air monitor)	0.02	0.006	0.004
Occupational bystander (adjacent to farm bin during fumigation)	0.3	0.3	0.2
Occupational bystander (adjacent to farm bin during aeration)	0.3	0.3	0.2
Residential bystander (adjacent to farm bin during fumigation and aeration)	0.1	0.1	0.07
Commodity fumigation flat storage facilities (DPR, 2012: Table 15)			
Applicator	0.005	0.05	0.03
Aerator	0.01	0.3	0.2
Occupational bystander (adjacent to flat storage facility during fumigation)	0.3	0.3	0.2
Occupational bystander (adjacent to flat storage facility during aeration)	0.3	0.3	0.2
Residential bystander	0.1	0.1	0.07
Commodity fumigation in warehouses (DPR, 2012: Table 16)			
Applicator	0.02	0.006	0.004
Aerator	0.01	0.3	0.2
Spent fumigant retriever	0.005	0.12	0.08

Occupational bystander (adjacent to warehouse during fumigation)	0.3	0.3	0.2
Occupational bystander (adjacent to warehouse during aeration)	0.3	0.3	0.2
Residential bystander	0.1	0.1	0.07
Commodity fumigation in bulk rail cars (DPR, 2012: Table 17)			
Applicator	0.02	0.004	0.003
Occupational bystander (assistant worker)	0.01	0.2	0.13
Occupational bystander (nearby worker: post-application/pre-aeration)	0.004	0.1	0.07
Aerator	0.04	0.01	0.007
Occupational bystander (assistant aerator)	0.06	0.06	0.04
Occupational bystander (nearby worker: post-aeration)	0.004	0.2	0.13
Occupational bystander (packaging line for consumer products worker)	0.04	0.2	0.13
Residential bystander	0.1	0.1	0.07
Commodity fumigation in box cars (DPR, 2012: Table 18)			
Applicator	0.04	0.005	0.003
Occupational bystander (assistant worker: application)	0.01	0.004	0.003
Occupational bystander (nearby worker: application)	0.02	0.3	0.2
Occupational bystander (nearby worker: post-application)	0.03	0.3	0.2
Residential bystander	0.1	0.1	0.07
Commodity aeration in box cars (DPR, 2012: Table 19)			
Aerator (outdoor)	0.03	0.01	0.007
Aerator (indoor)	0.05	0.02	0.01
Occupational bystander (assistant aerator: outdoor aeration)	0.005	0.17	0.11
Occupational bystander (nearby worker: indoor post-aeration)	0.02	0.009	0.006
Occupational bystander (packaging line for consumer products worker)	0.04	0.2	0.13
Residential bystander	0.1	0.1	0.07
Commodity fumigation in ship holds (DPR, 2012: Table 20)			

Applicator	0.005	0.05	0.03
Aerator	0.04	0.01	0.007
Occupational bystander (application)	0.004	0.1	0.07
Occupational bystander (aeration)	0.004	0.2	0.13
Occupational bystander (in-transit fumigation)	0.1	0.1	0.07
Commodity fumigation in ship containers (DPR, 2012: Table 21)			
Applicator	0.04	0.005	0.003
Aerator	0.03	0.01	0.007
Occupational bystander (application)	0.02	0.3	0.2
Occupational bystander (aeration)	0.004	0.2	0.13
Occupational bystander (in-transit fumigation)	0.1	0.1	0.07
Spot fumigation (DPR, 2012: Table 22)			
Applicator	0.004	n/a	n/a
Aerator / retriever / deactivator	0.008	n/a	n/a
Occupational bystander	0.3	n/a	n/a
Residential bystander	0.1	n/a	n/a
Burrowing pest fumigation (DPR, 2012: Table 23)			
Applicator (certified)	0.22	0.03	0.01
Applicator (non-certified)	0.24	0.06	0.03
Reentry worker	0.06	n/a	n/a
Occupational bystander in structure 100 ft. from treated field	0.03	n/a	n/a

C. RISK CHARACTERIZATION

1. Introduction

The potential for non-oncogenic health effects resulting from exposure to phosphine was expressed as the margin of exposure (MOE). MOEs are the ratio of the critical NOEL value, derived from the definitive acute, subchronic or chronic studies, divided by the estimated human exposure value. In the case of phosphine---which was assumed to act primarily at the point of contact with the affected tissue (eg., the lung) and only secondarily after absorption through the gut or lung and distribution to tissues---both the NOEL and exposure values are expressed as air concentrations (ppm) rather than as internal doses (mg/kg).

$$\text{Margin of Exposure (MOE)} = \frac{\text{NOEL (ppm)}}{\text{Exposure dose (ppm)}}$$

MOEs of 100 or above were considered to be protective of human health if the relevant adverse effects were observed in experimental animal studies, as was the case in this assessment. This reflected the default assumptions that (1) humans are 10-fold more sensitive than animals and (2) a 10-fold range of sensitivity exists within the human population. All of the critical endpoints used in this report were derived from animal studies on phosphine gas. The critical acute, subchronic and chronic NOELs were 5, 1 and 1 ppm, respectively.

2. Risk from occupational and bystander exposure

Many acute, seasonal and annual use scenarios produced MOEs of under 100, indicating insufficient health protection for workers and bystanders under those scenarios. Moreover, some acute MOEs for occupational bystanders were as low as 17, including those adjacent to farm bins, flat storage facilities or warehouses during fumigation or aeration. In addition, residential or occupational bystanders under most occupational scenarios showed MOEs of 50. Finally, MOEs of less than 10 were common for many seasonal and annual scenarios. In light of the severity of the acute endpoint (death) and the proximity of the critical acute and subchronic / chronic NOELs, these low MOEs were cause for concern and mitigation measures should be considered.

MOEs for estimated occupational and bystander exposures appear in Table IV-2.

3. Risk from ambient air exposure

As noted above in section IV.B.3., ambient exposure (*i.e.*, exposure to the general public distal to, and not associated with, specific applications) was not anticipated.

4. Risk from dietary exposure

A dietary analysis was not carried out---see section IV.B.4. above.

Table IV-2. Risk estimates (MOEs) for occupational and bystander scenarios as a result of exposure to phosphine gas

Exposure scenario	Margins of exposure		
	Acute	Seasonal	Annual
Commodity fumigation in upright concrete grain elevator bins (DPR, 2012: Table 13)			
Occupational bystander (inside and outside of grain-elevator)	250	5	8
Residential bystander	50	10	14
Occupational bystander (inside and outside of grain-elevator), post application	500	7	11
Residential bystander, post application	50	10	14
Occupational bystander (outside of grain-elevator), post aeration	1000	14	20
Residential bystander, post aeration	50	10	14
Commodity fumigation in farm bins (DPR, 2012: Table 14)			
Applicator	100	143	200
Aerator	500	3	5
Occupational bystander (air monitor)	250	556	250
Occupational bystander (adjacent to farm bin during fumigation)	17	3	5
Occupational bystander (adjacent to farm bin during aeration)	17	3	5
Residential bystander (adjacent to farm bin during fumigation and aeration)	50	10	14
Commodity fumigation flat storage facilities (DPR, 2012: Table 15)			
Applicator	1000	20	33
Aerator	500	3	5
Occupational bystander (adjacent to flat storage facility during fumigation)	17	3	5
Occupational bystander (adjacent to flat storage facility during aeration)	17	3	5
Residential bystander	50	10	14
Commodity fumigation in warehouses (DPR, 2012: Table 16)			
Applicator	250	167	250
Aerator	500	3	5

Spent fumigant retriever	1000	8	13
Occupational bystander (adjacent to warehouse during fumigation)	17	3	5
Occupational bystander (adjacent to warehouse during aeration)	17	3	5
Residential bystander	50	10	14
Commodity fumigation in bulk rail cars (DPR, 2012: Table 17)			
Applicator	250	250	333
Occupational bystander (assistant worker)	500	5	8
Occupational bystander (nearby worker: post-application/pre-aeration)	1250	10	14
Aerator	125	100	143
Occupational bystander (assistant aerator)	83	17	25
Occupational bystander (nearby worker: post-aeration)	1250	5	8
Occupational bystander (packaging line for consumer products worker)	125	5	8
Residential bystander	50	10	14
Commodity fumigation in box cars (DPR, 2012: Table 18)			
Applicator	125	200	333
Occupational bystander (assistant worker: application)	500	250	333
Occupational bystander (nearby worker: application)	250	3	5
Occupational bystander (nearby worker: post-application)	167	3	5
Residential bystander	50	10	14
Commodity aeration in box cars (DPR, 2012: Table 19)			
Aerator (outdoor)	167	100	143
Aerator (indoor)	100	50	100
Occupational bystander (assistant aerator: outdoor aeration)	1000	6	9
Occupational bystander (nearby worker: indoor post-aeration)	250	111	167
Occupational bystander (packaging line for consumer products worker)	125	5	8
Residential bystander	50	10	14

Commodity fumigation in ship holds (DPR, 2012: Table 20)			
Applicator	1000	20	33
Aerator	125	100	143
Occupational bystander (application)	1250	10	14
Occupational bystander (aeration)	1250	5	8
Occupational bystander (in-transit fumigation)	50	10	14
Commodity fumigation in ship containers (DPR, 2012: Table 21)			
Applicator	125	200	333
Aerator	167	100	143
Occupational bystander (application)	250	3	5
Occupational bystander (aeration)	1250	5	8
Occupational bystander (in-transit fumigation)	50	10	14
Spot fumigation (DPR, 2012: Table 22)			
Applicator	1250	n/a	n/a
Aerator / retriever / deactivator	625	n/a	n/a
Occupational bystander	17	n/a	n/a
Residential bystander	50	n/a	n/a
Burrowing pest fumigation (DPR, 2012: Table 23)			
Applicator (certified)	23	33	100
Applicator (non-certified)	21	17	33
Reentry worker	83	n/a	n/a
Occupational bystander 100 ft. from treated field	167	n/a	n/a

MOE = (critical NOEL) ÷ (exposure dose)

^a Critical acute NOEL = 5 ppm

^b Critical subchronic NOEL = 1 ppm

^c Critical chronic NOEL = 1 ppm

V. RISK APPRAISAL

Risk assessment is the process by which the toxicity of a compound is compared to the potential for human exposure under specific conditions in order to estimate the risk to human health. Every risk assessment has inherent limitations relating to the relevance and quality of the toxicity and exposure data. Assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment and exposure-assessment processes, resulting in uncertainty in the risk characterization, which integrates the information from those three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the magnitude of those uncertainties varies with the availability and quality of the toxicity and exposure data, and with the relevance of that data to the anticipated exposure scenarios.

In the following sections, the uncertainties associated with characterization of health risks from exposure of workers and the general public to phosphine gas are described. The exposure scenarios examined include only inhalation exposure to workers and to the general public. Dietary exposure was considered unlikely and thus was not addressed in this document.

A. HAZARD IDENTIFICATION

Selection of the appropriate laboratory animal toxicity studies to characterize human risk, a central task of pesticide risk assessment, is presented in the following sections.

1. Non-oncogenic effects

a. Acute toxicity

Uncertainties associated with the critical acute NOEL of 5 ppm were reflected in the range of LC₅₀ values and toxicologic characteristics observed in rodent inhalation studies. The reasons for the discrepancies were not clear, but may reflect (1) technical variability in the delivery and/or detection of the gas, (2) species or strain differences in sensitivity, or (3) differences in total exposure times.

With regard to lethality, Waritz and Brown (1975) observed deaths in CD rats at or below an LC₅₀ air concentration of 11 ppm for a single 4-hr exposure (95% confidence limits, 8.1-15 ppm). Similarly, Morgan *et al.* (1995) saw deaths or moribundity in all Fischer 344 rats after two or three 6-hr exposures at 10 ppm and in all B6C3F mice after four such exposures. These were similar to the finding in the critical study of Newton (1990), where 4/10 female deaths occurred in Fischer 344 rats within 3 days of daily 6-hr exposures to 10 ppm, forcing premature termination of the dose group. On the other hand Newton (1991) recorded the deaths of only 3/5 Sprague-Dawley males and 2/5 females within one day of a single 6-hr exposure at the notably higher concentration of 28 ppm. Moreover, Omae *et al.* (1996), working with male ICR mice, established a 4-hr LC₅₀ between 26.5 ppm, where no deaths occurred, and 33.4 ppm, where all animals died. Newton (1989) saw no effects in Fischer 344 rats at 11 ppm following a single 6-hr exposure; Schaefer (1998a) saw no deaths in CD rats at 40 ppm with a 4-hr exposure; and Roy (1983) observed only 1/5 female deaths at 43 ppm and 1/5 male and 4/5 female deaths in Wistar rats at 83 ppm within 24 hours of a 4-hr exposure. As the critical endpoint value of 5 ppm is below the concentrations shown to cause death, it is recognized that MOEs calculated with this value could be low estimates. However, the high quality of the Newton (1990) study

combined with the obvious severity of the endpoint argue against using a higher critical endpoint value.

With regard to species differences as a possible explanation for discordances, Klimmer (1969) demonstrated similar time vs. lethality regressions for rats, rabbits, cats and guinea pigs. The lethality threshold was $\sim 7 \text{ mg/m}^3$ ($\sim 5 \text{ ppm}$) at ~ 11 - 12 hours of exposure, supporting the critical value identified here⁸. The steep dose-response relation between air concentrations which cause little or no toxicity and those which kill animals must therefore be seriously considered when assessing human health risks of phosphine.

Uncertainty was also implicit in the assumption that mortality was more a function of absolute air concentration than absorbed dose. Using Klimmer's data, Pepelko *et al.* (2004) demonstrated neither toxicity nor mortality at concentrations below 5 ppm. They cited a concentration vs. exposure time (C x T) mortality product of 202.4 ± 40.7 (grand mean) in mice, rats, guinea pigs, cats, rabbits, turkeys and hens as evidence that the lethal effects of phosphine were similar across species and reflected a similar mode of action. Thus the Klimmer / Pepelko dataset appeared to minimize the importance of absorbed phosphine in the inhalation mortality studies, suggesting that the absolute air concentration was the crucial factor driving the mortality curves. In apparent contrast, Schaefer (1998a) observed decrements in motor activity, body temperature, arousal and respiration rate in CD rats at sub-lethal doses ($\leq 40 \text{ ppm}$). It is possible that such effects were secondary to absorption. Histopathology of the kidney and liver was observed in other studies (Newton, 1990; Omae *et al.*, 1996), also supporting a toxicologic role for absorbed phosphine. However, absolute air concentration was considered a more accurate approach to risk assessment involving workers, bystanders and the general public, obviating the need for default assumptions regarding breathing rate and percent oral and dermal absorption in those risk calculations.

The lack of a functional observational battery in the critical acute study was a source of additional uncertainty since FOBs impart a high level of sensitivity in neurotoxicology studies. Thus the absence of such an assay in the critical acute study raised the possibility that adverse events occurred but were undetected at low phosphine concentrations.

Uncertainty also derived from the fact that the critical acute value did not originate in a strictly acute exposure regimen. Death in most of the cited studies occurred after several exposure days at phosphine concentrations around 10 ppm. Higher concentrations were required to induce death from single (4-hr to 6-hr) exposures (Newton, 1991; Omae *et al.*, 1996; Shaefer, 1998a). It was thus probable that the "short term" exposure regimens resulting in death at and around 10 ppm overestimated the degree of toxicity that might result from a single exposure incident.

Finally, the lack of percutaneous absorption data led to a default assumption that exposure to phosphine did not occur through the skin. If dermal absorption does indeed occur, the exposure estimates and resultant MOEs underestimate the health risks associated with phosphine. For further discussion of this issue, see section VI.A. below.

⁸ Klimmer's work, published in German, was reviewed by Garry and Lyubimov (2001).

b. Subchronic toxicity

The 1 ppm critical subchronic NOEL, based on palpebral closure (sleeping behavior), lowered body temperature and slowed respiration at 3 ppm in rats in the 13-wk study by Schaefer (1998b), was used evaluate seasonal risk. Uncertainties in this designation centered on the possibility that palpebral closure may have been elevated even at 0.3 and 1 ppm (Table III-8). This was discounted due to the high incidence of palpebral closure among control animals⁹. In addition, the toxicologic significance of sleeping behavior was not known, particularly as it was not clear if it represented avoidance behavior or was a neurotoxic response. In any event, observations of toxicity at similar concentrations in the subchronic studies of Waritz and Brown (1975), Omae *et al.* (1996) and Barbosa *et al.* (1996), along with the dose proximity of these effects to lethality, supported the establishment of the critical NOEL at 1 ppm.

c. Chronic toxicity

The availability of only one chronic toxicity study, that of Newton (1989), underscored the uncertainty in designating a chronic endpoint value for phosphine. As toxicity was not observed in that study even at the high dose of 3 ppm (making the NOEL >3 ppm), it was considered prudent to base the chronic NOEL on the subchronic value of 1 ppm.

d. Reproductive toxicity

Due to data waivers (see section II.B. above), a reproductive toxicity study was not available for analysis. Consequently, the potential for phosphine-mediated toxicity to the reproductive systems of males or females is unknown.

e. Developmental toxicity

Only one developmental toxicity study, that of Schroeder (1989) in rats, was available for analysis. No developmental effects were seen through the highest sublethal dose of 4.9 ppm. A rabbit developmental study, required along with a rat developmental study for most chemicals, was not submitted. Consequently, the risk of developmental toxicity was not sufficiently understood for risk assessment purposes.

f. Genotoxicity

Uncertainties in the genotoxicity database stem from the fact that while all gene mutation and DNA damage studies were negative, four structural chromosome aberration studies, including one *in vivo* rat study, were positive. Two further *in vivo* studies in mice showed no increases in chromosome aberrations, sister chromatid exchanges, micronucleus formation or dominant lethal effects, nor were there changes in cell cycle kinetics.

Despite the apparent inconsistencies in laboratory animal studies, two studies from Garry's laboratory showed elevated chromosome aberrations in phosphine applicators (Garry *et al.*, 1989, 1992). When these studies are viewed in conjunction with the positive animal studies, phosphine should be viewed as genotoxic.

2. Oncogenicity

Only one chronic study, a 2-yr study by Newton in rats (Newton, 1998), was available for analysis. No oncogenic effects were seen through the highest dose of 3 ppm in that study. Since a mouse chronic / oncogenicity study was not submitted, the risk of oncogenicity was not

⁹ It is plausible that an increase in statistical power, such as would be achieved through an increase in animal numbers, might show an effect at those air concentrations.

sufficiently understood for risk assessment purposes and was regarded as an uncertainty in the current analysis.

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B. EXPOSURE ASSESSMENT

1. Occupational and bystander exposure

Uncertainties in the assessment of occupational and bystander exposure are presented in detail in the accompanying exposure assessment document (DPR, 2012). Briefly, uncertainties pertaining to all of the exposure scenarios were due to a lack of data on percutaneous absorption, data quality control issues and the following assumptions:

1. Workers and bystanders exposed under seasonal and annual application scenarios reside in the highest use county for the entire season. This may result in exposure overestimation.
2. Personal protective equipment instead of engineering controls was used by workers. If this is actually the case, the possibility of percutaneous exposure increases, though the toxicologic effect such an increase might have was not clear.
3. Time weighted averages taken from measurements of less than the anticipated work period (*i.e.*, 8, 9.7 or 12 hours) were equal to 8-, 9.7- or 12-hr time weighted average. This may lead to over- or underestimation of exposure.

As noted, these considerations, along with uncertainties pertaining to the specific exposure conditions presented, appear in detail in DPR (2012).

2. Dietary exposure

As noted in section IV.B.5. above, a dietary analysis was not carried out for this report.

C. RISK CHARACTERIZATION

All MOE calculations in this document utilized the NOELs derived directly from the critical studies without adjustment for varying human exposure times. All handler exposure estimates were based on 8-, 9.7- and 12-hr time-weighted averages (except for residential bystanders, which assumed 24-hr time-weighted averages). Uncertainties were injected into the MOE calculations by virtue of the absence of adjustments to the critical NOELs to account for the expected human exposures, which were different than the exposure times used in the animal toxicity studies. In particular, the use of time weighted averages presupposed that significant, but very short-term excursions above the TWA either did not occur or were toxicologically unimportant. This may result in an underestimation of risk.

Under the assumption that toxicity resulting from use of the precursor compounds aluminum phosphide, magnesium phosphide and zinc phosphide reflected airborne phosphine exposure, only phosphine toxicity data were considered relevant to this risk assessment. This assumption minimized the possibility that exposure to precursors could elicit additional toxicity over and beyond that of environmental phosphine. This might occur, for example, after precursor ingestion, when digestive tissues would react directly with the metal phosphides to create a unique toxic profile. Alternatively, unique toxicity could result from breakdown to phosphine in the gut, creating an exposure route not considered in this analysis.

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D. CRITICAL TOXICITY ENDPOINTS - USEPA vs. DPR

Points of departure established by the USEPA to assess acute and chronic risks from exposure to phosphine are described in their Reregistration Eligibility Decision document for aluminum and magnesium phosphide (USEPA, 1998). The following paragraphs delineate the USEPA's points of departure and compares them to those established by DPR in the present document. The conclusions of the two agencies are also summarized in Table V-1.

1. Acute inhalation toxicity

USEPA's "short term" point of departure was 5 ppm, with the internal dose calculated to be approximately 2.0 mg/kg. This was the NOEL established in the 90-day rat inhalation study of Newton (1990). DPR agreed with USEPA's analysis of that study, also assigning a NOEL of 5 ppm, which was the highest dose employed. DPR calculated the the internal dose to be 1.7 mg/kg, with the difference due to the fact that DPR used a lower default rat breathing rate of 40 L/kg/hr (DPR / Medical Toxicology Risk Assessment Handbook) compared to USEPA's value of 47 L/kg/hr. Like USEPA, DPR considered 5 ppm to be the critical acute NOEL.

2. Subchronic inhalation toxicity

USEPA's point of departure for "intermediate term" exposures was 3 ppm (1.2 mg/kg/day) based on no effects at this dose in the 90-day rat inhalation study of Newton (1990)¹⁰. DPR chose instead to regard the effects noted at 3 ppm in the 13-wk rat neurotoxicity study of Schaefer (1998b)---sleeping behavior, body temperature reduction and decreased respiration---as toxicologically relevant. This resulted in a critical subchronic NOEL of 1 ppm, one-third of the value used by USEPA¹¹.

3. Chronic inhalation toxicity

USEPA's chronic point of departure was 3 ppm, the high dose and NOEL in the 2-year rat inhalation study of Newton (1998). DPR agreed with USEPA's analysis of that study, also assigning to it a NOEL of 3 ppm. However, DPR opted to use its subchronic value of 1 ppm to estimate chronic risk, particularly as the Newton chronic study did not employ a functional observational battery to detect possible subtle neurotoxicologic impacts.

4. Oncogenicity

Based on the data supplied in the 2-year rat inhalation study of Newton (1998), neither the USEPA nor DPR considered phosphine to constitute an oncogenic risk. It should be reiterated, however, that a comparable chronic/oncogenicity study in mice, which would be required for most pesticide registrations, was not carried out.

¹⁰ Note, however, that a parallel dosing regimen in the same study using different animals (Newton, 1990) showed mortality within 3 days at 10 ppm (~3.6 mg/kg/day). This resulted in the critical acute NOEL of 5 ppm used as the critical acute endpoint value used both by USEPA and DPR.

¹¹ USEPA established a tentative NOEL at the high dose of 3 ppm in the Schaefer (1998b) study. It is not clear why they did not consider sleeping behavior / palpebral closure to be sufficient for a LOEL determination, especially as the 1998 RED considered those effects to be due to treatment.

Table V-1. Critical toxicity endpoints for phosphine: USEPA vs. DPR

Study type	USEPA RED (USEPA, 1998)	DPR
Inhalation exposure		
Acute toxicity,	Newton, 1990 13-day inhalation, 6 hr/day, 5 days/wk - rat LOEL > 5 ppm (hdt) NOEL = 5 ppm \approx 2.0 mg/kg/day ^a	Newton, 1990 13-day inhalation, 6 hr/day, 5 days/wk - rat LOEL > 5 ppm (hdt) NOEL = 5 ppm \approx 1.7 mg/kg/day
Subchronic toxicity	Newton, 1990 90-day inhalation, 6 hr/day, 5 days/wk - rat LOEL > 3 ppm (hdt ^a) NOEL = 3 ppm \approx 1.2 mg/kg/day	Schaefer, 1998b 13-wk inh. ntx, 6 hr/day, 5 days/wk - rat LOEL = 3 ppm NOEL = 1 ppm \approx 0.24 mg/kg/day (palpebral closure, ↓ respiration, ↓ body temp.)
Chronic toxicity	Newton, 1998 2-yr inhalation, 6 hr/day, 5 days/wk - rat LOEL > 3 ppm (hdt) NOEL = 3 ppm \approx 1.13 mg/kg/day	Schaefer, 1998b 13-wk inh. ntx, 6 hr/day, 5 days/wk - rat LOEL = 3 ppm NOEL = 1 ppm \approx 0.24 mg/kg/day (palpebral closure, ↓ respiration, ↓ body temp.)
Oncogenicity	not considered oncogenic	not considered oncogenic

Abbreviation: hdt: highest dose tested. Note, however, that a parallel dosing regimen in the same study using different animals (Newton, 1990) showed mortality within 3 days at 10 ppm (~3.6 mg/kg/day).

^a USEPA's calculated internal dose of 2.0 mg/kg/day was recalculated from their assessment because that document contained an arithmetic error resulting in an incorrect value of 1.8 mg/kg/day. The corrected USEPA value varied from the DPR value because USEPA used a default rat respiration rate of 47 L/kg/hr while DPR used 40 L/kg/hr.

VI. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated the USEPA to “upgrade its risk assessment process as part of the tolerance setting procedures” (USEPA, 1997a and b). The improvements to risk assessment were based on recommendations made in the 1993 National Academy of Sciences report, “Pesticides in the Diets of Infants and Children” (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. USEPA was required to invoke an extra 10-fold safety factor to account for potential pre- and post-natal developmental toxicity, as well as the possibility that the database was incomplete, unless they determined, based on reliable data, that a different margin would be safe. In addition, the USEPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

A. AGGREGATE EXPOSURE

The potential for aggregate exposure to phosphine---that is, simultaneous exposure involving more than one route---exists because the gas would likely contact both the dermal and pulmonary surfaces. Despite the absence of a dermal absorption study, this assessment recognizes the *possibility* that the dermal route comprises a toxicologically significant fraction of the total exposure. The exposure assessment document cites two studies and product labels to the effect that phosphine gas may even penetrate concrete or cinder block, with the implication that dermal penetration would occur in similar fashion (DPR, 2012). Nonetheless, the risk characterization assumes that the absolute air concentration of phosphine, not the absorbed dose, is the major arbiter of toxicity. It was thus unclear how dermal absorption of phosphine might contribute to that toxicity, making a quantitative aggregate risk assessment impractical.

In addition, because there were no dermal toxicity studies on phosphine or on phosphine generators, it was not possible to determine if there might be a *unique* toxicity profile that originates in the dermal exposure route.

Finally, simultaneous exposure by the *oral* and inhalation routes was considered to be unlikely outside of intentional ingestion of aluminum or magnesium phosphide.

B. CUMULATIVE EXPOSURE

Exposure to other pesticides with similar mechanisms of toxicity was considered to be unlikely.

C. IN UTERO EFFECTS

One epidemiologic study from the open literature suggests that children born to couples in which the father is a phosphine applicator have a higher likelihood of birth defects, with an odds ratio of 2.48 (Garry *et al.*, 2002). However, in the only laboratory developmental toxicity study available for analysis, Schroeder (1989) failed to detect developmental effects in CD rats at phosphine inhalation doses through 4.9 ppm.

One recent report brought up the possibility that children are more susceptible to phosphine-mediated death or morbidity, citing several incidents where that may have been the case (O'Malley *et al.*, in press). This possibility has not yet been verified under controlled conditions.

D. ENDOCRINE EFFECTS

There is no current evidence to suggest endocrine impacts of phosphine.

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VII. ACUTE, SUBCHRONIC AND CHRONIC REFERENCE CONCENTRATIONS (RfCs)

Air concentrations of phosphine below a calculated reference concentration (RfC) were considered unlikely to pose risks to human health. RfCs were calculated for acute, subchronic and chronic inhalation exposure by dividing the critical NOELs by an uncertainty factor of 100, which was a product of the 10x interspecies and 10x intraspecies uncertainty factors. All of the uncertainties that accompanied selection of the toxicologic endpoints were applicable to these calculations (see section V.A.).

Acute RfC = Critical acute NOEL \div 100 = 5 ppm \div 100 = **0.05 ppm**

Seasonal RfC = Critical subchronic NOEL \div 100 = 1 ppm \div 100 = **0.01 ppm**

Annual RfC = Critical chronic NOEL \div 100 = 1 ppm \div 100 = **0.01 ppm**

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VIII. TOLERANCE ASSESSMENT

In the absence of a dietary analysis, a tolerance assessment on phosphine was considered unnecessary.

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IX. CONCLUSIONS

A comprehensive human health risk assessment for the rodenticide / insecticide phosphine--including hazard identification, dose-response analysis, exposure assessment, risk characterization and risk appraisal--was carried out. Phosphine is marketed not only as a pressurized gas, but also in solid precursor form as aluminum phosphide and magnesium phosphide.

The present report is accompanied by an exposure assessment document prepared by the Worker Health and Safety Branch of DPR (DPR, 2012). That document provided the occupational and resident bystander exposure estimates used in the present analysis to evaluate risks to those populations. It concluded that currently approved application scenarios create the potential for acute, seasonal and/or annual (chronic) exposure to phosphine, primarily by the inhalation route. Due to phosphine's penetrative ability, the dermal route was also considered a potential exposure route. As all of the inhalation toxicity studies in animals employed whole-body chambers, in which the animals were exposed by both the inhalation and dermal routes, separate dermal toxicity studies were not considered necessary (they were not, in any event, available for analysis).

Because the critical NOELs were based on laboratory animal studies, margins of exposure (MOEs) of 100 for acute, seasonal and annual exposure scenarios were considered sufficient to protect human health. The severity of the critical acute endpoint (death), the steepness of the dose-response curve in rats between no detected effect and death, and the demonstrated relevance of the effects to people argue for an inflexible interpretation when the MOE of 100 is impinged.

Critical NOELs. The following values, based on laboratory animal studies, were established for phosphine:

- ◆ Acute inhalation NOEL = 5 ppm, based on the death of 4/10 female rats (0/10 males) within 3 daily 6-hr exposures to 10 ppm phosphine
- ◆ Subchronic inhalation NOEL = 1 ppm, based on statistically significant total palpebral closure (sleeping behavior) at week 4, slowed respiration at weeks 8 and 13 and statistically significant lowered body temperatures at week 13 with exposure of rats to 3 ppm phosphine gas (6 hr/day, 5 days/wk).
- ◆ Chronic inhalation NOEL = 1 ppm, based on statistically significant total palpebral closure (sleeping behavior) at week 4, slowed respiration at weeks 8 and 13 and statistically significant lowered body temperatures at week 13 with exposure of rats to 3 ppm phosphine gas (6 hr/day, 5 days/wk).

The single 2-yr chronic inhalation toxicity study available for analysis did not show oncogenesis at daily phosphine concentrations as high as 3 ppm.

Exposure scenarios and risk calculations. Several occupational tasks were examined for this document. Exposure scenarios included not only those involving direct engagement in phosphine application or post-application activities, but also residential bystanders within a short distance of those applications. Tasks considered included commodity fumigations in grain

elevators, farm bins, flat storage facilities, warehouses, bulk and box rail cars and ship holds and containers, as well as spot fumigations and burrowing pest fumigations.

Many acute, seasonal and annual use scenarios produced MOEs of under 100, indicating insufficient health protection for workers and bystanders under those scenarios. Moreover, some acute MOEs for occupational bystanders were as low as 17, including those adjacent to farm bins, flat storage facilities or warehouses during fumigation or aeration. In addition, residential or occupational bystanders under most occupational scenarios showed MOEs of 50. Finally, MOEs of less than 10 were common for many seasonal and annual scenarios. In light of the severity of the acute endpoint (death) and the proximity of the critical acute and subchronic / chronic NOELs, these low MOEs are cause for concern and mitigation measures should be considered.

Reference doses (RfDs).

Acute RfC = Critical acute NOEL ÷ 100 = 5 ppm ÷ 100 = **0.05 ppm**

Seasonal RfC = Critical subchronic NOEL ÷ 100 = 1 ppm ÷ 100 = **0.01 ppm**

Annual RfC = Critical chronic NOEL ÷ 100 = 1 ppm ÷ 100 = **0.01 ppm**

Many exposure estimates from the various occupational scenarios exceed these reference doses, again emphasizing the need to develop mitigation measures.

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DRAFT

APPENDIX I. Summaries of toxicology data reviews on phosphine prepared by the Medical Toxicology Branch, Department of Pesticide Regulation, California Environmental Protection Agency

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

**SUMMARY OF TOXICOLOGY DATA
PHOSPHINE**

**Chemical Code #3541, Tolerance # 51882
SB 950 # NA**

**Original Date 2/26/1
Revised 5/01/02, 9/14/07**

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	Data gap, no study on file †
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, no study on file †
Reproduction, rat:	Data gap, no study on file †
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	Data gap, no study on file †
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

† Aluminum phosphide and magnesium phosphide both release phosphine upon exposure to water. These two metal phosphides are “grouped” with one another for purposes of registration. The studies evaluated under SB-950 for these two metal phosphides are all found in the Summary of Toxicology Data for aluminum phosphide. None of those studies are acceptable under FIFRA guidelines. Data waivers have been extended for SB-950-mandated studies for

these two metal phosphides, and a similar waiver has been requested for phosphine, based on its relationship to the metal phosphides. All of the studies in the present Summary of Toxicology Data involve the exposure of test animals or test systems to phosphine gas. Aldous, 2/26/01.

All record numbers for phosphine (Tolerance No. 51882) through Record #233798 (Document No. 51882-029) were examined. This includes all records indexed by DPR as of 9/14/07.

Revised by Moore, 9/14/07.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 51882-006 176429 Newton, P.E., "2-Year combined inhalation chronic toxicity and oncogenicity study of phosphine in rats," MPI Research, Mattawan, MI, 9/10/98. MPI Research Study ID: 750-001. Charles River Fischer [CDF® (F-344)/CrI/BR VAF/Plus®] rats, 50/sex/group, were dosed with phosphine gas by whole body inhalation for 5 days/wk, 6 hr/day at 0, 0.3, 1.0 or 3.0 ppm for 2 years. An additional 10/sex/group were similarly maintained for 1 year for interim sacrifice. There were no treatment effects evident at any dose levels tested (NOEL \geq 3 ppm). Study is acceptable, with no adverse effect. Aldous, 2/26/01.

51882-011 176435 (Identical to 51882-017 186174) Newton, PE., R.J. Hilaski, D.A. Banas, N.H. Wilson, W.M. Busey, and D.G. Shaheen, "A 2-year inhalation study of phosphine in rats" *Inhalation Toxicology* 11:693-708 (1999). This article summarized information Record No. 1764209 above. No DPR worksheet of this review. Aldous, 4/23/02.

CHRONIC TOXICITY, RAT

See combined, rat: above.

CHRONIC TOXICITY, DOG

No chronic dog studies have been submitted at this time.

ONCOGENICITY, RAT

See combined, rat: above.

ONCOGENICITY, MOUSE

No mouse oncogenicity studies have been submitted at this time.

REPRODUCTION, RAT

No reproduction studies have been submitted at this time.

TERATOLOGY, RAT

**51882-007 176430 Schroeder, R. E., "An inhalation developmental toxicity study of phosphine (PH₃) in rats," Bio/dynamics, Inc., 5 Dec. 1989. Project No. 89-3413. CD® dams, 24/group, were dosed on gestation days 6-15 for 6 hr/day with phosphine by whole-body inhalation at 0, 0.03, 0.3, 3.0, or 5.0 ppm [equivalent to 0, 0.042, 0.42, 4.2 and 7.0 mg/m³] in a standard teratology study. An additional group was initiated on study at 7.5 ppm [10.5 mg/m³], however this group was terminated after the first 14 dams at this dose died on or before day 10

of treatment. Aside from the terminated group, there were no treatment effects on body weight, food consumption, clinical signs, or necropsy changes in any groups. Maternal NOEL = 5 ppm (mortalities at 7.5 ppm). Developmental NOEL = 5 ppm (no treatment effects observed). The study is acceptable, with some deficiencies as noted in the review. No adverse effects. Aldous, 2/26/01.

TERATOLOGY, RABBIT

No rabbit teratology studies have been submitted at this time.

GENE MUTATION

****51882-008 176431** Stankowski, Jr., L. F., "Ames/Salmonella plate incorporation assay on hydrogen phosphide (PH₃)," Pharmakon Research International, Inc., 2/10/90. Lab Project ID: PH 301-DA-001-89. Phosphine (from a cylinder containing 1% phosphine in nitrogen) was mixed with air in a range of concentrations and introduced into dessicators containing plates, prepared in triplicate with six strains of Salmonella typhimurium in the plate incorporation assay. Functional positive controls validated the responsiveness of the strains to known mutagens. There were no consistent patterns of revertants suggestive of a treatment effect over five trials. The study has several deficiencies, including difficulties at providing the desired concentrations of a.i. Gas samples were assayed from each treated dessicator, providing sufficient numbers of plates over an acceptable range for an interpretable study. Acceptable, with no adverse effects. Aldous, 2/15/01.

CHROMOSOME EFFECTS

****51882-009 176432** SanSebastian, J. R., "Structural chromosomal aberration: Chinese hamster ovary (CHO) cell induced by hydrogen phosphide (PH₃)," Pharmakon Research International, Inc., 3/8/90. Lab Project ID: PH 320-DA-001-89. CHO-K1-BH4 cells, Lot #A-12 and A-1, were treated for 5 hr with phosphine ("10,000 ppm in N₂") at 500, 2500, or 5000 ppm (phosphine was metered into serum bottles). After treatment, cells were maintained for an additional 8, 18, or 26 hr (with or without S-9) in fresh medium. Colcemid was added during the last 2-3 hr of post-treatment incubations. Cells were collected after trypsinization, then prepared for reading of 300 metaphase spreads for each dose level, time interval, with or without S-9. Positive controls were MNNG (without S-9, functional) and 1,2-butadiene (with S-9, weakly functional or dysfunctional). Phosphine was weakly positive with and without S-9 at 2500 and 5000 ppm in the 8-hr incubation series only (a possible adverse effect). Study is acceptable, with several deficiencies as noted in the review. Aldous, 2/26/01.

51882-0029; 233798; "Determination of Genotoxic and Other Effects in Mice Following Short Term Repeated-Dose and Subchronic Inhalation Exposure to Phosphine"; (A. Barbosa, E. Rosinova, J. Dempsey and A.M. Bonin; Toxicology Unit, National Institutes of Occupational Health and Safety, Worksafe Australia, Sydney, Australia; Department of Occupational Health, FHDF, Brasilia, Brazil; Department of Human Nutrition, CSIRO, Adelaide, Australia; *Environmental and Molecular Mutagenesis* 24:81-88 (1994)); Twelve Balb-c mice/sex/group were exposed whole-body to 0, 0.3, 1.0 or 4.5 ppm (0, 0.4, 1.4, 6.3 mg/m³ at STP) of phosphine for 6 hours/day, five days/week for 13 weeks. Upon conclusion of the exposure period, assays for the induction of micronuclei in the polychromatic erythrocytes (PCE) of the bone marrow and in the binucleated lymphocytes (BN) of the spleen were performed. In addition, an assay for the mutation of the HPRT locus in the splenic lymphocytes was undertaken. A preliminary study was performed in which 6 mice/sex were exposed to 5.5 ppm of the test material for 6 hours/day, 5 days/week for 2 weeks. At the conclusion of this period, assays for the induction of micronuclei in keratinocytes of the skin and in polychromatic erythrocytes of the peripheral blood were performed. The mean body weights gains of both sexes in the exposed groups of the subchronic study were lower than the control values in a dose-related manner. Although some of the relative organ weights of the exposed females were greater than the values for the controls, the biological significance of these effects could not be determined as no microscopic examination of these organs was performed. The females in the 4.5 ppm demonstrated an

increased incidence of micronuclei in the PCE of the bone marrow (0: 2.6/1000 PCE vs. 4.5: 5.8/1000 PCE). However, in the authors' evaluation this increase did not constitute a relevant effect. The increased induction of micronuclei in the binucleated lymphocytes of both sexes in the 4.5 ppm exposure group was reported to be significant ((M) 0: 3.3/1000 BN vs. 4.5: 6.3/1000 BN, (F) 0: 3.4/1000 BN vs. 4.5: 7.5/1000 BN) ($p < 0.05$). However, no analysis of the splenic lymphocytes from the animals in the intermediate exposure groups was performed. Analysis of the HPRT mutation frequency did not reveal any treatment-related effect. In the shorter-term study, no increase in the induction of micronuclei in the keratinocytes or in the PCE in the peripheral blood was noted. **Possible adverse effect:** The increased induction of micronuclei in the PCE of the bone marrow of the females and in binucleated lymphocytes of the spleen of both sexes at the highest exposure concentration indicate a potential for genotoxicity in the mouse. **Study supplemental** (not a guideline genotoxicity study). (Moore, 6/28/07)

DNA DAMAGE

**51882-010 176433 McKeon, M. E., "Genotoxicity test on phosphine in the in vivo/in vitro assay for unscheduled DNA synthesis in rat primary hepatocyte cultures at two timepoints," Hazleton Washington, Inc. [in-life phase performed at Pharmaco LSR Inc.], 7/2/93, HWA Study No. A0040-0-494. Male CDF@(F-344)/Cr1BR rats, generally 5/dose/time interval, were exposed by inhalation for 6 hr to 0, 5, 13, 18, or 23 ppm phosphine (99.98% purity). Labored breathing was seen at 18 and 23 ppm immediately post-exposure, returning to normal within 2 hr. Body weight losses occurred at 13 to 23 ppm. Sacrifice intervals were about 2 or 12 hr after dosing. Positive controls received dimethylnitrosamine (DMN) ip (10 or 15 mg/kg for 2 and 12-hr post-exposure groups, respectively). Hepatocytes were obtained by collagenase treatment, and were allowed to form monolayers on plastic slides within dishes, each containing about 5×10^5 viable cells. After about 2 hr incubation to establish monolayers, unattached cells were removed and medium was added containing 10 μ Ci/ml of 3 HTdr. After 4 hr, labeled medium was replaced with fresh medium containing 0.25 mM thymidine, and incubation continued for about 18 hr. Slides were removed, dried, and nuclei were swollen. Slides were fixed, dried, dipped in emulsion, which exposed to record radiolabel, and then cells were stained for automatic evaluation. Typically, 3 slides per rat providing 150 readable cells were evaluated for UDS. Results were uniformly negative in the presence of viable positive controls. Study is acceptable, with no adverse effect. Aldous, 2/26/01.

NEUROTOXICITY

Not required at this time (no studies have been submitted).

OTHER STUDIES

**51882-005 176428 Newton, P. E., "A thirteen week inhalation toxicity study of phosphine (PH_3) in the rat," Bio/dynamics, Inc., 3/2/90. Project No. 87-8030. Thirty Fischer 344 rats per sex per group were exposed to phosphine gas, 1.04% average a.i. in nitrogen, by inhalation at 0, 0.3, 1.0, or 3.0 ppm for up to 13 weeks in the core study. Exposures were 6 hr/day, 5 days/wk. Of the 30 rats/sex in each group, 10 were allocated for interim sacrifice after 4 weeks, 10 at the end of 13 weeks, and 10 after 13 weeks of exposure plus 4 weeks of recovery. Due to a meager treatment response in this range, additional groups of 10/sex were dosed with 10 ppm and 5 ppm phosphine, dividing each of these groups between terminal sacrifice and recovery sacrifice subgroups. Groups of 6/sex controls were run in parallel with each of the latter groups. Basic subchronic study parameters were evaluated. This study did not define a NOEL. The most consistent evidence of an organ effect at 3 ppm was in kidneys, where pelvic mineralization was exclusively limited to 3 ppm males, and tubular mineralization was elevated in 3 ppm males (incidence of 10/10, vs. 5/10 in controls). Intermediate dose groups were not evaluated for histopathology. Four of the ten 10 ppm females placed on study died after 3 days of dosing, at which time that treatment level was terminated. Kidneys of all 10 ppm rats examined at death or immediately after the 3-day dosing regimen showed renal tubular

necrosis. The study is acceptable, however the report would be improved if appended by histopathology for kidney sections of intermediate dose groups of males (0.3 and 1.0 ppm), in order to avoid use of an "estimated no effect level." No adverse effects are indicated. Aldous, 2/26/01.

51882-004 176427 Newton, P. E., "An acute inhalation toxicity study of phosphine (PH₃) in the rat," Bio/dynamics, Inc., 9/5/89. Project No. 87-8029. Fischer 344 rats, 15/sex/group, were dosed in one 6-hr exposure to phosphine gas. Chamber atmospheres were supplied from a tank containing 1.06% a.i. in nitrogen, at assayed levels of 0, 2.4, 4.9, or 11 ppm. Parameters evaluated included clinical signs, body weights, full necropsies, and limited histopathology (of only the 5/sex/group which were killed on the day of exposure, with only 5 major organs evaluated). There were no definitive effects noted (NOEL = 11 ppm). Study is supplemental (not a required study design), but valid for its intended purposes. No adverse effects are indicated. Aldous, 2/26/01.

51882-011 176436 Schaefer, G. J., P. E. Newton, M. M. Gruebbel, W. M. Busey, and D. G. Shaheen, "Acute and subchronic inhalation neurotoxicity of phosphine in rats," *Inhalation Toxicology* **10**:293-320 (1998). In the **acute** study, CD rats (11/sex/group) were dosed with 0, 21, 28, or 40 ppm phosphine for 4 hr in a single whole-body inhalation exposure. Motor activity and FOB assessments were performed pre-test, and after exposure at 1 hr (peak response time) and at 7 and 14 days. Neurohistopathological evaluations were performed on 6/sex/group after 14 days. The 1-hr motor activity responses included about 50% decrements in horizontal and vertical activity counts in all treated groups (no clear dose-response) compared to controls during at least the first two 10-minute intervals. There were also marked decrements for at least the first 20 minutes in "total distance traveled" per time and in the amount of time spent in stereotypy (defined by investigators as total time spent in repetitive movements). After 20 minutes, all of these measures were reduced in all groups as rats habituated to the motor observation arena, but some treatment effects were still evident. None of these changes were evident after 7 or 14 days of recovery. The acute study did not elicit treatment responses in the FOB at any evaluation period. None of these rats demonstrated neurohistopathologic changes. All of these rats survived, however a single 40 ppm male displayed emaciation and discolored urine as a plausible treatment effect. In the **subchronic** study, 16 rats/sex/group were dosed with 0, 0.3, 1, or 3 ppm phosphine for 13 wk at 6 hr/day, 5 days/wk. Motor activity and FOB assessments were performed pre-test, and after weeks 4, 8, and 13 of treatment. An additional 6 rats/sex/group in 0 and 3 ppm groups were taken off treatment for 2 weeks at termination for recovery evaluation. All of the protocol parameters were negative for the subchronic tests. Thus these acute and subchronic neurotoxicity studies found no noteworthy findings except for a transient pharmacological response after dosing with 20-40 ppm phosphine. No worksheet (insufficient detail for DPR review), no adverse effects indicated. Note: Another copy of this publication was later submitted as 51882-017 186173. Aldous, 2/26/01, edited by Aldous, 4/23/02.

51882-011 176434 Newton, P. E., R. E. Schroeder, J. B. Sullivan, W. M. Busey, and D. A. Banas, "Inhalation toxicity of phosphine in the rat: acute, subchronic, and developmental," *Inhalation Toxicology* **5**:223-239 (1993). This article summarized information Record Nos. 176427, 176428, and 176430, above. No DPR worksheet of this review. Aldous, 2/6/01.

51882-016 186146 Klimmer, O. R., "Contribution to the study of the action of phosphine (PH₃)," reprinted translation of "Beitrag zur Wirkung des Phosphorwasserstoffes (PH₃)" from "Archiv für Toxikologie" **24**:164-187 (1969). This article sought to find whether a truly "chronic" response exists to phosphine. Two groups of animals were exposed via whole body exposure for 24 weeks (6 hr/weekday plus 4 hr/Saturday for a total inhalation exposure of about 820 hours) at 1 ppm and 2.5 ppm. Subjects in the 1 ppm group were 4 female cats and 10 juvenile male Wistar rats (initial mean rat weight of 110 g). There was no measurable toxicity at 1 ppm. The 2.5 ppm group had the same numbers of cats and rats, plus 4 female guinea pigs. This

dose did not alter liver function (sulfobromophthalein test) and did not alter hematology profile nor the color of the blood. Histopathology of 2.5 ppm animals indicated "fatty liver infiltration" in some cats and swelling of kidney tubular epithelium in some rats. Consulting pathologists had varying opinions as to whether these findings represented treatment effects. Brains of some 2.5 ppm group animals suggested "slight and non-specific changes of the Purkinje cells," judged to be agonal or post-mortem changes. Higher treatment groups received 5.0 ppm PH₃ (eight 6-hr doses for 48 hr, or a combination of 6 hr and 4 hr treatments for a total of 80 hr). Four of 6 cats and nearly all rodents died at 5 ppm, usually before completion of the 48 hr exposure time. Other rats were administered about 200 ppm PH₃ in subsequent tests, either with or without prior exposure to 1 ppm phosphine, for a total of 102 hr: the pre-treatment at 1 ppm had no influence on time of death nor on histopathology of decedents. In summary, this study pre-dates modern guidelines in many respects, and this study is not suitable for establishment of NOEL's. Data are consistent with the concept that "chronic" toxicity of PH₃ is either non-existent, or is limited to exposures close to lethal levels on subacute exposure. This is consistent with FIFRA studies in this Summary. No worksheet. Aldous, 2/24/02.

51882-015 186145 Mansdorf, S. Z., T. W. Knupp, and M. D. Bold, "Phosphine exposure monitoring for applicators, workers, and nearby persons, Volume I," report by S. Z. Mansdorf & Associates, 4/15/88. Study was prepared to evaluate exposures to persons resulting from phosphine gas generated from aluminum or magnesium phosphide. This record will be routed to Worker Health and Safety Branch for review. Aldous, 4/26/02.

51882-014 186142 Shimizu, Y., "Acute inhalation toxicity evaluation of hydrogen phosphide in rats," Nomura Research Institute, May, 1982. Phosphine was generated by addition of water to magnesium phosphide in closed chambers. Chamber phosphine levels were measured by "Kitagawa gas detector tubes of vacuum method and detector tubes manufactured by Dräger-Kag." Based on pilot tests, conditions of the present study were 1-hr exposures to CD rats (10/sex) at phosphine levels of 150, 165, 182, 200, 220, and 242 ppm. Estimated LD₅₀'s were 204 and 179 ppm for M and F, respectively. Common observations included tonic convulsions, sudden running about, and death in a prone position. All deaths occurred between just prior to end of exposure and 7 hr following end of exposure. Food consumption of both sexes was generally diminished on the first day after exposure, then returned to normal on day 2. Body weight was reduced at 220 ppm on day 1, with subsequent weight gain comparable between groups thereafter. Rats were necropsied upon spontaneous death or at day 14, survival permitting. Several tissues were preserved in formalin, however it is not clear whether or not they were evaluated microscopically. Investigators indicated that macroscopic evaluations found no alterations, and made no mention of histopathology. Supplemental data, not applicable to current data requirements. No worksheet. Aldous, 4/26/02.

51882-014 186144 Muthu, M., M. K. Krishnakumari, [no initials given] Muralidhara, and S. K. Majumder, "A study on the acute inhalation toxicity of phosphine to albino rats," Bull. Environ. Contam. Toxicol. 24:404-410 (1980). Investigators evaluated acute effects on CTF-Wistar rats of phosphine generated by addition of water to two aluminum phosphide materials in closed exposure chambers. Many features were not standardized, making the study of little value for hazard evaluation. LC₅₀ estimations for phosphine generated from the two compounds were 28 ppm (mean exposure time of 5.2 hr) and 33 ppm (mean exposure time of 7.4 hr). Unacceptable. No DPR worksheet. Aldous, 4/26/02.

51882-014 186143 Morgan, D. L., M. P. Moorman, M. R. Elwell, R. E. Wilson, S. M. Ward, M. B. Thompson, R. W. O'Connor, and H. C. Price, "Inhalation toxicity of phosphine for Fischer 344 rats and B6C3F1 mice," *Inhalation Toxicology* 7:225-238 (1995). Male rats and mice, at least 5/group for rats and 10/group for mice, were dosed with 0, 1, 5, and 10 ppm phosphine (from a commercial pressurized cylinder), for four consecutive daily exposures at 6 hr/session in a pilot study. Responses were limited to 10 ppm, as follows. All rats died and all mice were in moribund condition by the end of the fourth exposure. At 10 ppm, mice were anemic (reduced

RBC counts, Hb, HCT, platelet counts, lymphocyte counts, and monocyte counts). Clinical chemistry findings included remarkable increases in ALT and sorbitol dehydrogenase activities, and sharply elevated BUN. The 10 ppm mice had “minimal to mild degeneration and necrosis of the renal tubular epithelium,” and “minimal to mild subcapsular foci of hemorrhage and necrosis in the liver.” The primary (2-week) study employed at least 6 rats or mice per sex/time point combination at 0, 1.25, 2.5, and 5 ppm. Male rats and mice were killed after 1, 5, or 10 exposures. Female rats and mice were killed after day 10 only. NOEL = 2.5 ppm (2-week exposure led to significant decrease in lung weights in male rats and mice, significant increase in heart weights in female rats and mice, and very slight increase in BUN in male mice). Supplemental study, valid for parameters evaluated. No adverse effects: only exposures approaching the acutely lethal range appear to elicit toxic responses. Aldous, May 1, 2002.

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APPENDIX II. Phosphine environmental fate report prepared by the Environmental Monitoring Branch, Department of Pesticide Regulation, California Environmental Protection Agency

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FUMIGANTS: PHOSPHINE AND PHOSPHINE-GENERATING COMPOUNDS

RISK CHARACTERIZATION DOCUMENT

Environmental Fate

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INTRODUCTION

Phosphine, along with methyl bromide and sulfuryl fluoride, are among several active ingredients frequently used as agricultural fumigants against insects in stored commodities. Phosphine is also used for rodent control in landscape maintenance and rights-of-way. In its use as a fumigant, application of aluminum, magnesium or zinc phosphide pellets generates phosphine gas when exposed to moisture. Phosphine gas also can be applied directly as a fumigant.

In California, phosphine and two phosphine-generating compounds (aluminum and magnesium phosphide) are used as fumigants on stored commodities. Phosphine is a compound that penetrates deeply into materials such as large bulks of grain or tightly packed materials and it diffuses quickly.

This environmental review is part of the Department of Pesticide Regulation's (DPR) risk characterization document for phosphine and phosphine-generating products. The risk assessment process was initiated for phosphine and phosphine-generating compounds for the following two reasons:

- California law requires DPR to list in regulation as toxic air contaminants (TACs) those pesticides previously identified under federal law as hazardous air pollutants (HAPs) (TAC Control and Identification Act). Federal law classifies phosphine as a HAP (42 Code of Federal Regulations [CFR] §7412). Therefore, in 2003 DPR listed phosphine and phosphine-generating compounds as TACs in regulation (3 CCR §6860). Chemicals the federal government classifies as HAPs are administratively listed as TACs and not subject to the evaluation and control provisions of the TAC Identification and Control Act. However, they are subject to reevaluation and possible restrictions under other statutory mandates. In 2007 and 2008, DPR requested ARB to monitor for phosphine to determine the levels of phosphine in air from an agricultural application, as required by FAC §14022(c) (TAC Control and Identification Act; Warmerdam 2007 & 2008).
- They fall under the Birth Defect Prevention Act-mandated review of toxicology data for all active ingredients, which requires DPR to initiate a risk assessment for registered pesticide products containing the active ingredient phosphine and the phosphine generating active ingredients, aluminum phosphide and magnesium phosphine (Birth Defect Prevention Act; DPR 2007 & 2011).

This review summarizes the scientific literature about the environmental fate, physical and chemical properties, and DPR's databases about specific uses and formulations of phosphine and phosphine-generating products in California.

However, the review does not address zinc phosphide. Zinc phosphide is used to control rodents in agricultural and residential settings. It converts to phosphine gas in the presence of moisture and acid in the stomach. Due to its formulation (i.e., a solid pellet, tablet or cake) and method of application (inside rodent burrows), and its effectiveness as a rodenticide only when ingested, one would expect exposure to be low (US Environmental Protection Agency [EPA] 1998b). Therefore, risk to humans, fish and wildlife, and the environment from these baits would be negligible, so zinc phosphide products are not included in this review.

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2. PHYSICAL AND CHEMICAL DESCRIPTION

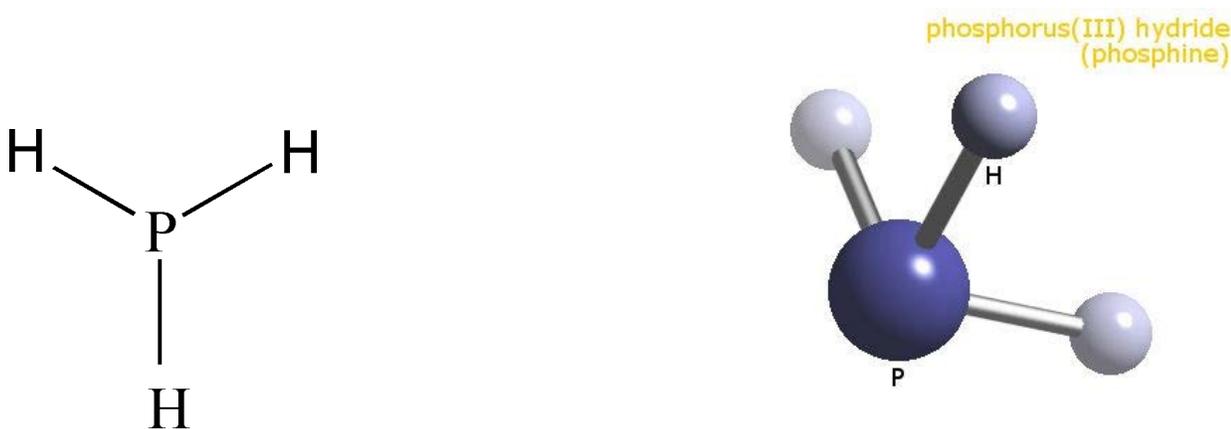
Aluminum and magnesium phosphide exist as yellowish to dark grey and chartreuse crystals, respectively (World Health Organization [WHO] 1988). These solids are stable when dry. However, they react with water as shown below to produce phosphine gas (Bond, 1984).



Phosphine gas in its pure form is odorless and colorless. Technical grade phosphine, due to impurities from the manufacturing process, has an odor similar to garlic or decaying fish (Fluck 1976; International Programme on Chemical Safety [IPCS] 1997). Figure 1 shows the structure of phosphine.

Table 1 lists some physical and chemical properties of aluminum phosphide, magnesium phosphide and phosphine. In addition to the chemical properties shown in Table 1, phosphine reacts with copper and precious metals (Bond 1984). It is also a flammable gas, igniting spontaneously in air.

Figure 1. Structure of phosphine gas (3D structure: WebElements.com 2012)



Phosphine is a trigonal pyramidal molecule with C_{3v} molecular symmetry. The length of P-H bond is 1.42 \AA , the H-P-H bond angles are 93.5° .

Table 1. Physical and chemical properties of aluminum phosphide, magnesium phosphide and phosphine

	Aluminum phosphide	Magnesium phosphide	Phosphine
Property	Aluminum phosphide	Magnesium phosphide	Phosphine gas
Common name	Phostoxin	Magtoxin	Hydrogen phosphide Phosphorus trihydrite
CAS Registry number ¹	20859-73-8	12057-74-8	7803-51-2
Chemical family	Inorganic phosphide	Inorganic phosphide	Inorganic phosphide
Physical state ¹	Solid	Solid	Gas
Color	Greenish gray ²	Grey ³	Colorless
Odor	Not available	Not available	Garlic, decomposing fish
Molecular formula	AlP	Mg ₃ P ₂	PH ₃
Molecular weight (g/mol)	58	135	34
Boiling Point at 1 atm (°C)	>1,000 ²	> 1,000 ³	-87.7 ⁴
Melting point (°C)	>1,000 ²	> 1,000 ³	-134 ⁴
Relative density (g/cm ³) (water = 1)	2.9 ²	2.1 ³	0.8 ⁴
Solubility in water (ml/100 ml at 17 °C)	Insoluble, reacts with water to form PH ₃ ²	Insoluble, reacts ³	26 ⁴
Octanol-water partition coefficient (K _{ow})	Not available	Not available	-0.271 (log L/kg) ⁵
Diffusion coefficient in water (cm ² ·s ⁻¹)	Not available	Not available	1.82e-005 ⁵
Diffusion coefficient in air (cm ² ·s ⁻¹)	Not available	Not available	0.381 ⁵
Henry's Law Constant (atm·m ³ /mol at 25 °C)	Not available	Not available	2.44 x 10 ⁻² 6
Vapor pressure (mm Hg at 25 °C)	0 ²	0 ³	31388 ⁵
Relative vapor density (air = 1)	Not available	Not available	1.17 ⁷

¹DPR 2012a & b²DEGESCH America, Inc. 2011³DEGESCH America, Inc. 2010⁴IPCS 1997⁵Groundwater Services, Inc. 2010⁶Hazardous Substances Data Bank 2012⁷WHO 1988

3. REGULATION

Table 2 shows the years aluminum phosphide, magnesium phosphide, and phosphine were first registered in the US and California (US EPA 1998a & b; US EPA 1999; DPR 2012c).

Table 2. Years aluminum phosphide, magnesium phosphide and phosphine were first registered in the US and California

Compound	Year registered	
	US	CA
Aluminum phosphide	1958	1958
Magnesium phosphide	1979	1979
Phosphine	1999	2001

At the federal level, registered aluminum and magnesium phosphide and phosphine gas products fall under provisions of a Memorandum of Agreement (MOA) between registrants and the US EPA (2000 & 2004). The major requirements of the MOA include site-specific fumigation management plans, incident reporting to US EPA, monitoring studies, establishment of worker exposure limits, development of training and certification programs and other label modifications. All phosphine and phosphine-gas generating products are federally classified as “Restricted Use Materials” (due to the high acute inhalation toxicity of phosphine gas), which limits their use to certified private or certified commercial applicators.

In California, aluminum phosphide, magnesium phosphide and phosphine are also restricted materials. With certain exceptions, restricted materials may be purchased and used only by or under the supervision of a certified commercial or private applicator under a permit issued by the County Agricultural Commissioner. Permits are time- and site-specific, and may include use practices to reduce adverse effects. [3 CCR §6400(e) & §6412(a)(3)]

In 2003, DPR listed phosphine and phosphine-generating compounds in regulation as TACs (3 CCR §6860), which is one of the factors that triggered monitoring and may lead to changes in use.

4. USE PROFILE

Many phosphine and phosphine-generating products are used in California. Currently, 27 products contain or produce phosphine gas with 20 of the products containing aluminum phosphide, 5 of the products containing magnesium phosphide. Two of the products consist of pressurized gas mixtures containing phosphine (Table 3) (DPR 2012d).

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Table 3. Registered phosphine and phosphine-generating products in California, their formulations, percent active ingredient t(a.i.), and registration number as of December 2012 (DPR 2012d).

Active Ingredient	Formulation	A.I. (%)	Registration Number
Aluminum phosphide			
Fumitoxin Tablets	Tablet	55	72951-1-ZA
Fumitoxin Pellets	Pellets	55	72959-2-ZA
Weevil-cide Tablets	Tablets	60	70506-13-AA
Degesch Phostoxin Tablets-R	Tablets	55	72959-4-ZB
Degesch Phostoxin Prepac Rope	Gas permeable blister packs	55	72959-8-AA
Degesch Phostoxin Pellets	Pellets	55	72959-5-AA
Degesch Phosphine Tablet Prepac	Tablets	55	72959-9-AA
Detia Fumex	Gas permeable bags	57	72959-10-AA
Detia Phos Pellets	Pellets	55	72959-5-ZA
Detia Phos Tablets	Tablets	55	72959-4-ZA
Fumitoxin Pellets	Pellets	55	72959-2-ZA
Gastoxin Fumigation Pellets	Pellets	57	43743-2-AA
Gastoxin Fumigation Sachet Chain	Sachets	57	43743-3-ZA
Gastoxin Fumigation Sachet	Sachets	57	43743-3-AA
Gastoxin Fumigation Tablets	Tablets	57	43743-1-AA
Phosfume Fumigation Tablets	Tablets	60	70506-13-AA-1015
Quickflo-R Granules	Granules for Generator	77.5	70506-69-AA
Weevil-Cide Gas Bags	Gas permeable bags	60	70506-15-AA
Weevil-Cide Pellets	Pellets	60	70506-14-AA
Weevil-Cide Tablets	Tablets	60	70506-13-AA
Magnesium phosphide			
Degesch Fumi-Cel	Trays	56	72959-6-AA
Degesch Fumi-Strip	Strip	56	72959-6-ZA
Degesch Magtoxin Granules	Granules	94.6	72959-11-AA
Degesch Magtoxin Prepac Spot Fumigant	Gas permeable blister packs	66	72959-7-AA
Magnaphos Gas Bags	Gas permeable bags	66	70506-17-AA
Gaseous phosphine			
Eco2Fume	Dilute gas	2	68387-7-AA
Vaporph3os Phosphine Fumigant	Concentrated gas	99.3	68387-8-AA

4.1 Formulations and Methods of Application

Table 3 lists the formulations and methods of application for phosphine and phosphine-generating products. Phosphine can be applied directly by injection or by way of aluminum phosphide or magnesium phosphide, which are solids that react with moisture in the air to generate phosphine gas.

Whether the pesticide is applied as a gas or as a solid metal phosphide in the fumigation structure, the fumigation typically lasts a few days to a month, depending on the type of structure and the ambient temperature. At the end of the fumigation period, the remaining phosphine gas in the chamber is vented out to the ambient air (Adler 2010; Dieterich et al. 1967).

Table 4 lists the general application rates for phosphine and phosphine-generating products registered for use in California (Cytec Industries, Inc. 2003; US EPA 1998a).

Table 4. General application rates for Al and Mg phosphide and phosphine in spaces (e.g., mills, warehouses, dried fruits and nuts) and bulk stored commodities (e.g., vertical storages, tanks, railcars and barges).

Product	Application rate (g phosphine / 1,000 ft ³)	
	<i>Lowest</i>	<i>Highest</i>
Aluminum phosphide	20	180
Magnesium phosphide	20	180
Phosphine	8	20

4.2 Use

Aluminum and magnesium phosphide fumigants are used primarily to control insects in stored grain and other agricultural commodities (US EPA 1998a). They are also used to control burrowing rodents in outdoor agricultural and other non-domestic areas, e.g., landscape maintenance and rights-of-way. The fumigants are restricted to use by specially trained pesticide applicators and in only narrow circumstances.

Phosphine is widely used indoors to control a wide range of insects for non-food and non-feed commodities (e.g., cotton, wool, leather, and tobacco) stored in sealed containers or structures (US EPA 1999).

Table 5 shows reported annual use of phosphine and phosphine-generating fumigants from 2005 through 2010 (DPR 2012d). In 2010, 109,656 pounds active ingredient phosphine were applied in California.

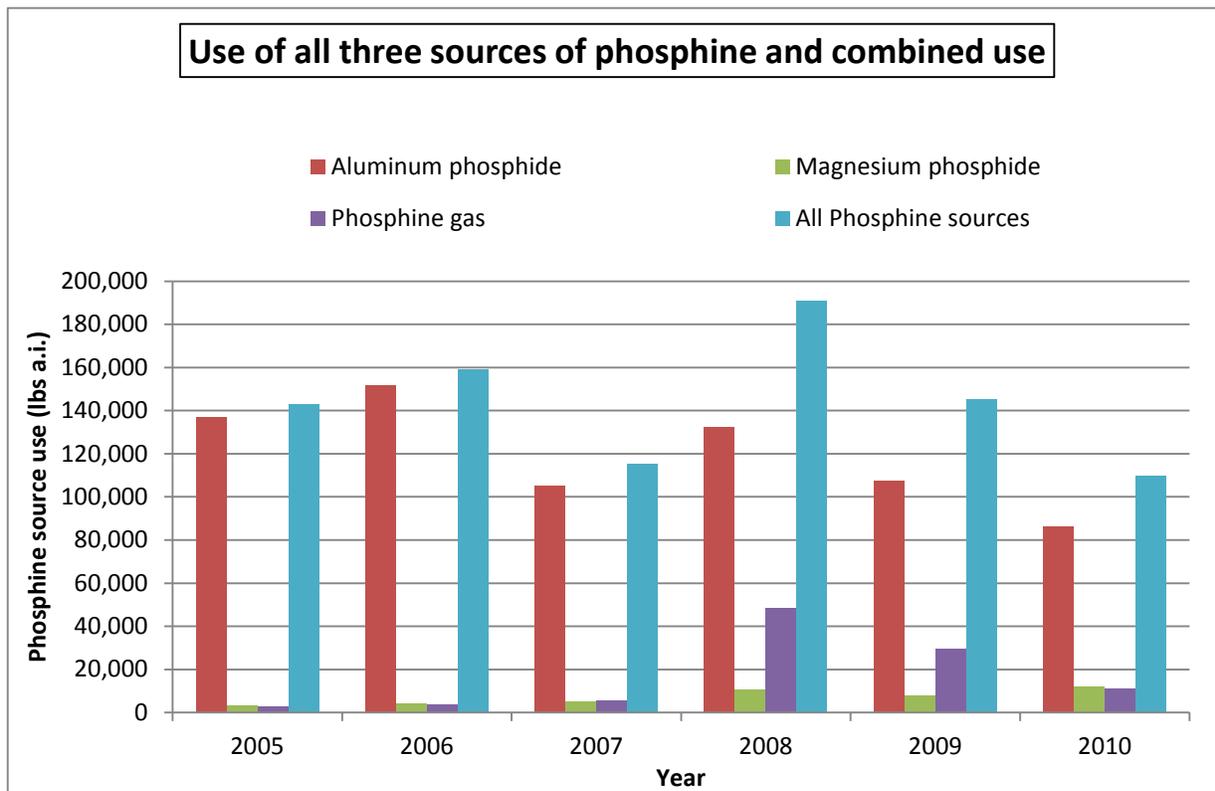
Table 5. Annual use of phosphine-generating fumigants and phosphine in California (2005 – 2010)

Year	Aluminum phosphide	Magnesium phosphide	Phosphine	Total
Use (Pounds a.i.)				
2005	136,829	3,144	2,699	142,672
2006	151,631	3,931	3,491	159,053
2007	104,994	5,132	5,286	115,412
2008	132,246	10,506	48,243	190,995
2009	107,487	8,009	29,527	145,023
2010	86,342	12,014	11,210	109,656
Total	718,920	42,735	100,557	882,212

4.2.1 Aluminum and Magnesium Phosphide

In general, aluminum phosphide use data follow the patterns seen with the total phosphine use data, since over 80% of the total use data come from aluminum phosphide use (Table 5 & Figure 2).

Figure 2: Annual use of phosphine generating products in California from 2005 to 2010 (lbs. a.i.) (DPR, 2012d).



From the above chart it is evident that the total phosphine use was generally stable, except for the spike seen in 2008. The last three years show a slight decreasing trend in use.

Table 6 shows the use data of three groups of phosphine-generating commercial products. Aluminum phosphide-based products dominate the phosphine pesticide market, and Fumitoxin tablets and pellets are the most used (annual average of about 39,000 and 20,000 pounds active ingredient [a.i.], respectively). Magnesium phosphide is a distant second with about 7,000 pounds a.i. used.

Table 6. Annual use of phosphine-generating brand-named products in California (2005-2010) (DPR 2012d).

Active Ingredient	Pounds a.i. applied					
	Year					
	2005	2006	2007	2008	2009	2010
<i>Aluminum phosphide products</i>						
FUMITOXIN TABLETS	36,989	43,007	37,474	53,666	30,599	32,480
FUMITOXIN PELLETS	14,507	18,120	18,992	25,007	28,657	16,275
WEEVIL-CIDE TABLETS	8,310	15,519	10,020	10,481	11,752	12,264
DEGESCH PHOSTOXIN TABLETS-R	12,272	9,455	4,465	8,521	4,586	5,815
FUMITOXIN NEW COATED TABLETS-R	9,721	9,498	7,997	4,455	3,856	3,210
PHOSTOXIN NEW COATED TABLETS	10,196	6,714	3,027	8,273	1,431	2,270
PHOSTOXIN COATED PELLETS	18,396	4,417	3,144	3,052	1,877	641
DEGESCH PHOSTOXIN PELLETS	7,880	10,827	6,438	1,936	1,131	1,541
DEGESCH PHOSTOXIN TABLET PREPAC	2,334	4,054	2,763	5,738	2,035	2,367
GASTOXIN FUMIGATION PELLETS	492	16,644	548	453	302	312
Aluminum phosphide products total	136,829	151,022	104,994	132,246	107,487	86,342
<i>Magnesium phosphide products</i>						
DEGESCH FUMI-CEL	1,885	3,053	3,431	9,425	6,006	10,769
DEGESCH FUMI-CEL PLATES	574	253	413	172	243	265
DEGESCH FUMI-STRIP	576	406	1,172	396	1,592	282
DEGESCH MAGTOXIN GRANULES				4	124	377
DEGESCH MAGTOXIN PELLETS	14	44		8		
DEGESCH MAGTOXIN PELLETS- PREPAC	1					
DEGESCH MAGTOXIN PREPAC SPOT FUMIGANT	94	175	113	501	38	27
DEGESCH MAGTOXIN TABLETS-R			3		5	1
MAGNAPHOS GAS BAGS						294
Magnesium phosphide products total	3,144	3,931	5,132	10,506	8,009	12,014

Table 7 summarizes the annual use data for aluminum phosphide by top ten counties. Leading aluminum phosphide use counties for this six-year period are Fresno, Kern, Los Angeles and San Joaquin Counties.

Table 7. Annual use of aluminum phosphide products by top ten counties (lbs. a.i.) (2005-2010) (DPR 2012d).

County (Co.)	Pounds a.i.							
	Year						County- by-Year Average	County Total
	2005	2006	2007	2008	2009	2010		
Fresno	30,332	21,418	13,032	13,295	20,242	19,401	19,620	117,720
Kern	9,387	14,090	12,724	14,378	9,746	1,746	10,345	62,070
Los Angeles	6,505	9,598	9,655	15,426	7,013	4,364	8,760	52,561
San Joaquin	5,515	20,301	4,237	4,336	7,179	1,831	7,233	43,400
Orange	8,129	3,964	4,353	10,389	5,751	7,449	6,673	40,036
Stanislaus	7,290	7,711	5,106	3,796	3,459	3,291	5,109	30,652
Colusa	5,124	3,334	4,511	4,963	5,789	6,330	5,009	30,052
Yolo	6,036	6,949	5,563	3,970	2,590	4,806	4,986	29,913
Riverside	5,078	8,484	4,925	6,073	3,151	2,115	4,971	29,826
San Bernardino	2,745	9,782	5,350	4,655	2,384	1,806	4,454	26,722
Top ten county total	86,140	105,631	69,456	81,279	67,304	53,140	77,159	462,952
Top ten county average	8,614	10,563	6,946	8,128	6,730	5,314	7,716	46,295
All counties' total	136,829	151,022	104,994	132,246	107,487	86,342	119,820	718,920

The top ten aluminum phosphide use sites for this six-year period are given in Table 8. Landscape Maintenance, Commodity Fumigation and Almonds, respectively, are the leading use sites.

Table 8. Top ten use sites of aluminum phosphide products in California by year (2005 – 2010) (lbs. a.i) (DPR 2012d).

Site	Pounds a.i.						Site Total
	Year						
	2005	2006	2007	2008	2009	2010	
Landscape maintenance	44,333	42,604	35,450	54,673	24,158	23,758	224,976
Commodity fumigation	15,905	31,333	12,307	14,715	10,531	11,332	96,123
Almond	13,895	18,195	12,960	11,310	9,839	10,540	76,739
Fruits (dried or dehydrated)	11,715	11,847	5,014	4,170	9,673	7,674	50,092
Pistachio	3,690	5,938	8,285	13,736	12,048	3,102	46,799
Structural pest control	9,253	8,031	6,584	8,988	2,931	3,108	38,895
Vertebrate pest control	7,624	11,546	2,646	3,365	10,017	3,676	38,874
Fumigation (other)	5,996	6,959	4,180	4,850	8,106	4,828	34,919
Rights of way	3,277	1,980	5,582	3,753	1,017	2,890	18,499
Grapes	2,320	2,353	3,687	2,822	3,887	2,506	17,575
Year total	136,829	151,022	104,994	132,246	107,487	86,342	718,920

The average month-by-county use data for aluminum phosphide is given in Table 9. October is the leading use month and most of the leading use counties had their biggest use on this month. The use in Fresno County is spread over the months, more than in Kern, Los Angeles, or San Joaquin Counties.

Table 9. Average monthly use of aluminum phosphide products by top ten counties during 2005 through 2010 (DPR 2012d).

County	Pounds a.i.												County Total
	Month												
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	
Fresno	2,884	1,115	1,679	1,310	1,145	1,056	1,110	1,519	2,824	2,391	1,448	1,113	19,620
Kern	708	349	568	1,311	688	606	675	1,076	1,840	1,794	394	335	10,345
Los Angeles	538	512	1,175	594	648	575	531	1,438	513	580	1,158	498	8,760
San Joaquin	317	213	359	352	416	1,099	193	189	329	3,005	431	329	7,233
Orange	347	468	881	832	517	828	388	405	631	494	485	397	6,673
Stanislaus	425	263	491	378	240	300	361	507	640	742	473	291	5,109
Colusa	96	66	208	581	811	703	797	547	549	282	301	67	5,009
Yolo	341	341	291	446	325	362	357	669	823	361	401	268	4,986
Riverside	388	375	511	447	478	631	333	290	334	327	474	382	4,971
San Bernardino	306	273	323	881	369	389	426	384	359	286	284	172	4,454
Average top ten county use total	6,350	3,974	6,486	7,133	5,637	6,548	5,171	7,024	8,841	10,262	5,850	3,853	77,159
Average monthly use of all counties	8,241	6,761	10,090	11,289	9,045	10,448	8,498	10,856	13,571	14,554	10,396	6,043	119,820

The average monthly use of aluminum phosphide by site is given in Table 10. Landscape Maintenance is the leading average use site, and the use is evenly distributed over the months for this site. Most use is in October and September. Monthly use of aluminum phosphide by site (Table 10) follows almost the same pattern exhibited by all phosphine sources (Table 5 and Figure 2). The same three sites—landscape maintenance, commodity fumigation, and almond—are among the leaders for both source types.

Table 10. Average monthly use of aluminum phosphide products (lbs. a.i.) by top ten use sites (2005-2010) (DPR 2012d).

Site	Pounds a.i.												Site Total
	Year												
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	
Landscape maintenance	2,337	2,680	3,824	5,139	2,728	3,499	2,323	3,794	2,826	3,177	3,099	2,070	224,976
Commodity fumigation	507	504	935	648	1,018	764	1,191	1,764	2,764	4,312	1,215	398	96,123
Almond	507	509	761	826	646	380	487	1,316	2,872	2,736	1,076	655	76,739
Fruits (dried or dehydrated)	819	597	944	595	641	633	765	683	591	775	685	621	50,092
Pistachio	512	133	514	724	939	552	659	476	1,290	1,070	493	430	46,799
Structural pest control	668	495	450	408	731	1,029	352	310	557	663	550	269	38,895
Vertebrate pest control	392	438	715	1,121	433	434	352	406	189	179	1,486	333	38,874
Fumigation, other	242	292	243	411	338	429	413	821	998	679	541	412	34,919
Rights of way	187	135	487	245	209	456	407	301	204	94	213	146	18,499
Grapes	204	258	300	305	352	292	220	229	157	245	245	122	17,575
Total top ten monthly averages	6,376	6,042	9,173	10,421	8,035	8,468	7,169	10,099	12,447	13,930	9,603	5,456	
Total use in top ten counties for all six years	49,445	40,563	60,539	67,734	54,268	62,690	50,987	65,138	81,425	87,325	62,375	36,256	718,920

The annual use of magnesium phosphide products in top ten counties from 2005 to 2010 is given in Table 11. Yolo, Fresno and Solano are the top three use counties. County of Yolo had a more or less even distribution in use for this period. A large use in 2008 pushed the total use to second place in Fresno County. For Solano County, one large use year in 2010 pushed the average use up in this county.

Table 11. Magnesium phosphide use by top ten counties (lbs. a.i.) during years 2005-2010 (CDPR, 2012d).

County	Pounds a.i.							County Average	County Total
	Year								
	2005	2006	2007	2008	2009	2010			
Yolo	615	765	1,750	1,328	2,532	2,168	1,526	9,160	
Fresno	446	40	13	5,722	26	382	1,105	6,630	
Solano	0.2	5	0	0		6,458	1,077	6,464	
San Joaquin	240	126	1,026	718	487	309	484	2,908	
Colusa	238	140	202	410	925	821	456	2,739	
Sacramento	205	1,406	557	485	0	1	442	2,656	
Stanislaus	119	33	48	79	2,211	101	432	2,592	
Butte	329	288	218	414	605	335	365	2,189	
Glenn	272	242	344	228	522	512	353	2,122	
Merced	81	111	224	179	173	161	155	930	
Year average	255	316	438	957	749	1126	640		
Year total	3,144	3,931	5,132	10,506	8,009	12,014		42,735	

Fumigation (other), commodity fumigation, and walnut fumigation were the top ten use sites (Table 12), The highest amount of use was in 2010. The use in commodity fumigation is generally even except for in 2009, which gave about 1.5 times the average yearly use for this site. The use reported in walnuts in 2008 pushed the average use to third place.

Table 12. Top ten use sites of magnesium phosphide products in California by year (2005-2010, lbs. a.i.) (CDPR, 2012d).

Site	Pounds a.i.							
	Year						Site Average	Site Total
	2005	2006	2007	2008	2009	2010		
Fumigation, other	535	1,779	1,281	1,926	1,059	6,794	2,229	13,377
Commodity fumigation	1329	1,204	1,945	1,011	3,205	2,859	1,926	11,556
Walnut	637	161	196	5,745	436	359	1,256	7,536
Almond	118	253	1,037	1,139	2,677	439	944	5,664
Structural pest control	156	52	201	411	366	119	217	1,306
Rice		143	210	29	8	731	187	1,122
Prune	156	176	5	35	156	260	131	791
Rights of way	17	30	117	144		51	60	360
Peach						293	49	293
Fruits (dried or dehydrated)	12	65	58	29	69	38	45	274.2
Top ten sites' average	296	386	505	1,047	797	1,194	704	
Year total of all sites	3,144	3,931	5,132	10,506	8,009	12,014		42,735

In Table 13, the top three counties in average use for magnesium phosphide by county and month are Yolo, Fresno, and Solano, in that order. The second highest user, Fresno, produced the highest average monthly use (947 pounds a.i.) in October.

Table 13. Average monthly use of magnesium phosphide products by top ten counties from 2005 to 2010 (lbs. a.i.) (CDPR, 2012d).

County	Pounds a.i.													County Average	County Total
	Month														
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC			
Yolo	73	77	69	180	90.6	142	110	341	146	131	130	33	127	9,160	
Fresno	0	0	0	22	3.0	1	3	7	64	946	5	49	92	6,630	
Solano	0	0	0	0	1073.4	0	0	0	0	0	0	0	89	6,464	
San Joaquin	49	40	31	12	28.7	25	21	48	51	73	56	45	40	2,908	
Colusa	17	16	12	18	90.9	44	60	47	99	11	23	14	38	2,739	
Sacramento	51	51	47	30	16.0	25	1	16	71	56	42	32	36	2,656	
Stanislaus	1	2	4	1	1.5	4	2	6	2	399	2	1	36	2,592	
Butte	28	32	36	45	12.7	49	26	16	14	35	41	27	30	2,189	
Glenn	9	5	2	3	2.9	0	7	0	52	133	123	14	29	2,122	
Merced	3	3	3	3	2.2	3	9	24	55	21	14	8	12	930	
Monthly average	39	38	34	53	220.3	49	40	84	93	301	73	37	88		
Total use in all counties	1,523	1,501	1,407	2,111	8,288.8	2,149	1,738	3,310	3,755	11,872	3,360	1,717		42,735	

With respect to month by site distribution (Table 14), fumigation (other), commodity fumigation and walnuts were the leading use sites. Monthly average use of over 1,118 pounds a.i. in May for fumigation (other) gave the largest use. Commodity fumigation had a more or less even distribution through the months.

Table 14. Average monthly use of magnesium phosphide by top ten sites (lbs. a.i.) from 2005 to 2010 (CDPR, 2012).

Site	Pounds a.i.												Site Average	Site Total
	Month													
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC		
Fumigation (other)	63	76	89	75	1,118	79	86	95	174	204	125	44	186	13,377
Commodity fumigation	119	110	88	216	133	167	115	375	188	163	152	99	161	11,556
Walnut	8	4	3	2	1	0	0	0	74	1,042	106	15	105	7,536
Almond	44	41	42	28	31	23	19	19	105	504	63	23	79	5,665
Structural pest control	8	2	5	4	49	40	24	9	9	18	28	22	18	1,307
Rice	0	2	2	9	40	18	24	15	66	3	6	2	16	1,123
Prune	0	0	0	0	0	0	6	5	1	32	65	22	11	791
Rights of way	8	9	3	3	0	6	6	14	3	3	0	5	5	361
Peach	0	0	0	0	0	0	0	0	0	0	0	49	4	294
Fruits (dried or dehydrated)	0	3	0	13	5	15	2	0	0	0	1	5	4	274
Monthly average of top ten sites	25	25	23	35	138	35	28	53	62	197	55	29	59	
Monthly total for all sites	1,523	1,502	1,407	2,111	8,289	2,149	1,739	3,310	3,755	11,872	3,360	1,717		42,735

4.2.2 Phosphine

Tables 5, 6 and 15 summarize the annual use of phosphine gas products from 2005 through 2010; a total of 100,000 lbs. a.i. was applied during this period. The large use of Vaporph3os on almonds in 2008 (in Sacramento County) gave an unusual spike in general use for this period. In 2009, the same product was used in a relatively large amount on two different sites (Almonds, and Regulatory Pest Control).

Table 15. Annual use of phosphine gas products in California (2005-2010)

	Pounds a.i.					
	<i>Year</i>					
	2005	2006	2007	2008	2009	2010
<i>Phosphine gas products</i>						
Eco2Fume	1,706	2,082	2,586	3,519	3,627	4,189
Vaporph3os	994	1,409	2,699	44,724	25,900	7,101
Phosphine gas product total	2699	3,491	5286	48,243	29,527	11,290

Table 16 shows the annual use of phosphine gas products in the ten counties that used the most. The counties of Sacramento, followed by Stanislaus and Kern are the leading use counties. In 2010, Stanislaus County was the highest use county with over 3,500 lbs. of phosphine a.i. applied (Table 16).

Table 16. Annual use of phosphine gas products in California by the top ten counties from 2005-2010.

County	Pounds a.i.						
	Year						County Total
	2005	2006	2007	2008	2009	2010	
Sacramento	0	11	32.0	37,668	16,106	1,036	54,854
Stanislaus	220	286	2,171	4,490	8,272	3,550	18,991
Kern	365	993	908	3,208	2,081	2,999	10,557
Fresno	459	640	315	466	958	983	3,823
San Joaquin	624	653	703	661	216	349	3,209
Butte	197	213	256	447	252	946	2,313
Merced	114	177	264	325	524	412	1,819
Glenn	61	95	213	368	455	409	1,603
Yolo	436	131	142	114	217	165	,206
Kings	108	131	117	67	106	74	605
Top ten use total	2,586	3,335	5,124	47,818	29,191,	10,929	98,984
Total use in all counties	2,699	3,490	5,285	48,243	29527	11,290	100,536

From 2005 to 2010, the three sites with the most phosphine use were: almonds (an average of over 10,000 lbs. a.i.), regulatory pest control (one large use of over 15,000 lbs. a.i in 2009) and commodity fumigation (an average over 1,000 lbs. a.i) (Table 17).

Table 17. Annual use of phosphine gas by top ten sites in California by year (2005-2010)

Site	Pounds a.i.						
	Year						Site Total
	2005	2006	2007	2008	2009	2010	
Almond	929	1,791	2,860	43,154	10,061	3,026	61,821
Regulatory pest control					15,950	1	15,951
Commodity fumigation	695	510	576	757	1,128	2,952	6,617
Pistachio	107	149	369	2,164	1,079	1,952	5,820
Fumigation (other)	103	102	492	1,012	279	2,087	4,075
Walnut	361	604	585	543	286	501	2,880
Structural pest control	331	107	117	165	159	202	1,080
Dried fruit	86	100		106	289	192	774
Tomato, processing	18		50	113	160	167	509
Tomato	26	93	110	55	61	72	416
Top ten sites by year total	2,657	3,456	5,159	48,069	29,451	11,152	99,943
All sites' year total	2,699	3,491	5,286	48,243	29,527	11,291	100,537

Traditionally, October and November are months (6-year average) when most of the use of phosphine gas occurs in the top ten counties (Table 18).

Table 18 Average monthly use of phosphine gas products by top ten counties during 2005 through 2010 (DPR 2012d).

County	Pounds a.i.													
	Month												County Average	County Total
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC		
Sacramento	17	46	1,550	75	1,008	21	8	9	24	5,034	1,316	35	762	54,854
Stanislaus	1,068	133	95	86	85	63	33	129	326	467	466	214	264	18,991
Kern	185	161	75	58	84	301	61	139	166	253	170	106	147	10,558
Fresno	43	46	47	41	39	48	37	47	69	96	80	44	53	3,823
San Joaquin	13	23	9	10	15	18	23	23	23	189	169	21	45	3,210
Butte	19	5	48	42	11	24	20	53	32	39	63	29	32	2,314
Merced	21	15	14	15	29	15	15	20	39	60	48	13	25	1,819
Glenn	11	18	19	16	16	17	17	20	49	32	28	25	22	1,604
Yolo	16	7	8	8	12	8	8	14	85	17	12	4	17	1,191
Kings	1	4	12	12	17	6	14	14	5	8	7	2	8	605
Monthly average	139	46	188	36	131	52	24	47	82	620	236	49	137	
Total of all counties	8,520	2,810	11,341	2,258	8,010	3,224	1,465	2,936	5,114	37,409	14,325	3,093		100,537

The month with the highest reported average use was October (Table 19). As stated previously, the majority of the use of phosphine gas products is on Almonds.

Table 19. Average monthly use of phosphine gas products by top ten use sites (2005 through 2010) (DPR 2012d).

Site	Pounds a.i.												Site Total
	Month												
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	
Almond	1,126	201	142	128	145	354	88	202	436	5,563	1,679	238	61,821
Regulatory pest control	0	0	1,542	63	996	11	0	0	0	36	11	0	15,951
Commodity fumigation	68	68	81	83	60	49	56	102	187	115	146	87	6,617
Pistachio	148	129	54	35	75	57	51	54	73	112	122	61	5,820
Fumigation (other)	19	15	14	18	25	21	10	76	68	116	215	82	4,075
Walnut	5	10	5	11	3	3	2	3	21	229	168	20	2,880
Structural pest control	33	14	10	10	12	10	6	15	20	27	15	8	1,080
Dried fruit	9	11	14	10	2	13	15	12	17	16	6	4	774
Tomato, processing	7	11	13	6	6	10	2	2	7	6	11	4	509
Tomato	4	1	3	7	5	3	12	9	3	10	6	7	416
Top ten sites' monthly average use	142	46	188	37	133	53	24	48	83	623	238	51	
Total of all sites by month	8,520	2,810	11,341	2,258	8,010	3,224	1,465	2,936	5,114	37,409	14,325	3,093	100,537

5. ENVIRONMENTAL FATE AND PERSISTENCE

The most likely routes of exposure to humans, fish, wildlife, and plants include air, water, and soil. Atmospheric exposure is not considered to be a significant route of exposure. In general, aluminum and magnesium phosphide may degrade rapidly to aluminum hydroxide, magnesium hydroxide, and phosphine (US EPA 1998a). Therefore, aluminum and magnesium phosphides and their residues do not appear to be persistent or mobile under most environmental conditions.

The following sections describe the environmental fate and persistence in air, water, and soil.

5.1 Air

The half-life of phosphine in air, exposed to light, is approximately five hours (Frank and Rippen 1987). It degrades due to photoreaction with hydroxyl radicals. The reaction products are non-volatile oxyacids of phosphorous and inorganic phosphate. Without light, the half-life can be as long as 28 hours.

5.2 Water

Phosphine has low solubility in water (Table 1). Phosphine degrades in days to phosphates and is at low risk for contaminating ground or surface water (WHO 1988).

5.3 Soil

Due to its high vapor pressure and high Henry's Law Constant (Table 1), phosphine near the soil's surface diffuses into the atmosphere where it degrades rapidly (Frank and Rippen 1987).

Hilton and Robison (1972) studied the degradation of phosphine in 3 types of soils at 5 different levels of moisture (0 – 100% saturation). They found that phosphine disappeared from air-dried soils within 18 days, but it took 40 days for it to disappear completely from 100% saturated soils. The interaction of phosphine with soil appears to be due to two processes--mixed chemisorption (irreversible) and physical adsorption (reversible)--with the extent of each depending on soil type (US EPA 1999).

6. NON-TARGET EFFECTS

Phosphine is very toxic to all forms of life; however, one would not expect exposure to occur. In general, risk of important environmental effects from phosphine or metal phosphides is low when proper transport, fumigation and industrial practices are used (WHO 1988; US EPA 1998a).

Given the characteristics and use patterns of aluminum and magnesium phosphide, these pesticides are not expected to pose a significant ecological risk to non-target organisms under most circumstances, with the exception of some endangered species. Since one of the uses of these pesticides is as a burrow fumigant for the control of rodents, concern exists that endangered or threatened species could be present in burrows targeted for fumigation. Also phosphine would be highly toxic to small mammals and birds that might remain in indoor sites (e.g., warehouses) during fumigation (US EPA 1999).

No research data exist on the wildlife toxicity of magnesium phosphide. Limited information on non-target effects, presented below, is available for aluminum phosphide and phosphine.

6.1 Birds

No oral or inhalation median lethal doses for aluminum phosphide or phosphine in birds have been identified. Klimmer (1969) reported that exposing male turkeys and hens to concentrations of 211 and 224 mg/m³ for 74 and 59 minutes, respectively, resulted in apathy, restlessness, difficulty in breathing, and other symptoms. The birds died in less than 2 hours. One would expect these results to apply to other bird species. However, exposure at these concentrations is unlikely, as phosphine dissipates quickly in air.

6.2 Fish and Other Aquatic Species

The concentrations of aluminum phosphide that are toxic to fish vary greatly (Table 20) (EXTOXNET 1996; WHO 1988). No data are available for toxicity from magnesium phosphide or phosphine. Aluminum phosphide reacts with water, forming phosphine gas which quickly dissipates. Therefore, the probability of aquatic exposure is low (Meister 1992). No data are available about the toxicity of magnesium phosphide to fish or other aquatic species.

Table 20. Acute toxicity of aluminum phosphide for freshwater fish

Species	96-h LC ₅₀
Rainbow trout (<i>Oncorhynchus mykiss</i>)	4.1 ug/L
Bluegill sunfish (<i>Lepomis macrochirus</i>)	0.178 mg / m ³

An LC₅₀ for phosphine for the frog from a 30-minute exposure was reported to be 0.56 mg/L. The LC₅₀ for a 15-min exposure was 0.84 mg/L (WHO 1988).

6.3 Seeds and Living Plants

Bond (1984) summarizes research that indicates that phosphine used to control insects does not normally affect seed germination. Little information exists on how growing plants are affected by exposure to phosphine.

7. RESIDUES OF PHOSPHINE FROM PHOSPHINE GAS AND PHOSPHINE-GENERATING PRODUCTS ON FUMIGATED COMMODITIES

Acceptable federal residue tolerances for various commodities vary from 0.01 to 0.1 ppm (US EPA 1985). For example, Dieterich et al. (1967) show that residues in most fumigated foods are unimportant at 0.01 mg/m³ (0.01 ppm) or less.

According to several studies, residues of phosphine may remain on commodities fumigated with phosphine gas or phosphine-generating products (Table 21).

Table 21. Summary of some studies on residues in phosphine-fumigated commodities.

Fumigant	Rate	Commodity	Average residue levels (ug/m ³)	Comments	References
Phosphine	4,000 ppm, 25 ^o C	Wheat	0.46 ppm	Duration: 12 days from fumigation. High initial dose, high residue levels	Sato & Suwanai 1974
		Millet	1.16 ppm		
		Milled rice	0.34 ppm		
		Soybeans	0.18 ppm		
		Azuki beans	0.24 ppm		
Phosphine		Wheat	0.2 ppb after 4 days of aeration; 0.004 ppb after 220 days of aeration	Low initial dose, low residue levels	Dumas 1980
Profume®	2 tabs/ton	Legumes	0.0001 ppm < 3 days	Residue decreased exponentially. Half-life depended on legume type & dose. Ranged from 0.66-1.33 ppm. Fell below detection limit. Acceptable residue levels even with higher dose.	Singh et al. 1983
	4 tabs/ton	Legumes			
	8 tabs/ton	Legumes	0.001 ppm < 6 days		
Aluminum phosphide tabs	5 g/ton	Wheat: hanging PH ₃ ; aerated < 1 ppm	12.01 ± 1.22 ppb		Pratt & Desmarchelier 1998
		Wheat PH ₃ admix; aerated < 1 ppm	> 10 ppm	Admixture is not desirable	

In a National Residue Survey by the Australian Government (2006), residue of phosphine was assessed in bulk export grains at ports. Eight commodities were surveyed and none carried phosphine residues above the Maximum Residue Limit of 0.1 ppm for phosphine.

8. ENVIRONMENTAL MONITORING

WHO (1988) reported a study that detected air concentrations of up to 280 mg phosphine/m³ near outer walls of a facility fumigated with phosphine. When the distance was > 10 m from the buildings, all concentrations, except for one, were < 0.14 mg/m³, which was below the exposure limit.

Thorn et al. (2002) described a method of monitoring inside and outside a sealed tobacco warehouse fumigated with phosphine, using a radio telemetry-based system. Phosphine was continuously monitored using two different types of electrochemical detectors. Phosphine concentrations outside the facility boundaries were < 0.3 ppm for five warehouses under simultaneous fumigation. Phosphine concentrations varied from 0 to 580 ppm inside sealed buildings.

In 2008, DPR requested that Air Resources Board (ARB) monitor one application site for phosphine because of its moderate pesticidal use, high volatility, and high priority for risk assessment (Warmerdam 2008). Therefore, ARB monitored an application of aluminum phosphide pellets at one application site for phosphine in Merced County in 2008 (Adler 2010). The fumigation lasted almost six days. The site, a large sealed chamber, was monitored before, during and after the use of phosphine as a post-harvest commodity fumigant. ARB conducted its monitoring at a commercial commodity fumigation facility. Monitoring occurred in December, historically one of the months with the highest phosphine use. A total of 75 samples were collected. Samples were collected from 8 locations (4 corners, 4 sides) from 15 to 40 feet away from the exterior walls of the chamber. One additional sampler was located inside the chamber. During the fumigation period, ambient samples ranged from 1 to 58.33 ug/m³ phosphine; the samples from inside the chamber were 510,000 to 7000,000 ug/m³. Concentrations of ambient samples taken during the venting of the chamber were < 1 – 6 ug/m³.

Neither DPR nor ARB is monitoring phosphine in its air monitoring at this time (Vidrio et al. 2012, ARB 2012).

9. PHOSPHINE AND METAL PHOSPHIDES AS POSTHARVEST REPLACEMENTS FOR METHYL BROMIDE

For a variety of crops, methyl bromide is currently the chemical of choice for preplant soil fumigation, commodity, and quarantine treatment requirements. Under the Clean Air Act, methyl bromide was declared an ozone depleting compound in 1993, and its production and importation was phased out by 2001. Methyl bromide will be phased out internationally according to the provisions of the Montreal Protocol, established in 1995. For many uses of methyl bromide, no alternatives exist or alternative strategies are not well studied for applicability.

Phosphine and phosphine-generating phosphides are used as postharvest alternatives to replace methyl bromide (USDA 2011). As of 1999, the US EPA recommends the use of the phosphine product, ECO₂FUME, as an alternative to methyl bromide. This product is effective at controlling a broad spectrum of economically important insect pests on commodities in sealed containers or structures. When used properly, it offers greater control of application rates as compared with the metal phosphide fumigants; therefore, one would expect to reduce the levels of peak concentrations of phosphine necessary for satisfactory performance within the fumigated areas. In addition, this product eliminates the need for applicators to enter a closed space and dispense tablets or pellets, thereby greatly reducing the possibility of exposure. This product eliminates the need to dispose of waste pellets, tablets or both when using metal phosphide products.

USDA (2011) summarizes research results to improve the usefulness of phosphine as an alternative to methyl bromide.

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