Phosphine

RISK CHARACTERIZATION DOCUMENT

Medical Toxicology Branch
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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, inappetance 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 ≈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

As indicated in the accompanying Exposure Assessment Document produced by DPR's Worker Health and Safety Branch, the primary route of human exposure is to phosphine gas by the inhalation route. Many acute, seasonal and annual use scenarios produced MOEs of under a target value of 100 (the product of the 10x interspecies and 10x intrahuman uncertainty factors), 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 exceeded 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 (WHO, 1988; ATSDR, 2002; Pepelko *et al.*, 2004). Finally, it is a by-product in the illicit synthesis of methamphetamine through the hydriodic acid / red phosphorus process (Willers-Russo, 1999; 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. 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). Nath *et al.* (2011) list three important potential toxic routes: neurotoxicity through inhibition of acetylcholinesterase, disruption of energy metabolism in actively respiring tissues through interaction with cytochromes in the electron transport chain, and generation of cytotoxic reactive oxygen species. 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, ECO_2FUME, 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 (AlP) and magnesium phosphide (Mg_2P_3) 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 AlP, 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 AlP and Mg_2P_3 (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 AlP and Mg_2P_3 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 AlP (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" [1]. Because Mg_2P_3 was grouped with AlP for testing purposes under SB950, this compound was included in the data exemption. Zinc phosphide was specifically *ex*cluded from this grouping because, in the language of a 1994 DPR memo, "As is well known,

[1] According to a recent memo from US EPA to DPR, "EPA's HASPOC [Hazard and Science Policy Council] actually recently recommended that a special acute inhalation study is required and that it should include respiratory histology, GSH measurements, kinetics / tissue dosimetry. HASPOC also recommended a range-finding study to determine appropriate doses for further studies, such as a 2-generation reproductive study and acceptable acute and subchronic neurotoxicity studies."

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 AlP for testing under SB950 (DPR, 2000), effectively exempting it from SB950 data requirements along with AlP 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/m^3)
- NIOSH Short Term Exposure Level (STEL): 1 ppm (1.4 mg/m^3)
- NIOSH revised Immediately Dangerous to Health or Life (IDHL): 50 ppm
- OSHA Permissible Exposure Limit (PEL): TWA 0.3 ppm (0.4 mg/m^3)
- 1993-1994 ACGIH Threshold Limit Value (TLV): TWA 0.3 ppm (0.42 mg/m^3)
- 1993-1994 ACGIH STEL: 1 ppm (1.4 mg/m^3)
- OEHHA chronic reference exposure level: 0.0006 ppm (0.0008 mg/m^3)

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.* (2013) argued that since "most of the phophine 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

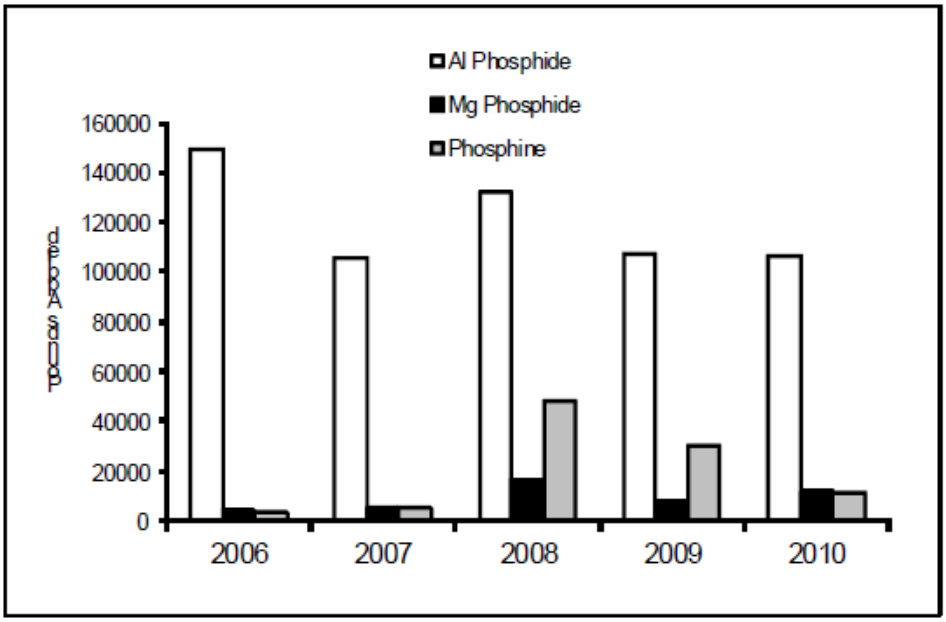
As of the most recent update in May 2008, the DPR database showed 2 products containing phosphine actively registered in California (Eco_2Fume and VaporPH_3Phos Phosphine Fumigant). In addition, there are 16 products containing aluminum phosphide (last database update: March 28, 2013) and 5 products containing magnesium phosphide (last database update: September 7, 1994). The accompanying Exposure Assessment(DPR, 2014) and Environmental Fate(Appendix I) documents provide additional information on these products.

D. USAGE

The following paragraphs are quoted directly from DPR's Exposure Assessment Document on phosphine, in the section entitled "Pesticide Use" (DPR, 2014). Citations appearing within these paragraphs refer to the Reference list in that document.

> The Pesticide Use Report (PUR) is a record of all of the pesticides used in the state of California each year. The PUR program was started in 1990 in order to generate a more comprehensive record of pesticide use data. The database provides annual summaries and specific data which can be obtained through the California Pesticide Information Portal (CalPIP) system (CalPIP, 2011). This search engine allows queries of pesticide related data from multiple sources including the PUR database (PUR, 2011).
>
> The total statewide amounts of aluminum phosphide, magnesium phosphide, and phosphine applied annually over multiple years were obtained using CalPIP and the PUR database. The latest 5 years (2006 – 2010) of data from the PUR database show that relatively low amounts of magnesium phosphide were used. In addition, while the annual amounts of aluminum phosphide and magnesium phosphide applied remained relatively constant, the application of phosphine declined from 2008 through 2010 (Figure 1).

EAD Figure 1. Total Pounds of Aluminum Phosphide, Magnesium Phosphide and Phosphine Applied Annually from 2006-2010



The highest use counties varied between the different formulations. Except for 2008, aluminum phosphide was used predominantly in Fresno County. The highest use counties for magnesium phosphide from 2006-10 were Sacramento, Yolo, Fresno, Yolo, and Solano, respectively. The highest-use counties for phosphine from 2006-10 were Kern, Stanislaus, Sacramento, Sacramento, and Stanislaus, respectively (Table 6).

EAD Table 6. Annual Number of Pounds of Al Phosphide, Mg Phosphide, and Phosphine Applied Statewide and in the Highest Use County (2006 – 2010)

Fumigant	Year	Total Pounds Applied (all counties)	Highest Use County
Al Phosphide	2006	149,217	Fresno
	2007	105,342	Fresno
	2008	132,458	Los Angeles
	2009	107,502	Fresno
	2010	106,234	Fresno
Mg Phosphide	2006	3931	Sacramento
	2007	5284	Yolo
	2008	16,086	Fresno
	2009	8008	Yolo
	2010	12,216	Solano
Phosphine	2006	3483	Kern
	2007	5341	Stanislaus
	2008	48,259	Sacramento
	2009	30,194	Sacramento
	2010	11,531	Stanislaus

Based upon the PUR data for 2006-10, four types of fumigation were conducted using aluminum phosphide and magnesium phosphide. These types of fumigation are commodity fumigation, space fumigation, spot fumigation, and burrowing pest control fumigation. The types of fumigation were determined via the site/crop selection on the PUR database. Commodity fumigation consisted of the term, “commodity fumigation”, as well as more specific terms such as “almond”, “barley”, or “cabbage”. Space fumigation was used to describe the following PUR site terms: “bldg. and structures (non-ag. outdoor)”, “commercial storages or warehouses (all or unspec.)”, “structural pest control”, “commercial, institutional or industrial areas”, “animal husbandry premises”, “food processing, handling, plant area (all or unspec.)”, “feed/food storage areas (unspec.)”, and “storage areas and processing equipment”. Spot fumigation was used to characterize the following site/crop terms: “farm or agricultural structures and equipment (all or unspecific)”, “food marketing, storages or warehouses (all or unspecific)”, and “storage areas and processing equipment”. Finally, burrowing pest control fumigation was suggested by site/crop terms such as “vertebrate pest control”, “animal burrow entrances”, and “landscape maintenance”.

E. ILLNESS REPORTS

This section is quoted in full from DPR's Exposure Assessment Document on phosphine, in the section entitled "Reported Illnesses" (DPR, 2014). The incidents were described in the California Pesticide Illness Query search engine. Additional human incidents are summarized below in section III of this document.

> Following the investigation of a potential case of pesticide poisoning, the County Agricultural Commissioner files a report, which is logged in the California Pesticide Illness Surveillance Program (PISP) database. Using the California Pesticide Illness Query (CalPIQ) search engine, for the latest 5 years of data (2005-2009), there are 10 reported cases of illness associated with aluminum phosphide, no cases associated with magnesium phosphide, and 27 cases associated with cylinderized phosphine. Exposure is described as being a "definite", "probable", or "possible" cause of each reported illness. As stated on the CalPIQ website, "A **definite** relationship indicates that both physical and medical evidence document exposure and consequent health effects. A **probable** relationship indicates that limited or circumstantial evidence supports a relationship to pesticide exposure. A **possible** relationship indicates that health effects correspond generally to the reported exposure, but evidence is not available to support a relationship" (CalPIQ, 2011).
>
> Ten cases of phosphine exposure are listed for "aluminum phosphide" in the PISP database from 2005-2009. Six of the cases occurred in 2005. The first case (case number 253) occurred in Fresno County. In this case, a feed mill worker located 2 floors below a fumigated and aerated feed bin was reported as smelling a garlic odor prior to suffering from a headache, abdominal pain, dizziness, and painful teeth. Other workers in the mill were reported as smelling the same odor. Phosphine exposure was reported as being "probable". In the second case (case number 601), also in Fresno County, an almond processing plant worker who sorted the almonds developed irritation in the left eye upon noticing a white powder. The report stated that the almonds are fumigated prior to being processed and the spent fumigant powder is removed in envelopes. Phosphine exposure in this case was reported as being "possible". The next three cases listed (case numbers 1307-1309) were due to a single incident where 3 individuals broke into a fumigating box car and closed all of the openings in order to avoid detection. All three individuals died. Phosphine exposure was reported as being "definite" in all three cases. In the fourth case (case number 1310), an intensive care nurse who treated one of the individuals developed shortness of breath, a burning sensation around the neck, and welts on the arms. Phosphine exposure in this case was reported as being "possible". These 4 cases occurred in Riverside County. The next case (case number 613) occurred in San Bernardino County in 2006 and consisted of a warehouse forklift driver who was reported to have inhaled fumes from improperly disposed of spent fumigant that had ignited. The driver was reported to have experienced pain in the eyes, stomach, and head. Phosphine exposure was listed as being "probable". One case (case number 844) occurred in 2007 in Merced County. In this case, a trainer without the proper qualifications instructed an inexperienced worker to fumigate sacks of almonds. The worker did not wear PPE and became ill after a

few hours. The worker's symptoms included nausea, vomiting, headache, fatigue, and a chemical taste in mouth. The last two cases in the report (case numbers 412 and 1031) occurred in 2009 in Merced and Fresno Counties, respectively. In case number 412, a field worker became ill (i.e., nausea and vomiting), on the 2nd day of applying aluminum phosphide to animal burrows. The worker was reported as not being a certified applicator. Phosphine exposure in this case was reported as being "possible". In case number 1031, an individual renting a house applied aluminum phosphide pellets to a squirrel hole adjacent to the garage and gas meter. A few hours later, the occupants of the house experienced coughing, dizziness, and a "sensation of fluid in the lungs". Phosphine exposure in this case was reported as being "probable" (CalPIQ, 2011).

For the years 2005-2009, 27 potential cases of phosphine exposure, due to the use of "phosphine" are listed in the PISP database. In 2007 in San Joaquin County, a bulk storage operator was reported as being exposed to phosphine gas escaping from a fumigated rail car with a faulty hatch cover. The operator was not wearing a respirator. The worker experienced symptoms including fatigue and skin irritation several hours after the incident (case number 703). In 2007 in Kern County, twenty three of the cases (case numbers 1229, 1231, 1234-1240, 1242-1245, 1446, 1449, 1453, 1456, 1459, 1464-1466, and 1478-1479), occurred in a single incident at an almond processing plant where the fumigant was applied using an illegal method. According to the label, the cylinderized phosphine is supposed to be applied from outside of the facility being fumigated. However, in this case, the applicators placed the cylinder of gas in the plant and then opened the valve. Following "aeration", the plant workers returned. During the application, the phosphine fumigant had penetrated into the cold room which was not monitored. Upon opening the doors, 23 workers complained of a strong odor and subsequently experienced symptoms including headache, nausea, and dizziness. Phosphine exposure in twenty-one of the cases was reported as being probable and, in 2 of the cases, as being possible. In 2008 in Butte County, workers entered an unlabeled bin containing walnuts undergoing fumigation. The warning placards were reported as being torn off by the weather prior to the workers entering the bin. One of the workers experienced symptoms including "burning throat pain", "chest constriction", and nausea. An applicator measured levels within the bin and found levels to be "high". Phosphine exposure in this case was reported as being "probable". The case number for this incident is 45. Another case (case number 894), in 2008 in Stanislaus County consisted of a worker sorting almonds in a "fogged" warehouse who experienced symptoms 2 days after the treatment. The symptoms included difficulty breathing, nausea, and a headache. However, in addition to phosphine, the pesticide, DDVP, was listed as the possible culprit. Phosphine exposure in this case was reported as being "possible". Finally, in 2008 in Kern County, a plant supervisor instructed a worker sorting almonds to place a fumigation "probe" into piles of almonds covered by tarpaulins. The worker was reported as having "smelled the fumigant", and experienced symptoms including nausea, vomiting, stomach pain, cramps, sweating, and weakness. Phosphine exposure in this case was reported as being "probable" (case number 1071) (CalPIQ, 2011).

F. PHYSICO-CHEMICAL AND ENVIRONMENTAL PROPERTIES

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

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	*absolute*: 1.529 g/L (0°C) [b]; 1.390 g/L (temp. not reported) [c] *relative to air:* 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)

G. ENVIRONMENTAL FATE

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

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 Gurisinge 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 (O_3) 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:

$$PH_3 + HOx \rightarrow H_20 + PH_2x \quad \underline{and} \quad PH_3 + HOx \rightarrow HOP + H_3$$

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. Nonetheless, reviews by WHO (1988) and Gehring *et al.* (1991) make the following points:

1. Phosphine gas is generally assumed to be quickly absorbed by the lung. Hepatic and neurologic effects suggest that it is distributed to liver and brain at the very least, with wide tissue distribution likely.

2. Inhaled aluminum and magnesium phosphide deposits in the lung, where phosphine gas is liberated upon hydrolysis.

3. There is virtually no absorption of phosphine gas or metal phosphides through skin, an observation supported by the effectiveness of gas masks in preventing toxicity.

4. Intact aluminum phosphide is detectable in blood and liver following human ingestion, suggesting that metal phosphide hydrolysis is not necessary for absorption.

5. Pulmonary excretion occurs regardless of route of absorption. Phosphine is excreted in expired air or is slowly oxidized to hypophosphite and phosphite for excretion in urine. There is evidence for at least one other undefined metabolite.

6. Phosphine has the potential to react with heme and copper-containing proteins, though this is incompletely understood.

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 $^{32}PH_3$ 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. WHO (1988) states that oxygen is required for phosphine uptake in insects.

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 AlP 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 AlP-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 AlP-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% AlP, which liberates 1 gram of phosphine gas, was attested to by the reported estimated lethal dose of 0.1 g AlP per 70-kg person, equivalent to about 1.4 mg/kg (Chugh *et al.*, 1991 [3]). For comparison, two oral studies of aluminum phosphide toxicity in rats and rabbits analyzed for this document identified LD_{50}s 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."

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

In contrast to AlP oral exposures, where the internal dose of phosphine was inferred from the 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/m^3), with death occurring within 1/2 - 1 hr of exposure to 400 - 600 ppm (560 - 840 mg/m^3). The gas was considered "dangerous to life" after 1/2 - 1 hr at 290 - 400 ppm (400 - 600 mg/m^3), 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/m^3), 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 AlP 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 AlP 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 symptomology 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) and Lyubimov and Garry (2010) cited O.R. Klimmer's work published in German documenting lassitude, ataxia, apnea and cardiovascular collapse in laboratory animals exposed to high levels of phosphine (Klimmer, 1969). Death occurred within 0.5 hr at concentrations greater than ~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.

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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 H_2SO_4 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 LC_{50} 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 $12.5x10^3$ (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 LC_{50}. 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 LC_{50}s. 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, reinstituting 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 determined [4]. This study was considered supplemental [5].

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[4] 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 calcualtion:

To convert ppm to mg/L:

MW [=34 g/M] ÷ molar volume [=24.4 L @ 25°C] = 1.4 g/L

1.4 g/L x (4 ppm x 10^{-6}) = 0.0056 mg/L

To convert mg/L to mg/kg:

0.0056 mg/L x absorption factor [=1] x 40 L/kg/hr x 4 hr = 0.9 mg/kg/day

[5] 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.

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

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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.

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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 bodies [6] were not detected at any exposure concentration. The toxicologic significance of the blood observations was was not known.

Because the LD_{50} 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.

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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

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[6] Heinz bodies: "coccoid inclusion bodies resulting from oxidative injury to and preciptation 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.

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 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.

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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 LC_{50} 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 LC_{50} 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 LC_{50} of >59.2 ppm. The mortality curve for the 4-hr LC_{50} 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 LC_{50} 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.

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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 LC_{50} (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 LD_{50} 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.

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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 (AlP). 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 LD_{50} 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 AlP 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 AlP-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 Ca^{2+}-ATPase and Mg^{2+}-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.

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 LD_{50}	no studies available			
Dermal LD_{50}	no studies available			
Inhalation LC_{50}				
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.

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

Species	Tox. Cat.	LD_{50}	NOEL / LOEL	Effects at LOEL
Oral LD_{50}				
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 LC_{50}				
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 LD_{50} 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 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 ($6.85x10^6$ *vs.* $7.18x10^6$ / µl; 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 (♂, IU/L: 79, 72, 60 and 49*; ♀: 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 x 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 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.

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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.

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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 vetricular 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.

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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.

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	% ∆ 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] $p < 0.001$

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)/Crl/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 reminder 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♂ / 14♀; 0.3 ppm: 16♂ / 15♀; 1 ppm: 14♂ / 9♀; 3 ppm: 12♂ / 12♀), 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 *et al.* (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 *et al.* (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 *et al.* (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 *et al.* (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 G_0-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/m^3; n=10) and in open spaces (range=0.1-0.9 mg/m^3 [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/m^3. 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-acentrics) 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*,[y]	2.52±0.53***,[y]	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.

[y] p<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.

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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), ±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±4.5 *vs.* 7.1±4.0 micronuclei per 1000 binucleated cells, respectively) or between smokers and non-smokers (7.2±3.9 *vs.* 6.8±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±3.4 *vs.* 8.1±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% Mg_3P_2 + 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 LC_{50} 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.

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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, ±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, ±S9. Thus at 0 (untreated control), 0 (air control), 436, 2733 and 4957 ppm, -S9, the total abberration 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.

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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±0.09*, 1.61±0.18* and 1.56±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±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 ~$5x10^5$ viable cells. After ~2 hours incubation to establish monolayers, unattached cells were removed and medium was added containing 10 µCi/ml of ^{3}H-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.

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

Test type / system	Species / strain / culture	Dose range	S9	Result	Reference / comment
Gene mutation:					
E. coli and Ames / *Salmonella*	*E. coli* B/r WP2 TRP$^-$ HCR$^-$; *S. typhimurium* (6 tester strains);	640 - 25600 ppm [a]	±	negative	Sutou (1972) [a] / *unacceptable*
Ames / *Salmonella*	*S. typhimurium* (6 tester strains)	4.52 - 4340 ppm	±	negative	Stankowski (1990) [c] / *unacceptable*
Ames / *Salmonella*	Urine from phosphine applicators tested in *S. typhimurium* (2 tester strains)	<2.4 ppm over a 1-hr period	na	negative	Barbosa and Bonin (1994) / *supplemental*
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 *et al.* (1994) / *supplemental*
Structural chromosome aberration:					
Chromosome aberration	Phosphine applicators, G_0 stage lymphocytes	0-4.5 µg/L (0-3.2 ppm)	-	positive	Garry *et al.* (1989) / *supplemental*
Chromosome rearrangements	Phosphine applicators, lymphocytes	unknown	-	positive	Garry *et al.* (1992) / *supplemental*
Chromosome aberration	Chinese hamster ovary cells	426 - 4957 ppm	±	positive [b]	SanSebastian (1990) / *acceptable*
Micronucleus formation	Phosphine applicators	<2.4 ppm over a 1-hr period	na	negative	Barbosa and Bonin (1994) / *supplemental*
Micronucleus formation	Balb-c mice, 13-wk, 6-hr daily exposures	0.3 - 4.5 ppm	na	positive	Barbosa *et al.* (1994) / *supplemental*
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 *et al.* (1994a) / *supplemental*
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 *et al.* (1994b) / *supplemental*

Dominant lethal effects	male B6C3F1 mice	5 ppm	na	negative	Kligerman *et al*. (1994b) / *supplemental*
Recessive lethal effects	*Drosophila melanogaster*	575 ppm	na	positive	Al-Hakkak (1988) / *supplemental*
DNA damage:					
Unscheduled DNA synthesis	Fischer 344 rat	4.8 - 23 ppm	na	negative	McKeon (1993) / *acceptable*

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, ±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").

F. REPRODUCTIVE TOXICITY

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

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) / *acceptable*

[a] This was the highest non-lethal dose.

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, ♂: 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 (♂: 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 (♂: 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.

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

	Phosphine [a]				
	0 ppm	**21 ppm**	**28 ppm**	**38 ppm**	**LED_{10} / ED_{10} [b]**
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.

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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, opthalmologic, 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* x $10^3/mm^3$; *$p<0.05$), 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 (°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 them.

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.

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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.

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 (though see the comment in the next section supporting the subchronic / chronic 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 LED_{10} determination was forthcoming in four 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.

4. Newton (1990) noted renal pelvic and tubular mineralization, as well as an apparent reduction in liver weights (absolute weights in grams at 0.3, 1 and 3 ppm: 7.481, 6.791*, 6.309**, 6.662*; relative to bodyweight: 2.59, 2.41**, 2.36**, 2.37**; *,**$p<0.05$, 0.01) after 13 weeks of inhalation exposure. While neither effect was sufficiently toxicologically clear for LOEL designation, they were at least suggestive that toxicity would become manifest at higher doses or longer exposure times.

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.

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, 2014). 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, 2014), 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.

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

Exposure scenario	Short-term exposure (ppm)	Seasonal exposure (ppm)	Annual exposure (ppm)
Addition of aluminum phosphide to commodities in upright concrete grain elevator bins through auto-dispenser or manual operations (DPR, 2014: Table 12)			
Applicator (auto-dispenser)	0.12	0.02	0.01
Applicator (manual)	0.01	0.07	0.05
Commodity fumigation in upright concrete grain elevator bins (DPR, 2014: Table 13)			
Occupational bystander (inside and outside of grain-elevator)	0.04	0.2	0.13
Residential bystander	0.1	0.1	0.07
Occupational bystander (inside and outside of grain-elevator), post application	0.02	0.14	0.09
Residential bystander, post application	0.1	0.1	0.07
Occupational bystander (outside of grain-elevator), post aeration	0.01	0.07	0.05
Residential bystander, post aeration	0.1	0.1	0.07
Commodity fumigation in farm bins (DPR, 2014: Table 14)			
Applicator	0.1	0.007	0.005
Aerator	0.02	0.3	0.2
Occupational bystander (air monitor)	0.04	0.01	0.008
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 in flat storage facilities (DPR, 2014: Table 15)			
Applicator	0.005	0.11	0.07
Aerator	0.02	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, 2014: Table 16)			
Applicator	0.04	0.01	0.007
Aerator	0.02	0.3	0.2
Spent fumigant retriever	0.01	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, 2014: Table 17)			
Applicator	0.04	0.008	0.005
Occupational bystander (assistant worker)	0.02	0.2	0.13
Occupational bystander (nearby worker: post-application/pre-aeration)	0.007	0.1	0.07
Aerator	0.08	0.02	0.01
Occupational bystander (assistant aerator)	0.12	0.12	0.08
Occupational bystander (nearby worker: post-aeration)	0.009	0.2	0.13
Occupational bystander (packaging line for consumer products worker)	0.08	0.2	0.13
Residential bystander	0.1	0.1	0.07
Commodity fumigation in box cars (DPR, 2014: Table 18)			
Applicator	0.08	0.01	0.007
Occupational bystander (assistant worker: application)	0.02	0.008	0.005
Occupational bystander (nearby worker: application)	0.03	0.3	0.2
Occupational bystander (nearby worker: post-application)	0.05	0.3	0.2
Residential bystander	0.1	0.1	0.07
Commodity aeration in box cars (DPR, 2014: Table 19)			
Aerator (outdoor)	0.06	0.02	0.013
Aerator (indoor)	0.1	0.04	0.03
Occupational bystander (assistant aerator: outdoor aeration)	0.01	0.17	0.11
Occupational bystander (nearby worker: indoor post-aeration)	0.05	0.02	0.01

Occupational bystander (packaging line for consumer products worker)	0.08	0.2	0.13
Residential bystander	0.1	0.1	0.07
Commodity fumigation in ship holds (DPR, 2014: Table 20)			
Applicator	0.005	0.11	0.07
Aerator	0.08	0.02	0.01
Occupational bystander (application)	0.007	0.1	0.07
Occupational bystander (aeration)	0.009	0.2	0.13
Occupational bystander (in-transit fumigation)	0.1	0.1	0.07
Commodity fumigation in ship containers (DPR, 2014: Table 21)			
Applicator	0.08	0.01	0.007
Aerator	0.06	0.02	0.013
Occupational bystander (application)	0.03	0.3	0.2
Occupational bystander (aeration)	0.009	0.2	0.13
Occupational bystander (in-transit fumigation)	0.1	0.1	0.07
Spot fumigation (DPR, 2014: Table 22)			
Applicator	0.004	n/a	n/a
Aerator / retriever / deactivator	0.02	n/a	n/a
Occupational bystander	0.3	n/a	n/a
Residential bystander	0.1	n/a	n/a
Burrowing pest fumigation (DPR, 2014: 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
Addition of aluminum phosphide to commodities in upright concrete grain elevator bins through auto-dispenser or manual operations (DPR, 2014: Table 12)			
Applicator (auto-dispenser)	42	50	100
Applicator (manual)	500	14	20
Commodity fumigation in upright concrete grain elevator bins (DPR, 2014: Table 13)			
Occupational bystander (inside and outside of grain-elevator)	125	5	8
Residential bystander	50	10	14
Occupational bystander (inside and outside of grain-elevator), post application	250	7	11
Residential bystander, post application	50	10	14
Occupational bystander (outside of grain-elevator), post aeration	500	14	20
Residential bystander, post aeration	50	10	14
Commodity fumigation in farm bins (DPR, 2014: Table 14)			
Applicator	50	143	200
Aerator	250	3	5
Occupational bystander (air monitor)	125	100	125
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, 2014: Table 15)			
Applicator	1000	9	14
Aerator	250	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, 2014: Table 16)			
Applicator	125	100	143
Aerator	250	3	5
Spent fumigant retriever	500	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, 2014: Table 17)			
Applicator	125	125	200
Occupational bystander (assistant worker)	250	5	8
Occupational bystander (nearby worker: post-application/pre-aeration)	714	10	14
Aerator	63	50	100
Occupational bystander (assistant aerator)	42	8	13
Occupational bystander (nearby worker: post-aeration)	556	5	8
Occupational bystander (packaging line for consumer products worker)	63	5	8
Residential bystander	50	10	14
Commodity fumigation in box cars (DPR, 2014: Table 18)			
Applicator	63	100	143
Occupational bystander (assistant worker: application)	250	125	200
Occupational bystander (nearby worker: application)	167	3	5
Occupational bystander (nearby worker: post-application)	100	3	5
Residential bystander	50	10	14
Commodity aeration in box cars (DPR, 2014: Table 19)			
Aerator (outdoor)	83	50	77
Aerator (indoor)	50	25	33
Occupational bystander (assistant aerator: outdoor aeration)	500	6	9
Occupational bystander (nearby worker: indoor post-aeration)	100	50	100

Occupational bystander (packaging line for consumer products worker)	63	5	8
Residential bystander	50	10	14
Commodity fumigation in ship holds (DPR, 2014: Table 20)			
Applicator	1000	9	14
Aerator	63	50	100
Occupational bystander (application)	714	10	14
Occupational bystander (aeration)	556	5	8
Occupational bystander (in-transit fumigation)	50	10	14
Commodity fumigation in ship containers (DPR, 2014: Table 21)			
Applicator	63	100	143
Aerator	83	50	77
Occupational bystander (application)	167	3	5
Occupational bystander (aeration)	556	5	8
Occupational bystander (in-transit fumigation)	50	10	14
Spot fumigation (DPR, 2014: Table 22)			
Applicator	1250	n/a	n/a
Aerator / retriever / deactivator	250	n/a	n/a
Occupational bystander	17	n/a	n/a
Residential bystander	50	n/a	n/a
Burrowing pest fumigation (DPR, 2014: 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 LC_{50} 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 LC_{50} 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 LC_{50} 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 ~7 mg/m^3 (~5 ppm) at ~11-12 hours of exposure, supporting the critical value identified here [7]. 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 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.

However, the assumption that death occurred through portal of entry effects in the lung requires further support. Evidence for such effects should be specifically monitored in future studies. To this end, USEPA has requested submission of a “special” acute rat inhalation study, to include “histopathology of the respiratory tract, including incidence and severity at multiple tested concentrations; GSH measurements (*i.e.*, nose) [8]; pharmacokinetics / tissue dosimetry including time course; and sublethal portal of entry effects (i.e., within the respiratory tract) along with information on dose response, incidence, and severity” (USEPA, 2013). Data from such a study may support sublethal NOELs / LOELs that are lower than the mortality-dependent values currently recommended.

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. 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.

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

[8] GSH (glutathione) is an indicator of cellular oxidative stress and a marker for consequent repair activity.

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.

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 possiblity 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 animals [9]); palpebral closure occurred before exposure in both control (female) and treated groups; palpebral closure was sporadic, with the only statistically significant increase occurring among males at week 4; increased incidence of slowed respiration was noted only occasionally (weeks 8 and 13) and only in males, suggesting that it was not a treatment effect; the decrease in body temperature occurred in males (week 13); the decrease in body temperature was within the normal range in rats; and palpebral closure, slowed respiration and decreased body temperature were incidental and sporadic findings. In addition, the toxicologic significance of palpebral closure 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 acute 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.

[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.

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

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.

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). We agreed with USEPA's analysis of that study, also assigning a NOEL of 5 ppm, which was the highest dose employed. We calculated the the internal dose to be 1.7 mg/kg, with the difference due to the fact that we 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, we 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]. We 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 USEPA [11].

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). We agreed with USEPA's analysis of that study, also assigning to it a NOEL of 3 ppm. However, we 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 we nor USEPA 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.

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[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 in the current analysis and by USEPA.

[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 ≈ 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 ≈ 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 ≈ 1.2 mg/kg/day	**Schaefer, 1998b** **13-wk inh. ntx**, **6 hr/day, 5 days/wk - rat** LOEL = 3 ppm (palpebral closure, ↓ respiration, ↓ body temp.) NOEL = 1 ppm ≈ 0.24 mg/kg/day
Chronic toxicity	**Newton, 1998** **2-yr inhalation, 6 hr/day, 5 days/wk - rat** LOEL > 3 ppm (hdt) NOEL = 3 ppm ≈ 1.13 mg/kg/day	**Schaefer, 1998b** **13-wk inh. ntx**, **6 hr/day, 5 days/wk - rat** LOEL = 3 ppm (palpebral closure, ↓ respiration, ↓ body temp.) NOEL = 1 ppm ≈ 0.24 mg/kg/day
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 mandbhated 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.*, 2013). This possibility has not yet been supported under controlled conditions.

D. ENDOCRINE EFFECTS

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

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 ÷ 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**

VIII. TOLERANCE ASSESSMENT

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

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. Moreover, 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 would have to be considered when evaluating the need for mitigation.

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.

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. Mitigation measures should be considered.

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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)/Crl/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 (PH_3) 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/m^3] in a standard teratology study. An additional group was initiated on study at 7.5 ppm [10.5 mg/m^3], 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 (PH_3)," 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 (PH_3)," 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 N_2") 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/m^3 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 kerotinocytes 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 kerotinocytes 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)/CrlBR 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 µCi/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 (PH_3) 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 (PH_3)," reprinted translation of "Beitrag zur Wirkung des Phosphorwasserstoffes (PH_3)" 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 PH_3 (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 PH_3 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 PH_3 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 LD_{50}'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. LC_{50} 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.

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

SEE FOLLOWING PAGE

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.

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).

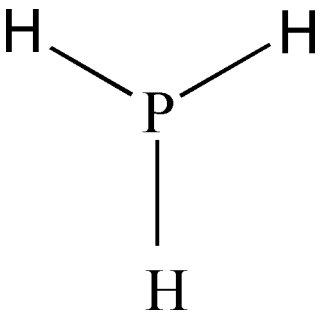
$AlP + 3H_2O \rightarrow PH_3 + Al(OH)_3$

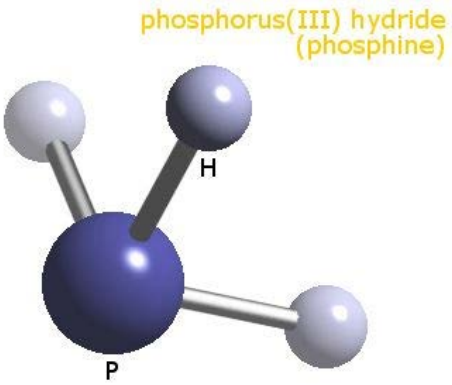
$Mg_3P_2 + 6H_2O \rightarrow 2PH_3 + 3Mg(OH)_2$

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: WebEments.com 2012**)**





Phosphine is a triagonal pyramidal molecule with C_{3v} molecular symmetry. The length of P-H bond is 1.42 A^0, the H-P-H bond angles are 93.5^0.

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_3P_2	PH_3
Molecular weight (g/mol)	58	135	34
Boiling Point at 1 atm (^{0}C)	>1,000[2]	> 1,000[3]	-87.7[4]
Melting point (^{0}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 ^{0}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 ($cm^2 \cdot s^{-1}$)	Not available	Not available	1.82e-005[5]
Diffusion coefficient in air ($cm^2 \cdot s^{-1}$)	Not available	Not available	0.381[5]
Henry's Law Constant ($atm \cdot m^3/mol$ at 25 ^{0}C)	Not available	Not available	2.44 x 10^{-2} [6]
Vapor pressure (mm Hg at 25 ^{0}C)	0[2]	0[3]	31388[5]
Relative vapor density (air = 1)	Not available	Not available	1.17[7]

[1]DPR 2012a & b
[2]DEGESCH America, Inc. 2011
[3]DEGESCH America, Inc. 2010
[4]IPCS 1997
[5]Groundwater Services, Inc. 2010
[6]Hazardous Substances Data Bank 2012
[7]WHO 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

	Year registered	
Compound	**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).

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 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})**	
	Lowest	***Highest***
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.

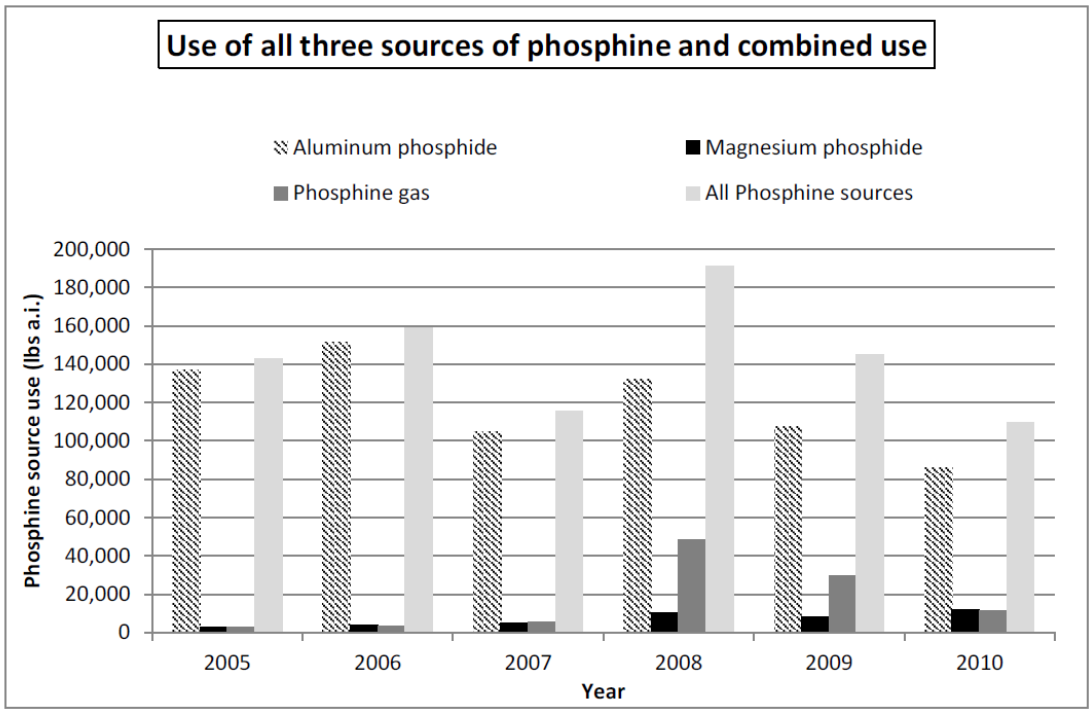
Table 5. Annual use of phosphine-generating fumigants and phosphine in California (2005 – 2010)

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**
Aluminum phosphide products						
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**
Magnesium phosphide products						
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	0	0	0	4	124	377
DEGESCH MAGTOXIN PELLETS	14	44	0	8	0	0
DEGESCH MAGTOXIN PELLETS-PREPAC	1	0	0	0	0	0
DEGESCH MAGTOXIN PREPAC SPOT FUMIGANT	94	175	113	501	38	27
DEGESCH MAGTOXIN TABLETS-R	0	0	3	0	5	1
MAGNAPHOS GAS BAGS	0	0	0	0	0	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.**						
	Year						***Site Total***
	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.												
	Month												*County Total*
	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.**												
	Year												***Site Total***
	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.**							
	Year						***County Average***	***County Total***
	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	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	0	51	60	**360**
Peach	0	0	0	0	0	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.**													
	Month												***County Average***	***County Total***
	JAN	**FEB**	**MAR**	**APR**	**MAY**	**JUN**	**JUL**	**AUG**	**SEP**	**OCT**	**NOV**	**DEC**		
Yolo	73	77	69	180	91	142	110	341	146	131	130	33	127	**9,160**
Fresno	0	0	0	22	3	1	3	7	64	946	5	49	92	**6,630**
Solano	0	0	0	0	1073	0	0	0	0	0	0	0	89	**6,464**
San Joaquin	49	40	31	12	29	25	21	48	51	73	56	45	40	**2,908**
Colusa	17	16	12	18	91	44	60	47	99	11	23	14	38	**2,739**
Sacramento	51	51	47	30	16	25	1	16	71	56	42	32	36	**2,656**
Stanislaus	1	2	4	1	2	4	2	6	2	399	2	1	36	**2,592**
Butte	28	32	36	45	13	49	26	16	14	35	41	27	30	**2,189**
Glenn	9	5	2	3	3	0	7	0	52	133	123	14	29	**2,122**
Merced	3	3	3	3	2	3	9	24	55	21	14	8	12	**930**
Monthly average	**39**	**38**	**34**	**53**	**220**	**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.**													
	Month												***Site Average***	***Site Total***
	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.					
	Year					
	2005	**2006**	**2007**	**2008**	**2009**	**2010**
Phosphine gas products						
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	**1,206**
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**	**29,527**	**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	0	0	0	0	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	0	106	289	192	**774**
Tomato, processing	18	0	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.												
	Month												*Site Total*
	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/m^3 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 (*Oncorhynchus mykiss*)	4.1 ug/L
Bluegill sunfish (*Lepomis macrochirus*)	0.178 mg / m^3

An LC_{50} for phosphine for the frog from a 30-minute exposure was reported to be 0.56 mg/L. The LC_{50} 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). According to several studies, residues of phosphine may remain on commodities fumigated with phosphine gas or phosphine-generating products (Table 21), however Dieterich et al. (1967) showed that residues in most fumigated foods are below a level of concern at 0.01 mg/m^3 (0.01 ppm) or less. 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.

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

Fumigant, rate	Commodity	Residue/Observations	References
Phosphine @ 4000 ppm and 25 ^{0}C	Wheat Millet Milled Rice Soybeans Azuki beans	Wheat 0.46 Millet 1.16 Milled Rice 0.34 Soybeans 0.18 Azuki beans 0.24 12 days from fumigation	Sato & Suwanai, 1974
Phosphine @ 5 ppm	Wheat	After 4 days of aeration: 0.2ppb After 220 days of aeration:0.004ppb	Dumas, 1980
Phosfume® @ 2 tabs/ton 4 tabs/ton 8 tabs/ton	Legumes	Ranged from 0.66 to 1.33 ppm Below detection limit; 0.001 ppm by < 3 days in 2 tabs/ton < 6 days in 8 tabs/ton	Singh et al., 1983
Aluminum phosphide tabs @ 5 gm/ton	Wheat	Residue in wheat 12.01 ± 1.22 ppb	Pratt & Desmarchelier, 1988

8. ENVIRONMENTAL MONITORING

WHO (1988) reported a study that detected air concentrations of up to 280 mg phosphine/m^3 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/m^3, 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/m^3 phosphine; the samples from

inside the chamber were 510,000 to 7,000,000 ug/m^3. Concentrations of ambient samples taken during the venting of the chamber were < 1 – 6 ug/m^3.

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, ECO_2FUME, 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.

ECO_2FUME fumigant gas is a non-flammable pre-mixed cylinderized mixture of phosphine and carbon dioxide. In most cases ECO_2FUME can be dispensed from outside the storage facility, which 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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MEMORANDUM

TO: Gary T. Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: November 19, 2013

SUBJECT: COMMENTS ON THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR PHOSPHINE

The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the draft Risk Characterization Document (RCD) for occupational and ambient air exposure to phosphine, prepared by the Department of Pesticide Regulation (DPR), dated February 15, 2013. Our comments are provided in the attachment. OEHHA has provided comments on the Exposure Assessment Document for Phosphine separately. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agricultural Code section 11454.1.

OEHHA has provided a number of comments on the risk characterization methodology and conclusions of the draft RCD. These comments are contained in the attachment. Thank you for providing this draft document for our review. If you have any questions regarding OEHHA's comments, please contact Dr. Charles Salocks at (916) 323-2605 or me at (510) 622-3200.

Attachment

cc: Charles B. Salocks, Ph.D., D.A.B.T.
Chief, Pesticide Epidemiology Section
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment

OEHHA's Comments on DPR's Draft
Risk Characterization Document for Phosphine
(Occupational and Ambient Air Exposures)

The Office of Environmental Health Hazard Assessment (OEHHA) is responding to a request from the Department of Pesticide Regulation (DPR) to comment on the February 15, 2013 draft Risk Characterization Document (RCD) for phosphine. The document addresses occupational and ambient air exposures. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agricultural Code Section 11454.1, which requires OEHHA to conduct scientific peer reviews of risk assessments conducted by DPR.

SUMMARY OF COMMENTS

The RCD addressed the fumigation product phosphine (PH_3), which is used as a rodenticide and insecticide for stored agricultural products such as grain, tobacco, processed foods and animal feed. The RCD was comprehensive and well-written with a thorough presentation of the toxicological studies, analysis of weight of evidence, and approaches used to identify the critical endpoints and derive No Observed Effect Levels (NOELs) to calculate margins of exposure (MOEs). From a public health perspective, this is a very important RCD because the usage of phosphine in California is increasing. Our principal comments and suggestions are as follows:

- Acute toxicity: Because of its severity, OEHHA does not recommend using lethality as a critical endpoint when determining an acute exposure advisory level. However, in this case because of data availability, OEHHA agrees with the selection of the Newton (1990) study in the RCD, but suggests adding an uncertainty factor (3-fold or higher) because the NOEL (5 parts per million [ppm]) is based on lethality. OEHHA also suggests an additional 3-fold uncertainty factor to protect infants and children as sensitive bystander subpopulations, as discussed below.

- Subchronic toxicity: OEHHA agrees with the use of the subchronic study selected for the subchronic exposure determination, and with the use of the observed NOEL (1 ppm) from the Schaefer (1998b) study as a point of departure for calculating the subchronic exposure advisory level. However, OEHHA suggests incorporating an additional 3-fold uncertainty factor to protect infants and children as sensitive bystander subpopulations, as discussed below.

- Chronic toxicity: OEHHA agrees with the use of the subchronic study for the chronic exposure determination, since an adequate chronic study was not identified, and with the point of departure (Schaefer 1998b). OEHHA suggests the use of an additional 3-fold uncertainty factor when using a NOEL from a subchronic study to assess hazard associated with chronic exposure. Furthermore, OEHHA suggests incorporating an additional 3-fold uncertainty factor to protect infants and children as sensitive bystander subpopulations, as discussed below.

- Carcinogenicity: OEHHA agrees with the approach in the RCD not to calculate cancer risk values. The weight of evidence for carcinogenicity is based on a single study in male and female rats (Newton 1998), which observed no carcinogenicity. However studies were not performed in a second species and this should be noted in the RCD. In addition, there were 99 unscheduled deaths in the study. DPR stated that these deaths were unrelated to phosphine exposure. The results of the Newton (1998) study are hard to interpret, but OEHHA believes there is not enough information in the RCD to justify stating that the deaths were unrelated to phosphine exposure.

- Sensitive subpopulations: As noted above, OEHHA is concerned that the exposure values used for occupational and residential bystanders, including infants and children, may not be sufficiently health-protective. Some of these bystanders such as office workers or nearby residents may not be aware that fumigation is taking place near them. Therefore, they would not be expected to use air-purifying respirators or other protective equipment. OEHHA suggests that infants and children may be more susceptible to the adverse health effects of phosphine and phosphine-generating products due to their higher susceptibility to airborne toxicants, higher breathing rates on per kilogram body weight basis and higher incidence of asthma. A recent report cited in the RCD stated the possibility of children being more susceptible to phosphine-induced or mediated death (O'Malley et al., 2013). OEHHA suggests considering an extra 3-fold uncertainty factor to account for increased susceptibility in children.

- Uncertainty factors: In summary, OEHHA is recommending additional uncertainty factors for the acute, subchronic and chronic exposure advisory levels. For the acute point of departure, OEHHA suggests an additional 3-fold uncertainty factor because the NOEL was based on lethality and a 3-fold factor to protect infants and children. For the subchronic point of departure, OEHHA suggests an additional 3-fold uncertainty factor to protect infants and children. Finally, for the chronic point of departure, OEHHA suggest a 3-fold uncertainty factor because the key study utilized subchronic exposure and a 3-fold factor to protect infants and children that are bystanders.

- Usage: Regarding the usage of phosphine and phosphine-generating products, a trend of increasing agricultural use of phosphine gas, aluminum phosphide and magnesium phosphide is apparent, although year-over-year data are quite variable. Given the high toxicity of phosphine and the low MOEs calculated in the RCD, this trend has possible public health implications. Occupational and residential bystanders may not be aware that fumigation is taking place near them and therefore would not be expected to use air-purifying respirators or other protective equipment. For similar reasons, residential bystanders may be exposed if they live close to grain elevators or close to other places where fumigation occurs. Increased usage of phosphine could result in increased exposure for these groups.

ACUTE TOXICITY

The RCD provides a clear review of human exposures (accidental, occupational and suicidal) to phosphine. These descriptions indicate the acute toxicity of phosphine resulting in severe illness and death following exposure. OEHHA suggests providing a summary table of the individual cases of human poisoning and observed adverse effects to improve this section.

- Study and Endpoint Selection
    - A study conducted by Newton (1990) was identified as the critical study supporting the point of departure for acute toxicity. The critical effect in this study was lethality based on the deaths of 4/10 female rats within 3 daily exposures to 10 parts per million (ppm) (6 hours/day, 5 days/week). The NOEL was 5 ppm (internal dose 1.7 milligrams/kilogram). As a policy, OEHHA does not use lethality as a critical endpoint when determining an acute exposure level. In addition, studies conducted by Misra et al. (1988) and Schaefer (1998a) suggest that neurological effects may occur following acute sub-lethal exposure. Therefore lethality may not represent the most sensitive acute toxicity endpoint for phosphine. However, in this case OEHHA supports identification of the 1990 Newton study as the critical acute toxicity study and lethality as the endpoint, but believes that incorporation of a 3-fold additional uncertainty factor is warranted due to the severity of the critical effect.

    - The discussion of acute toxicity endpoints was supported by several studies as presented on pages 12-18, 23-27, and 44 in the RCD. As noted above, the critical effect was lethality. Phosphine has a steep dose-response curve and there is a rapid transition from toxicity to lethality within a narrow exposure range. The RCD (page 63, paragraph 1) states, "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." This further supports OEHHA's recommendation to incorporate a 3-fold additional uncertainty factor due to the severity of the critical effect.

- Neurotoxicity
    - The RCD (page 50) noted the proximity of the no-effect and lethal levels and suggested the possibility that other effects, including subtle neurologic effects, may have been overlooked by Newton (1990). The studies that reported non-lethal effects at sub-lethal doses are discussed below. The risk appraisal section of the RCD noted that a functional observational battery (FOB) to assess neurotoxicity was not performed in the key study (Newton 1990). Had an FOB been conducted, it may have helped identify more sensitive adverse effects. This data gap further

supports the addition of an uncertainty factor to account for other potentially more sensitive adverse effects that occur prior to lethality.

- Supporting Studies
    - The Schaefer (1998a) study showed acute neurotoxic effects of phosphine gas on Sprague-Dawley rats after a 4-hour exposure. The lowest dose tested was 21 ppm, and similar neurotoxic effects may have occurred, if tested, at a lower exposure concentration and/or shorter duration. In a second study, Schaefer (1998b) used exposure concentrations of 0, 0.3, 1 and 3 ppm, but the results from the FOB were inconclusive.

    - The study published by Misra *et al.* (1988) showed some important respiratory and neurological effects in humans at non-lethal doses after acute exposure that support increasing the uncertainty factor. This study investigated phosphine-induced toxicity in workers at an Indian facility where stacks of bagged grain were treated with aluminum phosphide tablets. The breathing zone phosphine concentrations ranged between 0.17 and 2.11 ppm. Though no attempt to correlate symptoms with exposure was reported, many acute adverse health effects short of lethality were observed at these doses such as cough (18.2% incidence), dyspnea (31.8%), tightness around chest (27.3%), headache (31.8%), giddiness (13.6%), numbness /paresthesia (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.

    - Newton (1991) reported acute lethality after a single 6-hour exposure of Sprague-Dawley rats to phosphine at 28 ppm, but no lethality at doses ranging from 0 to 18 ppm. Mean body weight decreases were noted in the 10 ppm and 18 ppm groups. An acute NOEL of 6 ppm was identified in this study based on the body-weight decreases in the 10, 18 and 28 ppm groups. OEHHA again notes the steep dose-response curve and how close these mildly acutely toxic doses are to lethal concentrations. In addition, the Newton (1991) study only looked at a 6-hour exposure. The RCD should point out that if the study duration had been longer, adverse effects may have been observed at lower doses.

- <u>Uncertainty Factors</u>
    - DPR divided the critical NOELs by a total uncertainty factor of 100 using a 10-fold for interspecies extrapolation and a 10-fold for intraspecies variability. OEHHA suggests adding an additional uncertainty factor (3-fold or higher) because the NOEL is based on lethality, which is a severe

acute endpoint, and because of the proximity of the values of the NOELs for acute (5 ppm) versus subchronic/chronic (1 ppm) exposure. In cases where the point of departure is based on a severe endpoint such as lethality, an additional uncertainty factor is warranted. In addition, as noted above, neurological effects have been observed at acute sub-lethal doses. OEHHA also suggests adding a 3-fold uncertainty factor for the protection of sensitive bystander subpopulations such as infants and children (see section on sensitive subpopulations below).

SUBCHRONIC TOXICITY

This section of the RCD provided a thorough and well-written summary of the subchronic studies performed in laboratory animals.

- Study and Endpoint Selection
    - OEHHA agrees with DPR's identification of the study conducted by Schaefer (1998b) as the critical study for the subchronic exposure determination, and supports the conclusion that the observed NOEL in this study was 1 ppm. A NOEL of 1 ppm was identified from this study based on palpebral closure (sleeping behavior, week 4), slowed respiration (weeks 8 and 13) and lowered body temperatures (week 13) in rats at 3 ppm (6 hours/day, 5 days/week). OEHHA agrees with the use of these endpoints and the 1 ppm NOEL as a point of departure for calculating the subchronic exposure guidance level.

- Uncertainty Factors
    - DPR divided the critical NOELs by a total uncertainty factor of 100 using a 10-fold for interspecies and a 10-fold for intraspecies. OEHHA suggests adding a 3-fold uncertainty factor for the protection of sensitive bystander subpopulations such as infants and children (see below).

- Supporting Study:
    - DPR commented that the results reported by Newton (1990) did not follow Haber's Law (page 23, paragraph 4, and line 4). DPR postulated that there is a threshold for death at or above 5 ppm, since it was anticipated under Haber's Law that the 5 ppm group should have died after six exposures. The RCD concluded that a "short term" lowest observed effect level (LOEL) of 5 ppm was justified based on the Newton (1990) study. Histological effects in the kidney (pelvic and tubular mineralization) and decreases in absolute and relative liver weights were observed at 3 ppm. Although Newton (1990) was not used as the key study in determining the MOE, OEHHA suggests a LOEL of 3 ppm appears to be justified due to the histological effects observed.

CHRONIC TOXICITY

- Study Selection:
  - OEHHA agrees with the use of the subchronic study conducted by Schaefer (1998b) for the chronic exposure determination since an adequate chronic study was not identified.

- Point of Departure: OEHHA agrees with the use of the subchronic NOEL (1 ppm) as a point of departure (Schaefer, 1998b) to assess chronic exposure since the chronic toxicity study conducted by Newton (1998) did not fully assess all potential toxicity endpoints, particularly neurotoxicity.

- Uncertainty Factor: OEHHA suggests the use of an additional 3-fold uncertainty factor when using a subchronic study to determine a chronic exposure level. OEHHA also suggests adding a 3-fold uncertainty factor for the protection of sensitive bystander subpopulations such as infants and children, as discussed below.

CARCINOGENICITY

In the chronic 2-year study (Newton 1998), no carcinogenicity was observed in male and female Fischer 344 rats. Therefore, no cancer risk values were calculated in the RCD. The weight of evidence for carcinogenicity is based on these findings. The study in male and female rats was well-conducted with a sufficient number of animals and doses. However, there were 99 unscheduled deaths in the study. DPR stated that these deaths were unrelated to phosphine exposure. Although the results of the Newton (1998) study are difficult to interpret, OEHHA believes there is not enough information in the RCD to justify stating that the deaths were unrelated to phosphine exposure. The deaths in the study also reduced study power to detect carcinogenicity. Studies in male and female mice were not conducted. Studies in a second species would provide a more robust data set for carcinogenicity determination. The rat study with unscheduled deaths and the lack of a study in mice constitutes limited data available to judge carcinogenicity. OEHHA agrees with DPR that the available *in vivo* data do not provide evidence of carcinogenicity and are insufficient to calculate a cancer potency value.

GENOTOXICITY

DPR provided well-written descriptions of the genotoxicity studies in the RCD, and Table III-5 provided an excellent summary of these studies. OEHHA agrees with DPR's assessment of the genotoxicity studies and the conclusion that phosphine is potentially clastogenic.

REPRODUCTIVE / DEVELOPMENTAL TOXICITY

No male or female reproductive toxicity studies on phosphine were available for analysis. One developmental toxicity study was conducted in rats (Schroeder, 1989), but the investigators observed no developmental effects at sublethal doses (up to 4.9 ppm). OEHHA agrees with the RCD's characterization of the limited data available to judge reproductive toxicity, which represents a significant data gap in the toxicity dataset for phosphine.

SENSITIVE SUBPOPULATIONS

- Occupational and Residential Bystanders
    - OEHHA is concerned that the exposure values used for occupational and residential bystanders may not be sufficiently health-protective as some of these bystanders such as office workers or nearby residents may not be aware that fumigation is taking place near them. Therefore, they would not be expected to use air-purifying respirators or other protective equipment.

    - OEHHA agrees with the primary conclusion in the report, "*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. 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.*"

    - The RCD states that exposure to the general public is not anticipated. However, there are currently no restrictions on how close homes can be to structures where phosphine is used. No buffer zones are required between the fumigated structure (e.g., a grain-elevator) and a residence. However, a buffer zone of 100 feet must be established between the fumigated burrow opening(s) and a structure potentially occupied by humans and/or domestic animals (as noted in DPR's EAD). Due to lack of buffer zones and the high toxicity of phosphine at low doses, OEHHA does not believe it is justified to rule out the possibility of significant phosphine exposures for residents living adjacent to structures being treated with aluminum or magnesium phosphide.

- Phosphine is designated as a restricted use pesticide (RUP) in recognition of its acute inhalation hazard. Page 6 of the RCD detailed the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 0.3 ppm and the Short-Term Emergency Limit (STEL) of 1 ppm based on Jones et al. (1964). In that study, workers were exposed intermittently to phosphine at concentrations up to 35 ppm, but averaging below 10 ppm in most cases (ACGIH, 2001). Commenting on the methodology used in this study, the RCD referenced O'Malley et al. (2013), who pointed out, "*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.*" Based on this comment, OEHHA suggests that the TLV and STEL may not be health protective values, especially for bystanders. Bystanders may be exposed for longer periods of time than workers and would not be expected to be wearing respiratory protection equipment. OEHHA notes that the STEL is equivalent to the NOEL identified for the subchronic and chronic calculations, which supports the need for an additional uncertainty factor to assess the health hazards associated with longer duration exposures.

- OEHHA suggests that infants and children may be more susceptible to the adverse health effects of phosphine and phosphine-generating products. A recent report cited in the RCD stated the possibility of children being more susceptible to phosphine-induced or mediated death (O'Malley et al., 2013). This may be due to their higher susceptibility to airborne toxicants, higher breathing rates on per kilogram body weight basis, and higher incidence of asthma. OEHHA suggests an additional 3-fold uncertainty factor to account for the intraspecies toxicokinetic and toxicodynamic differences in infants and children to account for increased susceptibility.

MISCELLANEOUS

- Usage
  - The annual agricultural use rates for phosphine from 2001-2010 are very well detailed in Table II-1, which includes pesticide application rates to parks, golf courses, cemeteries, rangeland, and pastures. Total pounds sold (which includes agricultural uses as well as home, urban-commercial, industrial, and other non-agricultural scenarios) are indicated in separate rows of the table. OEHHA suggests that data from 2011 be incorporated into this table, as total use of phosphine gas increased more than ten-fold from 2010 to 2011, and total use of aluminum phosphide increased nearly 50 percent over the same period. Year-over-year data are quite variable,

although a trend of increasing agricultural use of phosphine gas, aluminum phosphide and magnesium phosphide is apparent. Given the high toxicity of phosphine, and the low MOEs calculated in the RCD, this trend has possible public health implications. Occupational and residential bystanders may not be aware that fumigation is taking place near them and therefore would not be expected to use air-purifying respirators or other protective equipment. For similar reasons, residential bystanders may be exposed if living close to grain elevators or close to other places where fumigation occurs. Increased usage of phosphine could result in increased exposure for these groups.

- Oral Toxicity of Aluminum Phosphide
    - The RCD discusses the acute oral toxicity/lethality of a specific "test article" called Celphos in three places in the RCD (pages 12, 19, 22). This product was not listed in Table 1 ("Aluminum Phosphide Products") of DPR's 2013 Exposure Assessment Document (EAD), and Table III-1b of the RCD notes that the exact composition of this material was not stated in the oral toxicity study published by Batra et al (1994). Page 19 of the RCD notes that this product contains "56% aluminum phosphide along with ammonium compounds, binding and lubricating agents, fillers, etc." However, as an imprecisely characterized test agent, Celphos may not provide the best understanding of aluminum phosphide's toxicity. OEHHA recommends that DPR insert a caveat to this effect in the RCD. Given the uncertainties regarding the test article composition in the Batra et al. study and a second oral toxicity study conducted by Okolie et al. (2004), which evaluated the oral toxicity of a similarly uncharacterized product referred to as "phostoxin," OEHHA agrees with DPR's decision to not calculate an acute oral Reference Dose for aluminum phosphide.

- Environmental Fate
    - DPR included a separate analysis of the environmental fate of phosphine as an appendix to the RCD. The main body of the RCD provides brief descriptions of phosphine's fate in air, soil, water and wildlife that are clear and concise. The relevance to real world applications of the disappearance rate of phosphine gas measured in dry sealed tubes is unclear and an analysis of the relevance of these studies should be provided in the RCD. In addition, there is no citation for these studies in the RCD text (page 10). In the Environmental Fate document, attached as an appendix to the RCD (page 88), a study by Hilton and Robison (1972) was cited. If this is the same study as the one discussed on page 10, it should be referenced on page 10 as well.

Editorial Comments

Page 1. I. Summary: OEHHA suggests adding to the summary the routes of exposure that will be covered in the report.

Page 4, paragraph 1, line 9 and paragraph 4 line 7: OEHHA suggests not using Wikipedia as a citation as it is not necessarily a reliable source of information. Original reports as opposed to secondary references should be cited in the document.

Page 6, paragraph 3, line 3: "*...headache and dizziness in a **anumber** of workers exposed intermittently to phosphine at concentrations up to 35 ppm.*" This typo should be corrected. (Bold added for emphasis)

Page 6 C. Technical and Product Formulations: The RCD states, "There were two phosphine gas products registered in California as of 2008." OEHHA suggests adding the names of these two phosphine gas products. In addition, there are 18 products containing aluminum phosphide and five products containing magnesium phosphide as the active ingredient. Both compounds generate phosphine on contact with moisture and were evaluated in DPR's Exposure Assessment Document (EAD) for phosphine. OEHHA suggests that DPR refer the reader to the EAD for additional information on phosphine gas and phosphine-generating products registered for use in California, and provide a statement that they are evaluated in the Environmental Fate section at the end of the RCD. OEHHA also suggests adding post-2008 product information, if available.

Page 9 E. Illness Reports: The RCD states that the illness reports and cases for 2005-2009 are detailed in the Exposure Assessment Document (EAD). OEHHA suggests adding additional information in this section summarizing the reported illnesses, since the RCD and EAD are stand-alone documents and the RCD is directed at evaluating risk. These data provide useful information to consider in evaluating risk.

Page 11: III. Toxicology Profile: A. Pharmacokinetics: The RCD provides limited ADME data. Therefore, OEHHA suggests that DPR review the WHO (1988) report that evaluated pharmacokinetic data and provide a brief summary of it in this section.
Page 13, paragraph 1, line 5: Childs and Coates (1971) quoted a 1937 reference from the German literature. OEHHA suggests that DPR provide a citation for the original German report, and indicate whether this is the same study as the O.R. Klimmer study mentioned later (page 14, paragraph 2, line 1).

Page 14, 3. Laboratory animal studies, a. Inhalation:

- This section began by introducing a study by Garry and Lyubimov (2001) that cited a publication by O.R. Klimmer in German; however the year of that German study was not indicated.

- The RCD then described a variety of adverse health effects in laboratory animals. OEHHA suggests including the species of laboratory animals that were tested.

Page 21-22, Table III-1a: The acute/short term toxicity of phosphine was an excellent summary of the data.

- There was a formatting issue with the table and several items in the first column cannot be viewed.
- In addition, it is not clear where footnote "i" is in the table.
- Table II-1b has the same formatting issue (page 22).

Page 30, Table III-3: Please re-format column 1 so the text is completely visible.

Page 40, Table II-3: There is a problem with the table formatting in the first column cutting off the text. It is unclear where footnote c is in the table.

Page 43, Table II-3: Column 1 of this table needs to be reformatted.

Page 70 (and elsewhere): The O'Malley manuscript has been published. OEHHA suggests changing the citation to read 2013 throughout the document and in the References Cited section.

In the RCD, pages 3, 58 and 75 say: "*Many acute, seasonal and annual use scenarios generated MOEs under 100,* ***which indicates*** *insufficient health protection for workers and bystanders under those scenarios.*" OEHHA suggests changing the words "which indicates" to "indicating". (Bold added for emphasis).

Environmental Fate of Phosphine (Appendix II of the end of the RCD)

Page 8: The Environmental Fate Report stated that 27 products contain or produce phosphine gas, with two formulations of phosphine gas, 20 products containing aluminum phosphide and 5 containing magnesium phosphide. These numbers should be reconciled with the numbers on page 6 under Technical and Product Formulations in the Risk Characterization Document (RCD), which stated there are 18 products that contain aluminum phosphide.

Citations

O'Malley M, Fong H, Sánchez ME, Roisman R, Nonato Y, Mehler L. (2013). Inhalation of phosphine gas following a fire associated with fumigation of processed pistachio nuts. J Agromedicine 18(2):151-73.

World Health Organization (1988). Phosphine and selected metal phosphides. Environmental Health Criteria 73:1-77. Geneva. Resource document. Accessed 11 January 2013. http://www.inchem.org/documents/ehc/ehc/ehc73.htm.

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M E M O R A N D U M

TO: Tom Moore, Ph.D.
Acting Branch Chief
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

FROM: Andrew Rubin, Ph.D., D.A.B.T.
Staff Toxicologist, Health Assessment Group
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

DATE: June 11, 2014

SUBJECT: RESPONSE TO OEHHA'S COMMENTS ON THE PHOSPHINE RISK CHARACTERIZATION DOCUMENT

In a memo dated November 19, 2013, OEHHA provided commentary on DPR's phosphine risk characterization document (draft of February 15, 2013). A summary of those remarks appears on pages 1-2 of the OEHHA memo, followed by more specific recommendations relating to the acute (pages 3-5), subchronic (page 5) and chronic (page 6) toxicity sections of the draft RCD. The OEHHA memo also comments on the carcinogenicity (page 6), genotoxicity (page 6) and reproductive / developmental toxicity (page 7) sections of the RCD, as well as on sensitive populations (pages 7-8), miscellaneous (pages 8-9) and various editorial issues (pages 10-11). DPR's responses to these comments appear in the following paragraphs.

Summary of comments (OEHHA memo, pages 1-2)

See responses to the detailed comments in the following sections.

Acute toxicity (OEHHA memo, pages 3-5)

OEHHA memo—page 3, paragraph 1: "OEHHA suggests providing a summary table of the individual cases of human poisoning and observed adverse effects..."

DPR response: We believe that the descriptions of human adverse effects in the text portions of the draft RCD are adequate for the ensuing risk analysis, obviating the need for restatement of those effects in table form.

OEHHA memo—page 3, paragraphs 2 and 3; page 4 paragraphs 1 and 5; page 5, paragraph 5; page 6, paragraph 3: "...OEHHA is recommending additional uncertainty factors for the acute,

subchronic and chronic exposure advisory levels. For the acute point of departure, OEHHA suggests an additional 3-fold uncertainty factor because the NOEL was based on lethality and a 3-fold factor to protect infants and children. For the subchronic point of departure, OEHHA suggests and additional 3-fold uncertainty factor to protect infants and children. Finally, for the chronic point of departure, OEHHA suggests a 3-fold uncertainty factor because the key study utilized subchronic exposure and a 3-fold factor to protect infants and children that are bystanders." (quoted from the Summary of Comments, page 2)

DPR response: We are not inclined to impose uncertainty factors over and beyond the standard 10-fold inter- and intraspecies factors (see sections III.C.1. and VII.), as the combined 100-fold factor is likely to protect exposed populations from the identified critical toxicologic effects (mortality for acute exposure, sublethal cholinergic effects for subchronic and chronic exposures). The concern that the acute risk evaluation for phosphine is based on mortality is understandable, of course, and is already clearly articulated in the RCD. Imposition of an extra factor to represent the seriousness of that endpoint would not be due to uncertainty, as there was little uncertainty surrounding the observation of mortality. In effect, it amounts to a safety factor, not an uncertainty factor. The decision to impose a a such a factor resides with DPR's management team.

The child-protective uncertainty factor recommended by OEHHA—essentially a database uncertainty factor—is technically defensible. FIFRA guidelines do require a developmental study in rabbits, though this was waived in the case of phosphine (see the discussion of regulatory history in section II.B.). We also note that the available developmental toxicity study on phosphine (Schroeder, 1989) did not indicate particular fetal toxicities in rats. Nonetheless, the history of phosphine-induced injury and death in humans (O'Malley et al., 2013, and section III.B.2. of the draft RCD) do raise the issue of possible unique child susceptibilities.

With respect to OEHHA's proposed subchronic-to-chronic factor, the available rat chronic study (Newton, 1989) did not establish a NOEL even at the high dose of 3 ppm. Consequently, setting the critical chronic NOEL at the subchronic NOEL of 1 ppm was likely to be health conservative. While we recognize that a mouse chronic study was not available, we considered an uncertainty factor based on the fact that the RCD used the subchronic NOEL to be unnecessary.

Subchronic toxicity (OEHHA memo, page 5)

OEHHA memo—page 5, final paragraph: "Histological effects in the kidney (pelvic and tubular mineralization) and decreases in absolute and relative liver weights were observed at 3

ppm. Although Newton (1990) was not used as the key study in determining the MOE, OEHHA suggests a LOEL of 3 ppm appears to be justified due to the histological effects observed."

DPR response: The toxicologic significance of the observed renal pelvic and tubular mineralization at 3 ppm was insufficiently clear to merit LOEL designation. The change in liver weights (absolute weights in grams at 0.3, 1 and 3 ppm: 7.481, 6.791*, 6.309**, 6.662*; relative to bodyweight: 2.59, 2.41**, 2.36**, 2.37**; *,**p<0.05, 0.01) was not strictly dose-dependent and did not appear to have a histopathologic correlate, so also was not a good candidate to establish a LOEL. Even so, the effects suggest that frank toxicity would occur at higher doses or longer exposure times, and thus support the critical subchronic NOEL designation of 1 ppm. Because of OEHHA's comment, this is now explicitly stated in section IV.A.1.b., as follows:

> "4. Newton (1990) noted renal pelvic and tubular mineralization, as well as an apparent reduction in liver weights (absolute weights in grams at 0.3, 1 and 3 ppm: 7.481, 6.791*, 6.309**, 6.662*; relative to bodyweight: 2.59, 2.41**, 2.36**, 2.37**; *,**p<0.05, 0.01) after 13 weeks of inhalation exposure. While neither effect was sufficiently toxicologically clear for LOEL designation, they were at least suggestive that toxicity would become manifest at higher doses or longer exposure times."

Chronic toxicity (OEHHA memo, page 6)

OEHHA memo---page 6, paragraph 3: "OEHHA suggests the use of an additional 3-fold uncertainty factor when using a subchronic study to determine a chronic exposure level. OEHHA also suggests adding a 3-fold uncertainty factor for the protection of sensitive bystander subpopulations such as infants and children..."

DPR response: See the response relating to uncertainty factors under "Acute toxicity" above.

Carcinogenicity (OEHHA memo, page 6)

OEHHA memo—page 6, paragraph 4: "Although the results of the Newton (1998) study are difficult to interpret, OEHHA believes there is not enough information in the RCD to justify stating that the deaths were unrelated to phosphine exposure."

DPR response: Mortality in the Newton (1998) study bore little or no relation to dose (0 ppm: 7♂ / 14♀; 0.3 ppm: 16♂ / 15♀; 1 ppm: 14♂ / 9♀; 3 ppm: 12♂ / 12♀), justifying the statement that the deaths were not phosphine-related.

Sensitive subpopulations (OEHHA memo, pages 7-8)

OEHHA memo—page 6, paragraph 4: "The RCD states that exposure to the general public is not anticipated. However, there are currently no restrictions on how close homes can be to structures where phosphine is used. No buffer zones are required between the fumigated structure (eg., a grain-elevator) and a residence. However, a buffer zone of 100 feet must be established between the fumigated burrow opening(s) and a structure potentially occupied by humans and/or domestic animals (as noted in DPR's EAD). Due to lack of buffer zones and the high toxicity of phosphine at low doses, OEHHA does not believe it is justified to rule out the possibility of significant phosphine exposures for residents living adjacent to structures being treated with aluminum or magnesium phosphide."

DPR response: Our statement "that exposure to the general public is not anticipated" was made in the context of the ambient exposure sections of the draft RCD. Ambient exposure is defined as exposure to the general public that is distal to, and not associated with, specific applications. As such, we considered exposures to individuals living in houses situated very close to fumigated structures to be a type of application site exposure, which is treated in detail in the RCD. For example, we state in section IV.C.2.:

> "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."

Nonetheless, we agree that for fumigations occurring very close to residential structures, special precautionary measures are called for.

Miscellaneous (OEHHA memo, pages 8-9)

OEHHA memo—page 8, paragraph 3: OEHHA requests the use rates table (Table II-1) to be updated to include 2011.

DPR response: Because the revised RCD simply copies the figures from the exposure assessment document, the use rates will cover only the years 2006-2010.

OEHHA memo—page 9, paragraph 2: "The RCD discusses the acute oral toxicity / lethality of a specific "test article" called Celphos in three places in the RCD (pages 12, 19, 22). This product was not listed in Table 1 ("Aluminum Phosphide Products") of DPR's 2013 Exposure Assessment Document (EAD), and Table III-1b of the RCD notes that the exact composition of this material was not stated in the oral toxicity study published by Batra et al. (1994). Page 19 of the RCD notes that this product contains "56% aluminum phosphide along with ammonium compounds, binding and lubricating agents, filler, etc." However, as an imprecisely characterized test agent, Celphos may not provide the best understanding of aluminum phosphide's toxicity. OEHHA recommends that DPR insert a caveat to this effect in the RCD."

DPR response: We consider our statement recognizing the undefined nature of the Celphos test article to provide adequate notice that its toxicologic effects may not be totally interpretable.

OEHHA memo—page 9, paragraph 3: "The relevance to real world applications of the disappearance rate of phosphine gas measured in dry sealed tubes is unclear and an analysis of the relevance of these studies should be provided in the RCD. In addition, there is no citation for these studies in the RCD text (page 10). In the Environmental Fate document, attached as an appendix to the RCD (page 88), a study by Hilton and Robison (1972) was cited. If this is the same study as the one discussed on page 10, it should be referenced on page 10 as well."

DPR response: The only point in mentioning the sealed tubes was to emphsize the effect of moisture in slowing the disappearance of phosphine gas from soils. As that was clearly stated in the RCD, there is no further reason to expand the discussion. The Hilton and Robison (1972) study was indeed the source of the data. However, we chose not to cite it directly, rather stating at the beginning of the Environmental Fate section (section II.G. of the RCD), " References to original [environmental fate] studies are found in that document [i.e., the Environmental Fate document by P. Gurusinghe noted in OEHHA's comment]."

Editorial comments (OEHHA memo, pages 10-11)

OEHHA memo—page 10, paragraph 1: "Page 1. I. Summary: OEHHA suggests adding to the summary the routes of exposure that will be covered in the report."

DPR response: We have added the following sentence to the Summary under "Risk calculations and appraisal":

> "As indicated in the accompanying Exposure Assessment Document produced by DPR's Worker Health and Safety Branch, the primary route of human exposure is to phosphine gas through inhalation."

OEHHA memo—page 10, paragraph 2: "Page 4, paragraph 1, line 9 and paragraph 4, line 7: OEHHA suggests not using Wikipedia as a citation as it is not necessarily a reliable source of information. Original reports as opposed to secondary references should be cited in the document."

DPR response: The references to Wikipedia have been removed from the RCD.

OEHHA memo—page 10, paragraph 3: typo, "...anumber..."

DPR response: Corrected.

OEHHA memo—page 10, paragraph 4: "Page 6 C. Technical and Product Formulations: The RCD states, "There were two phosphine gas products registered in California as of 2008." OEHHA suggests adding the names of these two phosphine gas products. In addition, there are 18 products containing aluminum phosphide and five products containing magnesium phosphide as the active ingredient. Both compounds generate phosphine on contact with moisture and were evaluated in DPR's Exposure Assessment Document (EAD) for phosphine. OEHHA suggests that DPR refer the reader to the EAD for additional information on phosphine gas and phosphine-generating products registered for use in California, and provide a statement that they are evaluated in the Environmental Fate section at the end of the RCD. OEHHA also suggests adding post-2008 product information, if available."

DPR response: In accord with OEHHA's suggestions, the RCD text in section II.C. now reads:

> "As of the most recent update in May 2008, the DPR database showed 2 products containing phosphine actively registered in California (Eco2Fume and VaporPH3Phos Phosphine Fumigant). In addition, there are 16 products containing aluminum phosphide (last database update: March 28, 2013) and 5 products containing magnesium phosphide (last database update: September 7, 1994). The accompanying Exposure Assessment (DPR, 2013) and Environmental Fate(Appendix I) documents provide additional information on these products."

OEHHA memo—page 10, paragraph 5: "Page 9 E. Illness Reports: The RCD states that the illness reports and cases for 2005-2009 are detailed in the Exposure Assessment Document (EAD). OEHHA suggests adding additional information in this section summarizing the reported illnesses, since the RCD and EAD are stand-alone documents and the RCD is directed at evaluating risk. These data provide useful information to consider in evaluating risk."

DPR response: The section from the EAD entitled "Reported Illnesses" now appears in full in the RCD.

OEHHA memo—page 10, paragraph 6 (beginning): "III. Toxicology Profile: A. Pharmacokinetics: The RCD provides limited ADME data. Therefore, OEHHA suggests that DPR review the WHO (1988) report that evaluated pharmacokinetic data and provide a brief summary of it in this section."

DPR response: This section has been enhanced in the revised RCD with information from the WHO (1988) review.

OEHHA memo—page 10, paragraph 6 (end): "Page 13, paragraph 1, line 5: Childs and Coates (1971) quoted a 1937 reference from the German literature. OEHHA suggests that DPR provide a citation for the original German report, and indicate whether this is the same study as the O.R. Klimmer study mentioned later (page 14, paragraph 2, line 1)."

DPR response: We don't consider the suggested amendment to be necessary, as the information cited in the draft RCD was meant to provide background only.

OEHHA memo—page 10, paragraph 7: "Page 14, 3. Laboratory animal studies, a. Inhalation: This section began by introducing a study by Garry and Lyubimov (2001) that cited a publication by O.R. Klimmer in German; however, the year of that German study was not indicated."

DPR response: The publication date, 1969, for Klimmer's work is now included in the revised RCD. An additional review by the same authors—Lyubimov and Garry (2010)—about Klimmer's 1969 work is also now cited.

OEHHA memo—page 11, paragraph 1: "The RCD then described a variety of adverse health effects in laboratory animals. OEHHA suggests including the species of laboratory animals that were tested."

DPR response: The Lyubimov / Garry reviews phrased their statement only in terms of "laboratory animals". The implication is that the various health effects were seen in several species.

OEHHA memo—page 11, paragraph 2: "Page 21-22, Table III-1a: The acute / short term toxicity of phosphine was an excellent summary of the data. There was [however] a formatting

issue with the table and several items in the first column cannot be viewed. In addition, it is not clear where footnote "i" is in the table. [And] Table II-1b has the same formatting problem (OEHHA's comment mistakenly refers to "Table II-1b", when it appears that the intended table was III-1b)."

DPR response: The left and right margins for Tables III-1a and III-1b were adjusted inward—all items in those tables should now be visible. Footnote "I" has been removed from the table.

OEHHA memo—page 11, paragraph 3: "Page 30, Table III-3: Please re-format column 1 so the text is completely visible."

DPR response: Done.

OEHHA memo—page 11, paragraph 4: "Page 40, Table II-3: There is a problem with the table formatting in the first column cutting off the text. It is unclear where footnote c is in the table."

DPR response: Corrected (OEHHA's comment mistakenly refers to "Table II-3", when it appears that the intended table was III-5). Footnote "c" refers to the Stankowski (1990) reference in the second row, right column.

OEHHA memo—page 11, paragraph 5: "Page 70 (and elsewhere): The O'Malley manuscript has been published. OEHHA suggests changing the citation to read 2013 throughout the document an in the References Cited section."

DPR response: Done.

OEHHA memo—page 11, paragraph 6: "In the RCD, pages 3, 58 and 75 say: 'Many acute, seasonal and annual use scenarios generated MOEs under 100, which indicates insufficient health protection for workers and bystanders under those scenarios.' OEHHA suggests changing the words 'which indicates' to "indicating".

DPR response: Done.

OEHHA memo—page 11, paragraph 6: "Page 8. The Environmental Fate Report stated that 27 products contain or produce phosphine gas, with two formulations of phosphine gas, 20 products containing aluminum phosphide and 5 containing magnesium phosphide. These numbers should be reconciled with the numbers on page 6 under Technical and Product Formulations in the Risk Characterization Document (RCD), which state there are 18 products that contain aluminum phosphide."

DPR response: Since DPR's registration database is constantly updated, the number of registered products changes with time. For example, the revised RCD now reports 16 currently registered products containing aluminum phosphide, which is different than the 18 products registered at the time of the draft RCD (February 2013). The difference between the RCD and the Environmental Fate Document with respect to the number of registered aluminum phosphide products is also likely a function of the date the registration database was consulted. We do not consider it necessary to change the Environmental Fate Document to maintain absolute consistency.

Office of Environmental Health Hazard Assessment

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MEMORANDUM

TO: Lisa Ross, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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DATE: September 26, 2013

SUBJECT: COMMENTS ON THE DRAFT EXPOSURE ASSESSMENT DOCUMENT FOR PHOSPHINE

The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed the draft Exposure Assessment Document (EAD) for occupational and ambient air exposure to phosphine (phosphorus trihydride), prepared by the Department of Pesticide Regulation (DPR), dated January 14, 2013. Our comments are provided in the attachment. We are currently reviewing the Risk Characterization Document (RCD) for Phosphine and will be sending comments on it separately. This review is conducted under the authority of Food and Agriculture Code Section 11454.1.

OEHHA has several general comments on the exposure assessment assumptions, methodology and conclusions of the draft EAD. These comments and our

recommendations, as well as some suggested clarifications, additions and corrections, are contained in the attachment.

Thank you for providing this draft document for our review. If you have any questions regarding OEHHA's comments, please contact Dr. Charles Salocks at (916) 323-2605 or me at (510) 622-3200.

Attachment

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OEHHA's Comments on DPR's Draft Exposure Assessment Document for Phosphine

The Office of Environmental Health Hazard Assessment (OEHHA) is responding to a request from the Department of Pesticide Regulation (DPR) to comment on the draft Exposure Assessment Document (EAD) for phosphine [phosphorus trihydride]. OEHHA reviews risk assessments prepared by DPR under the authority of Food and Agricultural Code Section 11454.1, which requires OEHHA to conduct scientific peer reviews of risk assessments conducted by DPR.

BACKGROUND ON THE DOCUMENT

The draft EAD covers use of phosphine gas (in cylinders), and the phosphine-generating solids aluminum phosphide and magnesium phosphide, as fumigants used primarily indoors to control insect pests in raw agricultural commodities, animal feed and processed foods. It also covers outdoor uses to control rodents and moles. As pesticide products, aluminum and magnesium phosphide are formulated as tablets, pellets, granules and impregnated plates. They react with moisture in the atmosphere to produce phosphine gas. Cylinderized phosphine is formulated as pure phosphine gas for onsite dilution or as ready-to-use gas pre-mixed with 98% CO_2 to reduce explosion and fire hazard. These three compounds are restricted use pesticides that may be used only by specially trained and certified pesticide applicators. There is no homeowner or agricultural row crop uses for these products.

The exposure estimates generated in this document were organized according to the type of fumigation or aeration performed (commodity, space, spot, or burrowing rodent fumigation), the type of structure fumigated, and the exposed populations. The EAD provided estimates of phosphine exposure for workers and bystanders exposed to phosphine gas during and after fumigation activities. Structures where these fumigants are applied include concrete upright bins of grain elevators, farm bins, flat storage facilities, warehouses, rail cars, box cars and ships. The exposed populations were fumigant applicators (present within or located outside the fumigated structure), workers who aerate structures, workers who assist in application and aeration, workers who retrieve the spent fumigant, various types of occupational bystanders, and residential bystanders. No exposure data were available on exposures resulting from use of cylinderized gas and granular formulations by applicators, aerators and bystanders, so DPR adopted default assumptions to generate surrogate exposure estimates.

OEHHA's comments are provided below. A summary of the major comments is first presented, followed by general comments and more detailed specific comments.

SUMMARY OF COMMENTS

The document is focused on phosphine as a fumigant and a related exposure assessment, but unfortunately limited data are available and the many gaps require assumptions to complete the assessment. Overall, the document addressed the important issues. The writing and especially the organization of the document could benefit from additional internal review and editing. Our principal comments and suggestions are as follows:

- It would be helpful if the scope of the EAD were clarified in the title, abstract and introduction by indicating that it covers exposures from the use of specific pesticides. However, exposure to the rodenticide zinc phosphide (for which there are several products registered for use in California) was not included in the assessment, and an explanation why that was the case could be provided.

- A screening evaluation of potential percutaneous absorption as an exposure pathway could be added to provide screening level estimates of absorbed doses – both from phosphine vapor and phosphide dust. This is needed to assess the significance of this dermal pathway relative to the inhalation pathway.

- Precautions regarding the appropriate use of respiratory protection need to be clarified. Specifically, it is unclear whether standard practices and precautions against entering an environment where the phosphine concentration is unknown or when monitoring equipment is unavailable are sufficient to prevent significant exposures. Further consideration of these scenarios is warranted in the EAD.

- The assumption, stated on pages 37, that occupational bystanders, working both inside and outside of grain elevators during fumigant application and commodity fumigation, will wear full-face respirators is not likely to hold. Consequently, the short-term exposure estimates presented for occupational bystanders in Table 13 do not represent "baseline" exposure estimates, but would be expected to be higher.

- Given the extreme acute toxicity of phosphine, OEHHA recommends that DPR conduct more in-depth evaluation of several short-term exposure scenarios. For example, in studies of aluminum phosphide applicators, the airborne concentrations detected would be well in excess of disabling or life-threatening

levels unless full-face respirators were worn. These results indicated that short-term exposures to phosphine were episodic and brief (less than 5 minutes), and occurred several times each day. In contrast, data from occupational studies where samples were collected over several hours do not reflect these very short concentration excursions. OEHHA recommends that DPR review the "instantaneous" exposure data and the analysis of short-term exposure to ensure that averaging of short-term peak concentrations over long-term sampling durations does not mask the potential for acute health effects.

- An exposure scenario that is not addressed in the EAD is the potential for phosphine to continue to "off-gas" (that is, be re-released) from fumigated materials after a facility or storage structure has been aerated. OEHHA recommends that DPR consider examining such a scenario, and attempt to estimate post-aeration exposure concentrations that might be produced in confined spaces.

- DPR appears to have not considered data from two different sources (the Pesticide Use Report database and the 2002 phosphine worker exposure study conducted by Dagesch America) that would lead to higher exposure estimates. These data may be useful in the exposure calculations for the various scenarios. If not, it would be helpful if the rationale for not including these data is revisited or additional justification be provided.

- A number of editorial comments and suggestions are also provided for your consideration.

GENERAL COMMENTS

Scope of the EAD

One pesticidal source of phosphine exposure that was not evaluated in the EAD is pesticidal use of zinc phosphide (used in rodenticide baits). An explanation in the introduction why zinc phosphide, a rodenticide, was excluded from the EAD would be helpful. Also, since the EAD looks at exposure resulting from the pesticidal use of phosphine, aluminum phosphide and magnesium phosphide, it would be more precise and informative for the document to be titled "Estimation of Exposure to Persons in California to Phosphine from Pesticidal Use of Phosphine, and Magnesium and Aluminum Phosphide".

Industrial use of phosphine in semiconductor manufacturing and chemical syntheses, and natural occurrence resulting from anaerobic decomposition of organic matter or

sewage treatment plant sediments, represent additional potential sources of phosphine exposure. A brief mention of this might be informative for many readers of the document.

Dermal Absorption of Phosphine Vapor and Phosphide Dust

Potential dermal absorption of phosphine was noted and discussed briefly on pages 11-12. The discussion included the following statement, excerpted from the U.S. Environmental Protection Agency's (U.S. EPA) 1998 Reregistration Eligibility Decision document for aluminum and magnesium phosphide: "Because the route of exposure anticipated for aluminum and magnesium phosphide is inhalation, the Agency does not expect significant dermal exposure. Therefore, dermal absorption studies are not required." Similarly, the document quotes from Hayes (1982), "The effectiveness of proper gas masks excludes the possibility of significant absorption by the skin." Both of these statements should be justified more explicitly.

In a quantitative health risk assessment, an exposure pathway may be excluded if it is shown using screening-level assumptions that it is not significant in comparison to other complete exposure pathways. Neither U.S. EPA nor DPR presented an analysis using screening-level assumptions to show that dermal exposure is not significant in comparison to other complete exposure pathways. In a recent review, Rehal and Maibach (2011) cited several proposed methods for mathematically modeling percutaneous absorption of chemical vapors (e.g.,Kezic et al. 2000) that DPR could utilize. Additionally, DPR could calculate an upper bound estimate of dermal exposure using measured air concentrations and a calculated skin permeation coefficient (Klein 2000). Such an assessment could be used to estimate the significance of percutaneous absorption relative to inhalation and provide justification for determining whether dermal exposure to phosphine is an issue that warrants more detailed, in-depth evaluation in a human health risk assessment.

The dermal absorption pathway may be of particular concern in scenarios where the airborne concentration of phosphine is high and a high level of respiratory protection (e.g., a full-face respirator or a self-contained breathing apparatus (SCBA)) is required. Under these conditions, the significance of dermal absorption of vapor relative to inhalation uptake is likely much greater because the latter is substantially mitigated by the use of personal protective equipment.

Dermal absorption of phosphide dust is another potential exposure pathway that warrants additional consideration in the EAD. On page 89, DPR described a study by Baker (1992), who observed that relatively high levels of phosphine were given off by

the clothing of workers who had handled aluminum phosphide tablets, and whose clothing became contaminated with dust from the tablets. In the *Medical Management Guidelines for Phosphine*, the Agency for Toxic Substances and Disease Registry (ATSDR) stated, "Most phosphine exposure occurs by inhalation of the gas or ingestion of metallic phosphides, but dermal exposure to phosphides can also cause systemic effects".

Regarding dermal absorption of phosphine vapor and metal phosphide dust, the Exposure Appraisal section (page 97) concluded that "...due to lack of data, percutaneous absorption was not factored into the exposure estimates. This may have *led to an underestimation of exposure." To evaluate the magnitude of underestimation,* OEHHA suggests that DPR evaluate the dermal exposure pathway in greater detail to determine whether screening level estimates of absorbed doses – both from phosphine vapor and phosphide dust – can be derived, and if so, provide such estimates.

Personal Protective Equipment (PPE) and Respiratory Protection

The first paragraph of this section, which begins on page 17, includes a statement that a self-contained breathing apparatus (SCBA) must be used when the air concentration of phosphine is unknown or exceeds 15 ppm. It also states that certain product labels indicate that a SCBA must be worn if the phosphine concentration is unknown or exceeds the short-term exposure limit of 1 ppm for 15 minutes. Still other labels indicate that an approved canister respirator must be worn if monitoring equipment is not available. Since phosphine concentration is unknown when monitoring equipment is not available, these recommendations appear to contradict one another: they indicate in one case that SCBA must be used when the concentration is unknown and in another that an approved canister respirator is appropriate for these situations. A statement pointing out this discrepancy should be included in the EAD. If the concentration is truly unknown, there is no basis for selecting the appropriate level of respiratory protection. Ultimately the effectiveness of different label requirements for mitigating exposure to phosphine may need to be evaluated more carefully in the EAD.

Similarly, the second paragraph on page 18 begins with the statement, "For indoor applications, all of the product labels contain the requirement that an approved full-face gas mask-phosphine canister combination or SCBA or its 'equivalent' to be available *within the structure being fumigated"* [italics added]. The next sentence states, "The Detia® FUMEX product label contains the statement, 'If SCBA or its equivalent is not available at the application site, it must be available locally, for example, *at a fire station or rescue squad*'" [italics added]. These two statements seem to contradict one another. While neither scenario guarantees that an SCBA unit will be used when

necessary, the presence of an SCBA unit at a local fire station – which could be miles from the fumigated structure – provides considerably less assurance that the unit will actually be used than if it were located within structure being fumigated. Later in this section, the discussion of precautions to be taken when using cylinderized phosphine gas indicates that respiratory protection must be available *at the site of application*. Overall, one would expect the respiratory protection requirements for use of aluminum and magnesium phosphide to be consistent with those stipulated for phosphine gas. If the labels for these products are inconsistent with one another with respect to the availability of SCBA (as they appear to be), then these inconsistencies should be addressed directly in the EAD. Ultimately the effectiveness of different label requirements for mitigating exposure to phosphine may need to be evaluated more carefully in the EAD.

On page 37, occupational bystanders working both inside and outside of grain elevators during fumigant application and commodity fumigation were assumed to wear full-face respirators. This scenario assumes (1) that the airborne concentration of phosphine is known to all workers in the vicinity of the fumigation, even those not directly engaged in fumigation activities, (2) that full-face air-purifying respirators (APRs) are available for all workers and all bystanders, and (3) that the APRs have been fitted with the appropriate air filtration cartridges. OEHHA is concerned that these assumptions may be overly optimistic in many circumstances, and would be interested in seeing the results of any occupational surveys on this subject, if available. Consequently, the short-term exposure estimates using these scenarios presented for occupational bystanders in Table 13 may not reflect "baseline" exposure estimates, but rather provide values that assume that an exposure mitigation strategy is in place at all locations where these fumigants are used and is effective 100 percent of the time. Therefore the estimated exposures are expected to be higher. We are concerned that bystanders might lack adequate respiratory protection, consistent with what has also been expressed by U.S. EPA: "...the Agency is concerned about the potential risks posed to occupational and residential bystanders who are not likely to be wearing the necessary respiratory protection" (U.S. EPA 1998).

The discussion of respirator selection on pages 17 and18 could be improved by including the protection factor provided by the different types of respirators (e.g., 99% protection afforded by a full-face air-purifying respirator).

Other Exposure Scenarios

An exposure scenario that is not addressed in the EAD is the potential for phosphine to continue to "off-gas" (that is, be re-released) from fumigated materials after a facility or storage structure has been aerated. From the results of the studies described on pages

11 and 12 ("Dermal Absorption of Phosphine"), it is clear that phosphine is capable of penetrating deep into porous building materials such as concrete and cinder block as well as biological materials such as baled sheep skins and wheat grain. DPR recently completed a series of intensive investigations demonstrating that high levels of methyl bromide can accumulate in enclosed spaces after aeration of fumigated grapes at the Port of Los Angeles, and it would be reasonable to conclude that off-gassing of phosphine-fumigated commodities also might have the potential to lead to a high-risk exposure scenario. OEHHA recommends that DPR consider examining such a scenario, and attempt to estimate post-aeration exposure concentrations that might be produced in confined spaces.

Excluding Some Pesticide Use and Monitoring Data

The paragraph at the bottom of page 16 states that 27 percent of the use data for aluminum phosphide on dry flowable commodities (grains and nuts) were assumed to be erroneous because they exceeded the product label maximum application rate. (These data were abstracted from DPR's Pesticide Use Report (PUR) database for the five-year period from 2006 through 2010.) Additional justification for excluding these data from calculation of seasonal application rates needs to be provided. An alternative assumption is that use of aluminum phosphide at levels above those specified on the product label is not an uncommon occurrence.

The first paragraph on page 27 begins, "No background PH_3 [phosphine] air concentration data were available for the TWA [time-weighted average] samples in either the registrant or NIOSH [National Institute for Occupational Safety and Health] studies. The registrants generated background samples via opening the sampling tube and then immediately sealing the tube for analysis. These samples were not used however, since they generated a false-positive signal that increased with increasing storage time…This instability was not present in their field fortification samples." It is unclear why DPR concluded that the phosphine concentrations detected in these samples represented false positive results, particularly if they were replicated in multiple samples. In light of the possibility, noted above, that building materials and stored grain have the capacity to absorb and re-release phosphine, an alternative hypothesis is that the background samples actually captured low levels of phosphine that were present in the ambient environment under investigation. Depending on where and how the background samples were stored, it is conceivable that the phosphine concentration in the sample tubes might increase, perhaps because they were stored in close proximity to materials that had previously absorbed the pesticide. Low background levels of phosphine would not necessarily be detected in field fortification samples if the latter had been spiked with a substantially higher concentration of phosphine. OEHHA

recommends that DPR consider alternative explanations for the results that were obtained in these studies. If exposure to low background levels of phosphine occurs in certain exposure scenarios, then background exposure needs to be accounted for in the EAD.

SPECIFIC COMMENTS

Pharmacokinetics

The dermal absorption data cited in this section of the document are of very poor quality. DPR determined that they could not identify an acceptable quantitative study and concluded that these results should not be used in the EAD. OEHHA agrees with this determination. A statement that the available pharmacokinetic data are not of sufficient quality for human health risk assessment, and a discussion of the deficiencies of the available studies that justifies this conclusion, should be included in the EAD.

OEHHA agrees with the use of a health-protective default value of 100 percent for inhalation absorption rate since no experimental data are available.

Information on phosphine metabolism is limited. Although the report recognized the data gap, their description of the Lyubimov and Garry review is too succinct and would benefit from inclusion of additional detail (Lyubimov and Garry 2010).

Reported Illnesses

The EAD covers phosphine- and metal-phosphide related illnesses for the five-year period spanning 2005 through 2009, based on information obtained from the California Pesticide Illness Surveillance Program (PISP) database. During this period, 10 cases of phosphine exposure were reported to have resulted from use of aluminum phosphide. However, 15 additional cases of phosphine exposure from aluminum phosphide use were reported in 2010. Similarly, in addition to the 27 cases of phosphine exposure resulting from use of cylinderized phosphine reported from 2005 through 2009, 14 cases were reported in 2004. To provide a more comprehensive description of actual scenarios for inadvertent or accidental exposure to phosphine, OEHHA recommends that this discussion include phosphine exposure cases reported during the period from 2004 through 2010.

Pesticide Use and Sales

Even though DPR used the latest available pesticide use report (PUR) data (2006-2010), the EAD should clearly indicate that PUR data only cover use in agricultural settings, and that use of zinc phosphide is not included. If the overall volume of

phosphine and phosphine-generating compounds sold in California is available, it would be possible to compare the amount sold for pesticidal use to the total amount sold in order to evaluate the importance of non-agricultural use.

Updates to Product Labels

OEHHA suggests that EAD include a sample label for each type of pesticide product in the appendix or a link to their location on DPR's website. The following two updates related to label information should be provided as well:

- Since 2010, new restrictions apply to all phosphine products for use against burrowing rodents (http://www.epa.gov/oppsrrd1/reregistration/alphosphide/aluminum-magnsm-phos-fs.html).
- An amendment to increase the application rate for cylinderized phosphine to match metallic phosphide labels was submitted to U.S. EPA on February 4, 2013, and accepted on March 12, 2013 (EPA Registration No. 68387-8).

Environmental Concentrations and Environmental Fate

The EAD did not include a section on environmental concentrations or environmental fate. Consequently, these processes cannot be incorporated into bystander and residential exposure scenarios. This information is available in other reports for phosphine (DPR 2013, EFSA 2012, U.S. EPA 1998) and in other EADs that OEHHA recently reviewed. If no data are available or if phosphine is not found in the ambient environment, then a statement to this effect should be included in the EAD.

Exposure Assessment

A registrant task force study (Degesch America 2002) was available for workers fumigating/aerating farm bins and flat storage facilities, warehouses, rail cars and equipment, and specific areas of a flour and corn mill (spot fumigation). NIOSH studies (NIOSH 1986a, b; 1987a, b) were also available for occupational exposure following commodity fumigation in concrete upright bins of grain elevators. Results from the NIOSH studies were combined with the registrant study in the exposure assessment. No data were available to document applicator, aerator and bystander exposures following use of cylinderized gas and granular formulations, so exposures were estimated using data from other facilities as surrogates. Although this appears to be reasonable, the decision to utilize surrogate exposure estimates would benefit from additional discussion and justification, and the consequent uncertainties should be articulated.

A California Air Resources Board (CARB) study (CARB 2008) of occupational and residential bystanders following commodity fumigation of concrete upright bins of grain elevators and farm bins was available, but DPR decided not to use these results for the bystander risk assessment because of poor data quality (bad recoveries and sample loss). OEHHA concurs with DPR's determination that inclusion of the CARB study might lead to underestimation of exposure.

In cases where data were lacking and no surrogate exposure estimates could be applied, exposures were based on the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL). A PEL is the maximum permitted 8-hour time-weighted average (TWA) concentration of an airborne contaminant during a 40-hour work-week. The PEL for phosphine is 0.3 parts per million (ppm). When the air concentration exceeds the PEL, workers (applicators as well as occupational bystanders) are required to use full-face respirators. The short-term exposure limit (STEL, a 15-minute TWA exposure that is not to be exceeded at any time even if the 8 hour TWA is below the PEL) is 1 ppm. Given the variability of actual exposure conditions that may exist when various facilities are fumigated (e.g., situations where the air concentration of phosphine is unknown or monitoring equipment is not available, as discussed on page 18 of the EAD), the validity of assuming that exposure concentrations will not exceed the PEL or the STEL is questionable, even if these values are legally enforceable. OEHHA recommends that DPR discuss the uncertainties associated with this assumption and provide additional justification for adopting it.

To estimate seasonal exposure, DPR used the arithmetic mean of the measured air concentrations, after correcting for recovery (if <90%), and then multiplying by the ratio of the estimated seasonal application rate to the application rate used in the exposure study. According to an internal DPR memorandum (2003), the arithmetic mean better reflects the expected magnitude of exposure compared to the median or geometric mean. OEHHA agrees that the arithmetic mean is a better estimate for this purpose than the median or geometric mean. OEHHA recommends taking the 90% or 95% upper confidence limit (UCL) of the arithmetic mean to estimate intermediate and long term exposures when the monitoring data are sufficiently robust to support a high-end estimate of the mean. In addition, it may not be valid to multiply the measured air concentration by the ratio of the label maximum application rate to the application rate used in the exposure study when the rates are very different. This approach assumes that the measured air concentration varies linearly with the application rate, and the EAD needs to provide justification for this assumption.

Short-term Exposure Spikes

As noted above, the STEL for phosphine is 1 ppm. Phosphine has a sharp acute dose-response relationship, ranging from little apparent effect to death just by doubling the dose (from 5 to 10 ppm in animal studies). Symptoms typically appear within the first few hours and continue to develop for days or weeks after exposure has ceased. The NIOSH studies included evaluation of short-term exposure to phosphine from the handling of aluminum phosphide tablets or pellets, as described on page 25 of the EAD. In these studies, breathing zone samples with a sampling period duration of five minutes or less (referred to as "instantaneous" in the EAD) were collected from applicators while they were filling and emptying fumigant auto-dispensers or manually adding fumigant to grain. Filling or emptying auto-dispensers was assumed to take about five minutes and to occur up to seven times each day. Airborne phosphine concentrations ranged from 0.1 to 52 ppm; the average concentration was 11.3 ppm. OEHHA recommends that the number of samples collected in these studies be indicated in the EAD.

The data from the NIOSH studies of aluminum phosphide applicators indicate that short-term exposures occur relatively frequently during the work day, and that the airborne concentrations that are present during commodity fumigation are high. OEHHA agrees that if full-face respirators (which are assumed to provide a 99% protection factor) are used, short term exposure to the concentrations detected in the NIOSH studies should not be a concern. However, given the short-term nature of exposure and the number of exposure events that occur each day, it appears that there is at least some potential for applicators not to wear full-face respirators each and every time when needed. Furthermore, short-term use of full-face respirators by occupational and residential bystanders should be regarded as less likely to occur. Since the use of full-face respirators is a critical aspect of the exposure assessment, the uncertainties inherent in assuming that they are always used appropriately in these settings need to be discussed in the EAD.

In the description of the short-term samples obtained by NIOSH, DPR stated, "Due to the extremely short exposure periods (i.e., ~5 minutes), the instantaneous samples were not directly used to estimate work shift exposures. However, these episodic exposures would *have been incorporated into the TWA samples* [italics added] which were also collected from the workers and were used for estimating exposure" (page 25). However, OEHHA questions whether 3- and 6.8-hour TWA sample data (the durations of samples collected in the registrant and NIOSH studies, respectively) are appropriate to assess the potential short-term health risk of phosphine. Assuming that short-term exposure peaks occur infrequently, averaging them over an 8- or 24-hour day essentially eliminates them. For example, assuming that a worker was exposed to 4

ppm for 15 minutes during an 8-hour work day, the TWA exposure concentration would be just 0.125 ppm, well below the PEL. Nevertheless, the likelihood that this individual's health would be adversely affected would be high. OEHHA recommends that DPR review the "instantaneous" exposure data and the analysis of short-term exposure to ensure that averaging of short-term peak concentrations does not mask the potential for acute health effects.

Exposure Appraisal

The General Assumptions section (page 97) said, "The first assumption is that the handler and occupational bystander are located in the highest use county for the entire season. This assumption, however, may be incorrect, leading to overestimation of exposure." OEHHA does not believe this is an assumption that leads to overestimation but rather that it represents a "plausible worst case" scenario. Since exposure assessments should be conducted using reasonable worst-case assumptions that are consistent with product labels, this assumption does not appear unrealistic.

EDITORIAL COMMENTS

The following elements are suggested for enhancing the document: numbering of the chapters and section; inclusion of examples of product labels; inclusion of data from the original studies when the results of different studies are combined in tables; and inclusion of a description and summary of the individual exposure studies once in their entirety early in the document which can then be referenced later in the document as appropriate.

The first paragraph of the Abstract (page 4) states, "The peak phosphine exposure estimates presented below consist of short-term and seasonal exposure estimates." The use of the term "peak" in this sentence and elsewhere is not clear. Is the report referring to the maximum concentration observed within recording time (that is, a concentration spike) or the highest concentration observed within the different sampling periods used in the registrant and NIOSH studies (that is, the highest concentration observed over a 3- or 6.8-hour interval)?

The second paragraph of the Abstract summarizes short-term (< 24-hour) exposure estimates for commodity fumigation of eight different types of structures. This information would be best presented as a table. Text could then be used to highlight important findings of the analysis.

Although very concise, the Abstract would be more informative by providing a rationale for selection of the different time-weighted average exposure calculations (8-, 9.7-, 12-

and 24-hours). Additionally, it could identify and briefly discuss the field studies that provided a basis for the estimated air concentrations.

The title for Figure 1 (page 13) needs to indicate that these pesticide use data are for California only.

The phosphine use data detailed in the text on pages 15-17 would be more easily understood if it were summarized in tables, which could highlight parameter values that are critical to the exposure assessment. Additionally, the fact that different units were used to characterize the amount, area or volume of use in the PUR database (pages 16-17) is a detail that does not appear to merit discussion in the main body of the report.

The first paragraph at the top of page 18 refers to Table 8. The referenced information is provided in Table 7.

The section on physical and chemical hazards of phosphine (page 19) refers to the "lower flammability limit" of 1.8% v/v. The correct term is lower *explosive* limit (LEL).

Statements that measured air concentrations from field studies were corrected for recovery if the recovery was <90% appear numerous times throughout the EAD, both in the text and in the tables. While a limited degree of redundancy is desirable in a detailed technical report, the fact that a description of the recovery correction procedure appears dozens of times in the EAD is excessive. OEHHA recommends that DPR provide a detailed description of the recovery correction procedure and an example calculation at the beginning of the report, and then refer to the page or section where this description is provided when necessary. For example, "If recovery from field fortification studies was less than 90%, data were corrected using the procedure described on page xx."

OEHHA suggests that DPR consider adding an introductory section that provides a general overview of the exposure scenarios at the beginning of the Exposure Assessment section (page 22), as was done in other EADs (e.g., chloropicrin and simazine).

The last paragraph on page 24 includes a detailed technical description of NIOSH method S322 for analysis of airborne phosphine concentrations in field samples. This level of detail is not needed in the body of the exposure assessment document and probably could be moved to an appendix.

Quantitative information and data that are presented as text in the EAD can often be summarized in tables that are much easier for the reader to comprehend. For example, most of the text in the second paragraph on page 26, which describes the results of the NIOSH grain elevator studies, can be summarized as follows:

Type of Application	n	Sampling Time (min)	Application Rate (g/bushel)	Mean Air Concentration (ppm)	Highest Air Concentration (ppm)
Auto-dispenser	26	335	0.05	0.52	1.67
Manual	9	219	0.04	0.05 (adjusted)	0.13 (adjusted)

In the Exposure Assessment section, OEHHA suggests that DPR provide an example of each major calculation and a description of how the information presented in the tables was used to provide details and exceptions for each individual exposure scenario. The text provided excessive details regarding the content of the tables (e.g., entire paragraphs regarding the number of replicates) and the same studies were described multiple times for each applicable scenario. It would be more efficient to describe fully each major study once and use tables to highlight the concentration data that are relevant to each scenario.

The first line of page 23 ends with "(HSM-03002)." It is not clear that this is actually a reference, and that the reference is a 2003 internal DPR memorandum from Sally Powell to Joe Frank. For clarity, OEHHA suggests that this memo be cited as "(Powell 2003)." (Note too that the correct memo designation is HSM-03022.) Similarly, "HSM-09004" could be cited in the text and references section by the author and year of preparation.

On page 25, the second paragraph includes the statement, "The phosphine air concentrations, in the absence of respiratory protection, ranged from 0.1 to 52 ppm with a mean value of 11.3 ppm." Note that it is the exposure, not the air concentration, is reduced by the use of PPE. Similarly, the first sentence on page 35 reads: "The occupational bystander scenario with the highest exposure value was used to estimate occupational bystander exposure post-aeration of the fumigated commodity." Does this refer to the highest exposure value or the highest airborne concentration?

On page 53, it would be more informative to state that the annual exposure estimate for the commodity fumigation/flat storage facility applicator was based in part on the assumption that fumigation occurs 8 months out of the year.

In the section titled "Bulk Car Fumigation and Aeration" (page 62), two sub-sections address the exposure of occupational bystanders (pages 64 and 67). It would be helpful if DPR specified the type of occupational bystanders in the title of the sub-section (during application or during aeration) to help distinguish them.

On page 67, the two-sub-sections "Assistant Operator" and "Occupational Bystander" were not included in the Table of Contents (page 2). There also appears to be a formatting difference: these titles, unlike the other ones in the same section, are underlined.

On page 76, change "Tables 19" to "Table 19."

Under the heading "Ship Hold" (page 77), the second sentence reads: "These [five] studies are presented in journal articles containing air monitoring data for a total of five ships carrying grain (e.g., corn and wheat)." References (author, year published) for these studies should be provided parenthetically immediately at the end of this sentence. Also, the first study was included in the registration package from Phos-Fume Chemicals Company, Ltd., and does not appear to have been published. Therefore it is not a journal article. Later in this section (page 80) a line needs to be inserted between the second and third lines to separate the discussion of the fourth and fifth studies.

On page 96, the entire second paragraph in the "Occupational Bystander" section referred to residential bystanders. This should be re-located to the residential bystander section.

References

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DATE: June 12, 2014

SUBJECT: RESPONSE TO THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT COMMENTS ON HS-1888: ESTIMATION OF EXPOSURE TO PERSONS IN CALIFORNIA TO PHOSPHINE

The draft exposure assessment document (EAD), for aluminum phosphide, magnesium phosphide, and phosphine was prepared on January 14, 2013 by the Worker Health and Safety (WHS) Branch of the Department of Pesticide Regulation (DPR). The EAD and the associated draft risk characterization document (RCD) were sent out for external review. The Office of Environmental Health Hazard Assessment (OEHHA) provided comments on the information in the EAD in a memo dated September 26, 2013. DPR appreciates OEHHA's review. This memo contains responses to OEHHA's comments. A separate memo was generated by OEHHA for the RCD and was addressed by the Medical Toxicology Branch.

Comment 1: One pesticidal source of phosphine exposure that was not evaluated in the EAD is pesticidal use of zinc phosphide (used in rodenticide baits). An explanation in the introduction why zinc phosphide, a rodenticide, was excluded from the EAD would be helpful.

As stated in the introduction, pesticide active ingredients (AI's) are prioritized for assessment of exposure and risk potential. Zinc phosphide was not prioritized with aluminum phosphide, magnesium phosphide, and phosphine due to its relatively low exposure/risk potential.

Comment 2: Also, since the EAD looks at exposure resulting from the pesticidal use of phosphine, aluminum phosphide and magnesium phosphide, it would be more precise and informative for the document to be titled "Estimation of Exposure to Persons in California to Phosphine from Pesticidal Use of Phosphine, and Magnesium and Aluminum Phosphide".

DPR agrees. The title was altered to include the information above.

Comment 3: Industrial use of phosphine in semiconductor manufacturing and chemical syntheses, and natural occurrence resulting from anaerobic decomposition of organic matter or sewage treatment plant sediments, represent additional potential sources of phosphine exposure. A brief mention of this might be informative for many readers of the document.

Alternate sources of phosphine are presented in the ambient exposure section of the EAD.

Comment 4: Potential dermal absorption of phosphine was noted and discussed briefly on pages 11-12. The discussion included the following statement, excerpted from the U.S. Environmental Protection Agency's (U.S. EPA) 1998 Reregistration Eligibility Decision document for aluminum and magnesium phosphide: "Because the route of exposure anticipated for aluminum and magnesium phosphide is inhalation, the Agency does not expect significant dermal exposure. Therefore, dermal absorption studies are not required." Similarly, the document quotes from Hayes (1982), "The effectiveness of proper gas masks excludes the possibility of significant absorption by the skin." Both of these statements should be justified more explicitly.

DPR is not attempting to justify these statements. This section of the EAD is simply a description of the available information on dermal absorption.

Comment 5: In a quantitative health risk assessment, an exposure pathway may be excluded if it is shown using screening-level assumptions that it is not significant in comparison to other complete exposure pathways. Neither U.S. EPA nor DPR presented an analysis using screening-level assumptions to show that dermal exposure is not significant in comparison to other complete exposure pathways. In a recent review, Rehal and Maibach (2011) cited several proposed methods for mathematically modeling percutaneous absorption of chemical vapors (e.g., Kezic et al. 2000) that DPR could utilize.

The references mentioned are for generating fat/air partition coefficients for volatile organic compounds. The air/fat partition coefficient approach was investigated during the preparation of the EAD. However, no pertinent data could be found for phosphine, an inorganic compound. Please see the response to the next comment for more detail.

Comment 6: Additionally, DPR could calculate an upper bound estimate of dermal exposure using measured air concentrations and a calculated skin permeation coefficient (Klein, 2000). Such an assessment could be used to estimate the significance of percutaneous absorption relative to inhalation and provide justification for determining whether dermal exposure to phosphine is an issue that warrants more detailed, in-depth evaluation in a human health risk assessment.

The author Klein could not be found for this article. Is the reference to Keil instead?

During preparation of the EAD, the use of a skin permeation coefficient was investigated. However, no investigations were found for inorganic compounds. Studies were found for organic compounds. For example, McDougal et al. (1990) generated permeability coefficients (K_p) for eight organic compounds, including styrene, m-xylene, toluene, benzene, halothane, hexane isoflurane, and perchloroethylene, using a physiologically based pharmacokinetic model and fat/air partition coefficients ($K_{f/a}$). The $K_{f/a}$ is a measure of the amount of gas which has partitioned from the atmosphere into fat. EPA then generated the following formula for calculating the skin permeability coefficient ($K_{p(est)}$), using data derived from the McDougal et al. study (EPA, 1992):

$$K_{p(est)} = (K_{f/a} \times 0.00049) - 0.0385$$

Unfortunately, a $K_{f/a}$ could not be found for phosphine. In addition, as mentioned earlier, the above formula was derived using K_p data for organic compounds which are chemically dissimilar to phosphine.

Comment 7: Dermal absorption of phosphide dust is another exposure pathway that warrants additional consideration in the EAD. On page 89, DPR described a study by Baker (1992), who observed that relatively high levels of phosphine were given off by the clothing of workers who had handled aluminum phosphide tablets, and whose clothing became contaminated with dust from the tablets. In the Medical Management Guidelines for Phosphine, the Agency for Toxic Substances and Disease Registry (ATSDR) stated, "Most phosphine exposure occurs by inhalation of the gas or ingestion of metallic phosphides, but dermal exposure to phosphides can also cause systemic effects".

The highest phosphine level measured was 40 ppm from gloves contaminated with aluminum phosphide dust. However, this phosphine was contained within a sealed 1.5 cubic foot sealed bag and was generated by the degradation of the aluminum phosphide dust over time. In this outdoor exposure scenario the phosphine, being a gas, would likely volatilize away from the clothing and, based on the inhalation data, dissipate to concentrations below the permissible exposure limit (PEL) of 0.3 ppm 8-hr TWA.

Comment 8: Regarding dermal absorption of phosphine vapor and metal phosphide dust, the Exposure Appraisal section (page 97) concluded that "…due to lack of data, percutaneous absorption was not factored into the exposure estimates. This may have *led to an underestimation of exposure*." To *evaluate the magnitude of underestimation*, OEHHA suggests that DPR evaluate the dermal exposure pathway in greater detail to determine whether screening level estimates of absorbed doses-both from phosphine vapor and phosphide dust-can be derived, and if so, provide such estimates.

It's unlikely that the metal phosphide dust would be absorbed percutaneously. It would likely degrade to generate phosphine gas which might be absorbed percutaneously. To evaluate the magnitude of underestimation, the amount of phosphine absorbed through the skin for each exposure scenario is required. These data are not available.

Comment 9: The first paragraph of this section, which begins on page 17, includes a statement that a self-contained breathing apparatus (SCBA) must be used when the air concentration of phosphine is unknown or exceeds 15 ppm. It also states that certain product labels indicate that a SCBA must be worn if the phosphine concentration is unknown or exceeds the short-term exposure limit of 1 ppm for 15 minutes. Still other labels indicate that an approved canister respirator must be worn if monitoring equipment is not available, these recommendations appear to contradict one another: they indicate in one case that SCBA must be used when the concentration is unknown and in another that an approved canister respirator is appropriate for these situations. A statement pointing out this discrepancy should be included in the EAD. If the concentration is truly unknown, there is no basis for selecting the appropriate level of respiratory protection. Ultimately, the effectiveness of different label requirements for mitigating exposure to phosphine may need to be evaluated more carefully in the EAD.

This contradictory language was limited to two product labels. The problematic language was corrected and the revised product labels approved for use in California. The language concerning this topic was removed from the EAD.

Comment 10: Similarly, the second paragraph on page 18 begins with the statement, "*For indoor applications, all of the product labels contain the requirement that an approved full-face gas mask-phosphine canister combination or SCBA or its 'equivalent' to be available within the structure being fumigated*" [italics added]. The next sentence states, "The Detia® FUMEX product label contains the statement, "If SCBA or its equivalent is not available at the application site, it must be available locally, for example, at a fire station or rescue squad" [italics added]. These two statements seem to contradict one another. While neither scenario guarantees that an SCBA unit will be used when necessary, the presence of an SCBA unit at a local fire station – which could be miles from the fumigated structure – provides considerably less assurance that the unit will actually be used than if it were located within structure being fumigated. Later in this section, the discussion of precautions to be taken when using cylinderized phosphine gas indicates that respiratory protection must be available at the site of application. Overall, one would expect the respiratory protection requirements for use of aluminum and magnesium phosphide to be consistent with those stipulated for phosphine gas. If the labels for these products are inconsistent with one another with respect to the availability of SCBA (as they appear to be), then these inconsistencies should be addressed directly in the EAD. Ultimately the effectiveness of different label requirements for mitigating exposure to phosphine may need to be evaluated more carefully in the EAD.

The problematic language was corrected and the revised product label approved for use in California. The language concerning this topic was removed from the EAD.

Comment 11: On page 37, occupational bystanders working both inside and outside of grain elevators during fumigant application and commodity fumigation were assumed to wear full-face respirators. This scenario assumes (1) that the airborne concentration of phosphine is known to all workers in the vicinity of the fumigation, even those not directly engaged in fumigation activities, (2) that full-face air-purifying respirators (APRs) are available for all workers and all bystanders, and (3) that the APRs have been fitted with the appropriate air filtration cartridges. OEHHA is concerned that these assumptions may be overly optimistic in many circumstances, and would be interested in seeing the results of any occupational surveys on this subject, if available. Consequently, the short-term exposure estimates using these scenarios presented for occupational bystanders in Table 13 may not reflect "baseline" exposure estimates, but rather provide values that assume that an exposure mitigation strategy is in place at all locations where these fumigants are used and is effective 100 percent of the time. Therefore the estimated exposures are expected to be higher. We are concerned that bystanders might lack adequate respiratory protection, consistent with what has also been expressed by U.S. EPA: "...the Agency is concerned about the potential risks posed to occupational and residential bystanders who are not likely to be wearing the necessary respiratory protection" (U.S. EPA 1998).

In each product label there is a requirement for a fumigation management plan (FMP). Within the FMP are the following statements:

1. “Consult company officials in the development of procedures and appropriate safety measures for nearby workers that will be in and around the area during application and aeration.”

2. “Consult with company officials to develop an appropriate monitoring plan that will confirm that nearby workers and bystanders are not exposed to levels above the allowed limits during application, fumigation and aeration. This plan must also demonstrate that nearby residents will not be exposed to concentrations above the allowable limits.”

Consistent with the purpose of risk assessment, DPR assumes that the label language is being followed by the user. The highest estimated 8-hr TWA phosphine air concentration of the scenario mentioned in the comment (occupational bystander working both inside and outside of the grain elevator), adjusted to the maximum application rate, was 2 ppm. It was assumed that in order to reduce the concentration to a level which was at or below the PEL of 0.3 ppm, the bystander would utilize a full-face respirator equipped with a phosphine canister, as specified in the product label. The statement from the U.S. EPA: "...the Agency is concerned about the potential risks posed to occupational and residential bystanders who are not likely to be wearing

the necessary respiratory protection" is a valid concern. However, the exposure estimates generated by DPR are based upon legal usage of the pesticidal product. Uses not in accordance with product label instructions are enforcement issues.

Comment 12: The discussion of respirator selection on pages 17 and18 could be improved by including the protection factor provided by the different types of respirators (e.g., 99% protection afforded by a full-face air-purifying respirator).

DPR agrees. The protection factor information has been incorporated into this section of the EAD.

Comment 13: An exposure scenario that is not addressed in the EAD is the potential for phosphine to continue to "off-gas" (that is, be re-released) from fumigated materials after a facility or storage structure has been aerated. From the results of the studies described on pages 11 and 12 ("Dermal Absorption of Phosphine"), it is clear that phosphine is capable of penetrating deep into porous building materials such as concrete and cinder block as well as biological materials such as baled sheep skins and wheat grain. DPR recently completed a series of intensive investigations demonstrating that high levels of methyl bromide can accumulate in enclosed spaces after aeration of fumigated grapes at the Port of Los Angeles, and it would be reasonable to conclude that off-gassing of phosphine-fumigated commodities also might have the potential to lead to a high-risk exposure scenario. OEHHA recommends that DPR consider examining such a scenario, and attempt to estimate post-aeration exposure concentrations that might be produced in confined spaces.

According to the product labels, phosphine is not used for fumigating grapes. However, exposure estimates were generated in the EAD for a post-aeration exposure scenario consisting of handlers of fumigated cereal. This worker was called the packaging line worker who packaged cereal which had been fumigated and then transferred several times to holding tanks prior to packaging. Exposure estimates for this scenario came from samples taken from the breathing-zone of each worker, which would include off-gassing from the treated commodity.

Comment 14: The paragraph at the bottom of page 16 states that 27 percent of the use data for aluminum phosphide on dry flowable commodities (grains and nuts) were assumed to be erroneous because they exceeded the product label maximum application rate. (These data were abstracted from DPR's Pesticide Use Report (PUR) database for the five-year period from 2006 through 2010.) Additional justification for excluding these data from calculation of seasonal application rates needs to be provided. An alternative assumption is that use of aluminum phosphide at levels above those specified on the product label is not an uncommon occurrence.

As stated earlier, the exposure estimates are based upon legal usage of the product. Moreover, the PUR database can contain outliers:

http://www.cdpr.ca.gov/docs/pur/pur97rep/appendxa.pdf

While not perfect, the PUR database was utilized to provide some basis or evidence for what the seasonal or typical application rates are in CA for aluminum phosphide, magnesium phosphide, and phosphine. Otherwise, a more arbitrary method would have to be used.

Comment 15: The first paragraph on page 27 begins, "No background PH3 [phosphine] air concentration data were available for the TWA [time-weighted average] samples in either the registrant or NIOSH [National Institute for Occupational Safety and Health] studies. The registrants generated background samples via opening the sampling tube and then immediately sealing the tube for analysis. These samples were not used however, since they generated a false-positive signal that increased with increasing storage time...This instability was not present in their field fortification samples." It is unclear why DPR concluded that the phosphine concentrations detected in these samples represented false positive results, particularly if they were replicated in multiple samples. In light of the possibility, noted above, that building materials and stored grain have the capacity to absorb and re-release phosphine, an alternative hypothesis is that the background samples actually captured low levels of phosphine that were present in the ambient environment under investigation. Depending on where and how the background samples were stored, it is conceivable that the phosphine concentration in the sample tubes might increase, perhaps because they were stored in close proximity to materials that had previously absorbed the pesticide. Low background levels of phosphine would not necessarily be detected in field fortification samples if the latter had been spiked with a substantially higher concentration of phosphine. OEHHA recommends that DPR consider alternative explanations for the results that were obtained in these studies. If exposure to low background levels of phosphine occurs in certain exposure scenarios, then background exposure needs to be accounted for in the EAD.

The investigators concluded that the background samples (field blanks) were unstable. Along with the background samples, which were opened and then immediately closed in the field, unopened sample columns (unopened blanks), which were opened in the lab and then stored in the lab until analysis, also showed an increase in signal over time. The field blanks were analyzed over a 90-day period. The unopened blanks were analyzed over a roughly 60-day period. This instability was also seen in a separate study where unopened blanks (opened in the lab and stored from 1 to 8 days before analysis) showed a “dramatic upward trend” in signal. In contrast, the field-fortified (spiked) samples were shown to be stable over time. The investigators conducting the residues analysis theorized that the, “field blanks are unstable until the introduction of minor amounts of phosphine or other phosphate source.” They go on to state, “This assumption is based on the results of the field blank samples, unopened blank samples

(unopened sorbent tubes), limited laboratory study on stability of the blank samples, grab samples, grab sampling, and the field sample results which in many cases were lower in actual analyte content than the blanks. This assumption is further supported by the excellent agreement of the field fortified (spiked) samples with the 'true' value of the fortifying gas." Hence, the field samples were not corrected for background (Phosphine Worker Exposure, Degesch America [2002] Registration Package 51882-015).

Comment 16: The dermal absorption data cited in this section of the document are of very poor quality. DPR determined that they could not identify an acceptable quantitative study and concluded that these results should not be used in the EAD. OEHHA agrees with this determination. A statement that the available pharmacokinetic data are not of sufficient quality for human health risk assessment, and a discussion of the deficiencies of the available studies that justifies this conclusion, should be included in the EAD.

As stated in the Pharmacokinetics section of the EAD, "No studies on the dermal absorption of phosphine, which is a gas with a vapor pressure of 29,300 mmHg at 25ºC (HDSB, 2011), were discovered." That is, no pharmacokinetic studies have been conducted via the dermal route.

Comment 17: Information on phosphine metabolism is limited. Although the report recognized the data gap, their description of the Lyubimov and Garry review is too succinct and would benefit from inclusion of additional detail (Lyubimov and Garry 2010).

To avoid delay in finalizing the risk assessment, the EAD will not be revised to include greater detail of the study. DPR acknowledges that the study could have been described in greater detail, but these details are not critical to the assessment of exposure.

Comment 18: The EAD covers phosphine- and metal-phosphide related illnesses for the five-year period spanning 2005 through 2009, based on information obtained from the California Pesticide Illness Surveillance Program (PISP) database. During this period, 10 cases of phosphine exposure were reported to have resulted from use of aluminum phosphide. However, 15 additional cases of phosphine exposure from aluminum phosphide use were reported in 2010. Similarly, in addition to the 27 cases of phosphine exposure resulting from use of cylinderized phosphine reported from 2005 through 2009, 14 cases were reported in 2004. To provide a more comprehensive description of actual scenarios for inadvertent or accidental exposure to phosphine, OEHHA recommends that this discussion include phosphine exposure cases reported during the period from 2004 through 2010.

The PISP data for 2010 were not available during preparation of the EAD. As with the PUR data, the latest five years of data were summarized. To avoid delay in finalizing the risk assessment, the EAD will not be revised to update the illness data.

Comment 19: Even though DPR used the latest available pesticide use report (PUR) data (2006-2010), the EAD should clearly indicate that PUR data only cover use in agricultural settings, and that use of zinc phosphide is not included.

As stated in the EAD, the PUR data was used to estimate seasonal use of aluminum phosphide, magnesium phosphide, and cylinderized phosphine gas. Since aluminum phosphide was used in the greatest amounts, the estimated use season was also utilized for magnesium phosphide and phosphine. Also, as stated in the EAD, non-agricultural uses were addressed such as seasonal use for burrowing pest control, or use in buildings and structures in non-agricultural settings. As mentioned earlier, zinc phosphide was not prioritized with aluminum phosphide, magnesium phosphide, and phosphine due to its relatively low exposure/risk potential.

Comment 20: If the overall volume of phosphine and phosphine-generating compounds sold in California is available, it would be possible to compare the amount sold for pesticidal use to the total amount sold in order to evaluate the importance of non-agricultural use.

All product label uses must be assessed for exposure. Moreover, according to the product labels, aluminum phosphide, magnesium phosphide, and cylinderized phosphine have only pesticidal uses.

Comment 21: OEHHA suggests that EAD include a sample label for each type of pesticide product in the appendix or a link to their location on DPR's website. The following two updates related to label information should be provided as well:

- **Since 2010, new restrictions apply to all phosphine products for use against burrowing rodents (http://www.epa.gov/oppsrrd1/reregistration/alphosphide/aluminum-magnsm-phos-fs.html).**
- **An amendment to increase the application rate for cylinderized phosphine to match metallic phosphide labels was submitted to U.S. EPA on February 4, 2013, and accepted on March 12, 2013 (EPA Registration No. 68387-8).**

The latest product labels have been reviewed. No changes to the exposure estimates in the EAD were necessary based upon the latest label revisions.

Comment 22: The EAD did not include a section on environmental concentrations or environmental fate. Consequently, these processes cannot be incorporated into bystander and residential exposure scenarios. This information is available in other reports for phosphine (DPR 2013, EFSA 2012, U.S. EPA 1998) and in other EADs that OEHHA recently reviewed. If no data are available or if phosphine is not found in the ambient environment, then a statement to this effect should be included in the EAD.

The environmental fate document was completed by the Environmental Monitoring Branch of DPR. The document, along with the EAD and the RCD, will be posted to DPR's website when finalized.

Comment 23: A registrant task force study (Degesch America 2002) was available for workers fumigating/aerating farm bins and flat storage facilities, warehouses, rail cars and equipment, and specific areas of a flour and corn mill (spot fumigation). NIOSH studies (NIOSH 1986a, b; 1987a, b) were also available for occupational exposure following commodity fumigation in concrete upright bins of grain elevators. Results from the NIOSH studies were combined with the registrant study in the exposure assessment. No data were available to document applicator, aerator and bystander exposures following use of cylinderized gas and granular formulations, so exposures were estimated using data from other facilities as surrogates. Although this appears to be reasonable, the decision to utilize surrogate exposure estimates would benefit from additional discussion and justification, and the consequent uncertainties should be articulated.

The justification is, as stated in the EAD, the lack of data for these formulations. The consequent uncertainties are stated in the appraisal section of the EAD.

Comment 24: In cases where data were lacking and no surrogate exposure estimates could be applied, exposures were based on the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL). A PEL is the maximum permitted 8-hour time-weighted average (TWA) concentration of an airborne contaminant during a 40- hour work-week. The PEL for phosphine is 0.3 parts per million (ppm). When the air concentration exceeds the PEL, workers (applicators as well as occupational bystanders) are required to use full-face respirators. The short-term exposure limit (STEL, a 15-minute TWA exposure that is not to be exceeded at any time even if the 8 hour TWA is below the PEL) is 1 ppm. Given the variability of actual exposure conditions that may exist when various facilities are fumigated (e.g., situations where the air concentration of phosphine is unknown or monitoring equipment is not available, as discussed on page 18 of the EAD), the validity of assuming that exposure concentrations will not exceed the PEL or the STEL is questionable, even if these values are legally enforceable. OEHHA recommends that DPR discuss the uncertainties associated with this assumption and provide additional justification for adopting it.

As stated earlier, exposure estimates are for legal uses. This is consistent with the purpose of the risk assessment.

Comment 25: To estimate seasonal exposure, DPR used the arithmetic mean of the measured air concentrations, after correcting for recovery (if <90%), and then multiplying by the ratio of the estimated seasonal application rate to the application rate used in the exposure study. According to an internal DPR memorandum (2003), the arithmetic mean

better reflects the expected magnitude of exposure compared to the median or geometric mean. OEHHA agrees that the arithmetic mean is a better estimate for this purpose than the median or geometric mean. OEHHA recommends taking the 90% or 95% upper confidence limit (UCL) of the arithmetic mean to estimate intermediate and long term exposures when the monitoring data are sufficiently robust to support a high-end estimate of the mean.

Long-term exposures were not assessed in this EAD since phosphine is not carcinogenic. As far as the intermediate (i.e., seasonal) exposures, DPR disagrees. The estimated seasonal exposures are supposed to represent typical exposures. Hence, the mean of the adjusted phosphine air concentrations was used for estimating exposure. DPR does estimate UCL on the mean when using low-confidence data (Frank, 2007), but has not made that determination for the data used to estimate seasonal exposure to phosphine. Applying the UCL in this case could result in an exposure estimate that is less representative of typical exposure than is given by the arithmetic mean.

Comment 26: In addition, it may not be valid to multiply the measured air concentration by the ratio of the label maximum application rate to the application rate used in the exposure study when the rates are very different. This approach assumes that the measured air concentration varies linearly with the application rate, and the EAD needs to provide justification for this assumption.

Due to the obvious variables, the adjustment of the phosphine air concentrations to the maximum or seasonal application rate is simplistic. However, in the absence of data and logical alternatives, this health-protective approach was taken.

Comment 27: As noted above, the STEL for phosphine is 1 ppm. Phosphine has a sharp acute dose- response relationship, ranging from little apparent effect to death just by doubling the dose (from 5 to 10 ppm in animal studies). Symptoms typically appear within the first few hours and continue to develop for days or weeks after exposure has ceased. The NIOSH studies included evaluation of short-term exposure to phosphine from the handling of aluminum phosphide tablets or pellets, as described on page 25 of the EAD. In these studies, breathing zone samples with a sampling period duration of five minutes or less (referred to as "instantaneous" in the EAD) were collected from applicators while they were filling and emptying fumigant auto-dispensers or manually adding fumigant to grain. Filling or emptying auto-dispensers was assumed to take about five minutes and to occur up to seven times each day. Airborne phosphine concentrations ranged from 0.1 to 52 ppm; the average concentration was 11.3 ppm. OEHHA recommends that the number of samples collected in these studies be indicated in the EAD.

Since the samples weren't used for estimating exposure, a data summary accompanied with a reference to the associated data volume is sufficient.

Comment 28: The data from the NIOSH studies of aluminum phosphide applicators indicate that short-term exposures occur relatively frequently during the work day, and that the airborne concentrations that are present during commodity fumigation are high. OEHHA agrees that if full-face respirators (which are assumed to provide a 99% protection factor) are used, short term exposure to the concentrations detected in the NIOSH studies should not be a concern. However, given the short-term nature of exposure and the number of exposure events that occur each day, it appears that there is at least some potential for applicators not to wear full-face respirators each and every time when needed. Furthermore, short-term use of full-face respirators by occupational and residential bystanders should be regarded as less likely to occur. Since the use of full- face respirators is a critical aspect of the exposure assessment, the uncertainties inherent in assuming that they are always used appropriately in these settings need to be discussed in the EAD.

Again, the estimated exposures are for legal product uses. Deviations from product label instructions are issues of enforcement rather than assessment.

Comment 29: In the description of the short-term samples obtained by NIOSH, DPR stated, "Due to the extremely short exposure periods (i.e., -5 minutes), the instantaneous samples were not directly used to estimate work shift exposures. However, these episodic exposures would have been incorporated into the TWA samples [italics added] which were also collected from the workers and were used for estimating exposure" (page 25). However, OEHHA questions whether 3- and 6.8-hour TWA sample data (the durations of samples collected in the registrant and NIOSH studies, respectively) are appropriate to assess the potential short-term health risk of phosphine. Assuming that short-term exposure peaks occur infrequently, averaging them over an 8- or 24-hour day essentially eliminates them. For example, assuming that a worker was exposed to 4 ppm for 15 minutes during an 8-hour work day, the TWA exposure concentration would be just 0.125 ppm, well below the PEL Nevertheless, the likelihood that this individual's health would be adversely affected would be high. OEHHA recommends that DPR review the "instantaneous" exposure data and the analysis of short-term exposure to ensure that averaging of short-term peak concentrations does not mask the potential for acute health effects.

DPR shares this concern. However, there are no compatible toxicity studies/data for 5 minute phosphine exposures.

Comment 30: The General Assumptions section (page 97) said, "The first assumption is that the handler and occupational bystander are located in the highest use county for the entire season. This assumption, however, may be incorrect, leading to overestimation of exposure." OEHHA does not believe this is an assumption that leads to overestimation but

rather that it represents a "plausible worst case" scenario. Since exposure assessments should be conducted using reasonable worst-case assumptions that are consistent with product labels, this assumption does not appear unrealistic.

DPR didn't state that the assumption led to overestimation of exposure. DPR stated that the assumption "may be incorrect" and, hence, may lead to overestimation of exposure. It's quite plausible that a worker may move throughout the state during the application season.

References

Frank, J.P. 2007. Method for Approximating Confidence Limits for Upper Bound and Mean Exposure Estimates from the Pesticide Handlers Exposure Database (PHED). Memo No. HSM-07005. Sacramento, CA: Worker Health and Safety Branch, Department of Pesticide Regulation, California Environmental Protection Agency.

Phosphine Worker Exposure, Degesch America (2002) Registration Package 51882-015. Registration Resource Center, Division of Registration and Health Evaluation, Department of Pesticide Regulation, California Environmental Protection Agency, 1001 I St, P.O. Box 4015, Sacramento, CA 95812-4015.

cc: Ann Hanger, Senior Environmental Scientist (Specialist), Registration Branch

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMCIAL SAFETY
AND POLLUTION PREVENTION

April 24, 2013

Gary Patterson, Phd., Chief, Medical Toxicology Branch
California EPA, Department of Pesticide Regulation
1001 I Street, P.O. Box 4015
Sacramento, CA 95812-4015

RE: U.S. EPA Comments- DPR Phosphine Risk Assessment

Dear Dr. Patterson

The United States Environmental Protection Agency is pleased to submit its comments on the risk characterization documents completed by the Department for phosphine that were recently provided to the Agency for review. The documents we reviewed can be identified by the following information: [1]

- **Draft Estimation of Exposure to Persons in California to Phosphine** (HS-1888), Ian Reeve (1/14/13)
- **Phosphine - Risk Characterization Document** (Med Tox Branch, DPR) Andrew Rubin (2/15/13)
- **Fumigants: Phosphine and Phosphine Generating Compounds, Risk Characterization Document, Environmental Fate** (Env. Monitoring Branch, DPR) Parakrama Gurusinghe (2/13)

Our comments are attached to this letter and they specifically address each major element of risk assessment including use information, exposure assessment, hazard, and risk characterization. Due to the timing associated with this effort EPA has completed a level of review intended only to identify major policy and science issues. Original data and citations were not procured to verify the DPR analyses (e.g., transcription and mathematical calculations). Further more in-depth reviews are possible but would require additional time.

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[1] Note that the environmental fate review comments will be sent under separate cover once complete.

During our review process we identified several issues for your consideration. Some notable ones include:

- the representativeness of the exposure data used relative to current use practices should be better described as well as the uncertainties associated the lack of robust data for some scenarios considered in the exposure assessment,
- There are differences in how inhalation risks are calculated compared to EPA. The Agency uses a route-specific inhalation based risk metric outlined in EPA's peer reviewed Reference Concentration methodology. This method also relieves an element of the applicable uncertainty factors and reduces our starting point level of concern from 100 to 30,
- EPA plans on using a distributional approach to air modeling for predicting residential bystander risks coupled with the appropriate term toxicological endpoint in its upcoming Registration Review Risk Assessment whereas DPR did not complete any modeling and used the current PEL in its screening approach,
- EPA evaluates epidemiological research based on the use of a modified Bradford Hill criteria as we described in a 2010 meeting of the FIFRA Scientific Advisory Panel. This approach was not considered by DPR, and
- more discussion should be included regarding ambient air as a source of exposure and why it is not a concern, especially given recent environmental justice concerns related to the use of fumigants.

Finally, phosphine will be starting the Registration Review Process later this fiscal year which may result in changes to our endpoints, our exposure assessments, etc. We will inform you on any of these chat1ges to keep you up-to-date on how our assessment is proceeding.

Please let me know if you have comments, questions or require further clarifications on this submission.

Sincerely,

Jack E. Housenger, Director
Health Effects Division
Office of Pesticide Programs

EPA Review Comments - DPR Phosphine Risk Assessment

Each document/key risk assessment element is addressed separately below.

Use Information (comments pertain to all of the referenced documents):

- The use numbers in the RCD are not the same as those in the exposure assessment. This discrepancy should be reconciled.
- Data presented in Table 6 of the RCD, Annual Number of Pounds, do not match the PUR 2010 Table 14 numbers. The following paragraphs indicate refinements have been made with Cal PIP, but it is not clear that the data in Table 6 are those numbers

Exposure Assessment Document:

- The assessment is based on data generated by NIOSH and a registrant that are from the late 1980's and 2002, respectively. Characterization should be provided regarding the representativeness of these data relative to current fumigation practices and settings. Characterization should also reflect any evolution of permit conditions in California. If data evaluation records are available for these studies it would aid in a review process. Perhaps a separate section in the document should be included to discuss the scientific credibility of each exposure data source used in the assessment. The overall quality of the assessment is difficult to understand without that type of discussion.
- Label requirements for PPE and respirator recommendations were not verified by EPA.
- The characterization of the potential for dermal exposure differs from the risk characterization document. The exposure assessment uses an analogy comparing phosphine penetration in cement and stored commodities to a potential for dermal absorption in workers. The risk assessment document says just that no data are available. EPA does not concur with the analogy because treatment concentrations and the time exposed are not the same as experienced by workers. Also, DPR should consider the discrepancy between the two documents.
- Incidents were only considered from California but other incidents outside the state, especially those of a more severe nature, should be considered as they could be informative.
- An inherent difference exists between CDPR and EPA risk assessments in that durations of exposure are defined differently between the two Agencies. This issue has been (addressed before in other forums.
- Risk findings are made in some cases are based on exposure data which are very limited. (For example, in Table 11 on page 34 there are two different subcategories of exposure both with very low numbers of monitoring units (as

low as 3 in one of the two scenarios). Consider, as an alternative, possible combinations of like activities in order to base decisions on larger datasets.

- The nomenclature used to describe workers differs somewhat between DPR and EPA. EPA does not use the term “Occupational Bystanders” but does consider those types of job tasks in assessments, just they are described in a different manner based on task.
- The DPR assessment cites the ANSI standard for respiratory protection factors that are outdated. EPA uses the OSHA protection factors available at http://www.osha.gov/Publications/3352-APF-respirators.pdf which alter the findings or the DPR assessment because ANSI used a PF of 100 for full faced respirators and OSHA has assigned a PF of 50 for these devices.
- This is a general issue which may apply to both DPR and EPA risk assessments but it is worth noting. The protection factor for SCBA (Self Contained Breathing Apparatus) varies depending upon how it’s used. For full face pieces, in demand mode SCBAs have a protection factor of 50 and in continuous flow mode they have a protection factor of 1000. On page 18 and in Table 7 (pg. 19) of the document the PF 50 is cited which seems appropriate given how SCBAs are used for routine tasks. However, in Table 13 (pg. 38) it appears the protection factor used in the calculation is 1000. The document should he checked for consistency.
- Community based exposures from ambient air should be discussed in more detail in the document especially in light of recent efforts focused on environmental justice related issues. More details should also be provided from the Han (2000) citation. Phosphine is not in the TAC network, nor does it appear to have been included in any special monitoring studies outside of a CARB study conducted in 2008.
- There should be a better cross walk between related tables such as those presenting data (e.g., Table 8 and Table 12).
- More discussions should be provided regarding the uncertainties associated with adjusting occupational exposure data for fumigants by application rate since exposures can occur based on the characteristics of a particular facility, how well an treated area is sealed, or how aeration takes place. Given these factors, exposures may not be expected to be as proportional to treatment rates (i.e., concentration x time) as conventional pesticides.
- The PEL was used as the basis for estimating residential bystander exposure for all durations of exposure and it was adjusted for number of months of typical treatments when estimating annual exposures. This approach did not utilize modeling to define peak emission values for other shorter exposure periods which historically have been the major risk concern for fumigants. EPA will model residential bystander exposures using PERFUM when it completes its registration review risk assessment.

- This is a general issue which may apply to both DPR and EPA risk assessments but it is worth noting. EPA is looking into the legality of regulations for ship holds, particularly if vessels are not of United States registry.
- More details should be provided regarding the dermal monitoring discussion on page 89 of the document.
- More details of the origin of the 100 feet buffer specified for occupational bystanders for burrowing pest applications (pg. 96) should be provided.

Risk Characterization/Hazard Identification and Endpoint Selection:

- EPA did not verify the odor threshold noted in the RCD. Additionally, EPA did not verify other regulatory limits (pg. 6) reported in the RCD.
- The potential for port of entry effects should be discussed in more detail (e.g., if they were considered as a part of the study design or if they were negative).
- Phosphine is listed as a HAP (Hazardous Air Pollutant) under the Clean Air Act. EPA did not investigate to see if there have been any regulatory status changes related to the HAP process and what its impact might be on a pesticide risk assessment considering there is a regulatory desire to ensure continuity amongst regulations where possible.
- The differences on dermal toxicity should be reconciled with the exposure assessment as noted above.
- DPR indicated EPA has ·waived requirements for future studies due to the severe acute toxicity. EPA's HASPOC actually recently recommended that a special acute inhalation study is required and that it should include respiratory histology, GSH measurements, kinetics/tissue dosimetry. HASPOC also recommended a range-finding study to determine appropriate doses for further studies, such as a 2-generation reproductive study and acceptable acute and subchronic neurotoxicity studies.
- The following summarizes DPR and EPA's hazard assessment for critical studies:
    - Acute Toxicity: same for both agencies (4hr, LC50 of 11 ppm)
    - Subchronic Toxicity: different studies and-PODs
        - (NOEL/LOEL-1/3ppm) DPR from Schaefer 1998
        - (NOEL/LOEL-3/10ppm) EPA from Newton 1990
    - Chronic Toxicity/Carcinogenicity: different studies and PODs
        - (NOEL/LOEL - 3/ >3ppm) EPA from Newton 1998
        - (NOEL/LOEL - 1/3ppm) DPR from Schaefer 1998b
    - Developmental Toxicity: same study and POD chosen
    - Reproductive Toxicity: same finding, no pertinent data available
    - Mutagenicity: same studies and conclusions reached
    - Metabolism: same finding, no pertinent data available
    - Dermal Absorption: same finding, no pertinent data available

- Neurotoxicity: same study and POD chosen
- Endocrine Disruptor Effects are not addressed by DPR while EPA has a screening program

Risk Characterization/Epidemiology & Incidents:

- See comments on incidents above and consideration of those which occurred outside California.
- The RCD cites a .number of epidemiological data sources by various investigators. The specific studies arc summarized and the outcomes (e.g., odds ratios) are presented and summarized. EPA has developed an approach for the consideration of such data into risk assessment based on modified Bradford Hill criteria (see the following for information: http://www.epa.gove/scipolv/sap/meetings/2010/020210meeting.html). EPA recommends that DPR utilize this approach to revise how these data are presented in the RCD.
- Research efforts focused on existing epidemiological cohorts, appropriate for this assessment, should be described at least qualitatively (e.g., Agricultural Health Study).
- Epidemiological findings should be evaluated in a context of timing of the findings relative to critical regulatory decisions.

Risk Characterization/Dietary Analysis:

- DPR did not conduct a dietary exposure assessment, stating it was unlikely residues would remain until consumption of the treated commodities. They state US EPA did conduct a dietary exposure assessment for the RED even though we essentially concurred with DPR that residues would not be present.
- A cold storage fumigation study was submitted to US EPA. This study may or may not be submitted to DPR. The following is the reference for this study:

  Muhareb, J.; Hartsell, P.; Hurley, J.; et al. (2010) Fate of Hydrogen Phosphide in Several Fruits and Vegetables following Fumigations with ECO2FUME Fumigant Gas at Cold Storage Temperatures: Project Number: CYTEC/1/2010. Unpublished study prepared by Dried Fruit & Nut Assoc. of California. 21 p.

Risk Characterization/Risk Assessment Methods:

- DPR adjusted animal NOELs by an uncertainty factor of 100 to calculate a concentration of concern for each exposure duration considered in their assessment. EPA uses a different methodology for defining human equivalent concentrations (i.e., RfC methodology) that is available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=719934Download. This methodology eliminates the need for a factor of 3 in the inter-species uncertainty factor so EPA uses a factor of 30 as a starting point to evaluate pesticides for this

situation. DPR used a UF of 100 in the RCD as their method does not account for this difference.

- More detail needs to be provided (e.g.. pg. 53) regarding the potential for exposure from ambient air and why it is hot of concern. May want to cite any research plans associated with the TAC network, or other pertinent documents, where the potential for phosphine exposures would have been discussed. Also, if there are environmental fate characteristics which would minimize the potential for such exposures they should also be discussed as characterization.
- Some of the citations summarizing incidents in the RCD may provide useful exposure information that should perhaps be incorporated in the exposure assessment. For example, Misra (1988) summarized on page 13 may have information pertaining to how long treated commodities off-gas phosphine after they have been fumigated.

Risk Characterization/Risk Assessment Findings:

- The respirator protection factor issue noted above could impact the findings of this assessment. EPA did not evaluate the sensitivity in the results of changing this parameter.
- Likewise, the use of the RfC methodology would alter the finding of this assessment and EPA did not evaluate such changes.
- The conclusions of the risk assessment should tie into existing labels and permit conditions established in California for phosphine use (pg. 75 of RCD).
- Please consider revising or removing ***Section VI: Issues Related To Food Quality Protection Act***. Of particular concern are the statements made in part C which discusses in utero effects based on epidemiological studies (e.g., Garry et al, 2002 and O'Malley et al, in press). EPA has several concerns over the interpretation of the epidemiological data presented in the RCD.

M E M O R A N D U M

TO: Tom Moore, Ph.D.
Acting Branch Chief
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

FROM: Andrew Rubin, Ph.D., D.A.B.T.
Staff Toxicologist, Health Assessment Group
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

DATE: June 11, 2014

SUBJECT: RESPONSE TO USEPA COMMENTS ON THE PHOSPHINE RISK CHARACTERIZATION DOCUMENT

USEPA's critique of DPR's draft phosphine risk characterization document (RCD) contains both specific recommendations and general statements detailing areas of agreement or disagreement with the methodology and conclusions found in the RCD (USEPA memo of 4.24.13). Accommodation by DPR of several of USEPA's recommendations would involve changes in DPR risk assessment policy and will not be addressed in this memo. The following responses are restricted to issues of toxicology and scientific judgment. Literature citations in this memo are found in the reference section of the RCD.

1. Use Information (USEPA memo, page 3)

USEPA memo, p. 3, 1st two bullets: "The use numbers in the RCD are not the same as those in the exposure assessment. This discrepancy should be reconciled." *and* "Data presented in Table 6 of the RCD, Annual Numbers of Pounds, do not match the PUR 2010 Table 14 numbers."

DPR response: The slight discrepancies in the use statistics in the draft RCD and the draft exposure assessment document (EAD) resulted from different data collection approaches taken by the Medical Toxicology Branch (RCD) and the Worker Health and Safety Branch (EAD) in accessing DPR's Pesticide Use Report. The revised RCD quotes the figures directly from the EAD. The revised reports are, as a result, identical in this regard.

2. Risk Characterization / Hazard Identification and Endpoint Selection (USEPA memo, page 5)

USEPA memo, p. 5, 3rd bullet: "The potential for port of entry effects should be discussed in more detail (*e.g.*, if they were considered as part of the study design or if they were negative)."

DPR response: Portal of entry effects are likely to be critical determinants of phosphine-mediated toxicity, and are considered major drivers of the acute risk assessment. However, as implied by USEPA's comment, there is insufficient proof for this assertion in the reviewed studies. The possibility of portal of entry effects should, therefore, be specifically monitored in future studies. To this end, we note that USEPA has requested submission of a "special" acute rat inhalation study, to include "histopathology of the respiratory tract, including incidence and severity at multiple tested concentrations; GSH measurements (*i.e.*, nose); pharmacokinetics / tissue dosimetry including time course; and sublethal portal of entry effects (*i.e.*, within the respiratory tract) along with information on dose response, incidence, and severity" (USEPA Memorandum: Phosphide [Al, Mg] and Phosphine: Human Health Scoping Document Supporting Registration Review. September 11, 2013; p. 7). Data from such a study may support sublethal NOELs / LOELs that are lower than the mortality-dependent values currently recommended.

The revised RCD now contains a statement to this regard in the Risk Appraisal section (V.A.1.a.).

USEPA memo, p. 5, 5th bullet: "The differences on dermal toxicity should be reconciled with the exposure assessment as noted above." (This statement refers to an earlier statement in the "Exposure Assessment" portion of the USEPA memo: "The characterization of the potential for dermal exposure differs from the risk characterization document. The exposure assessment uses an analogy comparing phosphine penetration in cement and stored commodities to a potential for dermal absorption in workers. The risk assessment document says just that no data are available. EPA does not concur with the analogy because treatment concentrations and the time exposed are not the same as experienced by workers. Also, DPR should consider the discrepancy between the two documents.")

DPR response: The potential for dermal toxicity does not play a substantive role in DPR's risk characterization for phosphine, as noted above. Even so, most of the inhalation toxicity studies considered for the draft RCD utilized "whole body" as opposed to "nose only" exposure. Whole body exposure to a gaseous substance implicitly takes into account the possibility that transdermal and/or grooming-induced oral exposure are occurring in addition to inhalation exposure.

USEPA memo, p. 5, 6th bullet: "DPR indicated EPA has waived requirements for future studies due to the severe acute toxicity. EPA's HASPOC [Hazard and Science Policy Council] actually recently recommended that a special acute inhalation study is required and that it should include respiratory histology, GSH measurements, kinetics / tissue dosimetry. HASPOC also

recommended a range-finding study to determine appropriate doses for further studies, such as a 2-generation reproductive study and acceptable acute and subchronic neurotoxicity studies."

DPR response: We acknowledge this point and have added most of the quoted passage to the revised phosphine RCD as footnote #1.

3. Risk Characterization / Epidemiology & Incidents (USEPA memo, page 6)

USEPA memo, p. 6, 2nd, 3rd and 4th bullets: USEPA provided general guidance regarding the handling of epidemiologic information in the RCD, including the following: (1) "The RCD cites a number of epidemiological data sources by various investigators. The specific studies are summarized and the outcomes (*eg*., odds ratios) are presented and summarized. EPA has developed an approach for the consideration of such data into risk assessment based on modified Bradford Hill criteria... EPA recommends that DPR utilize this approach to revise how these data are presented in the RCD." (2) "Research efforts focused on existing epidemiological cohorts, appropriate for this assessment, should be described at least qualitatively (*eg*., Agricultural Health Study). (3) "Epidemiological findings should be evaluated in a context of timing of the findings relative to critical regulatory decisions."

DPR response: As noted by USEPA, the draft RCD contains summaries of several epidemiologic studies. There are, in addition, several incident account summaries. The purpose of these summaries was to emphasize the toxic consequences of phosphine exposure to occupational cohorts and to the general public. Unfortunately, neither the exposure concentrations nor the exposure times were sufficiently characterized from a risk assessment standpoint to form a basis for risk calculations (*i.e*., margins of exposure). We continue to hold this position and do not anticipate revising the RCD with regard to these points.

USEPA memo, p. 6, 7th bullet: "DPR adjusted animal NOELs by an uncertainty factor of 100 to calculate a concentration of concern for each exposure duration considered in their assessment. EPA uses a different methodology for defining human equivalent concentrations (i.e., RfC methodology) that is available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=719934#Download. This methodology eliminates the need for a factor of 3 in the inter-species uncertainty factor so EPA uses a factor of 30 as a starting point to evaluate pesticides for this situation. DPR used a UF of 100 in the RCD as their method does not account for this difference."

DPR response: DPR did not calculate a human equivalent NOEL concentration, but rather used the absolute air concentrations employed in the critical inhalation toxicity studies to

establish the acute RfC value of 0.05 ppm. Use of absolute air concentration for both the MOE and RfC calculations was explained in the RCD (Section V.A.1.a.) as follows:

> "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 (≤40 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."

While not fully stated in their critique, USEPA's use of an uncertainty factor of 30 (as opposed to DPR's factor of 100) was presumably based on an intrahuman factor of 10 and an interspecies factor of 3. However, details on the interspecies factor were not provided, making it difficult to know whether it was the pharmacodynamic (receptor-related) or pharmacokinetic (distribution-related) component of the default 10x factor that was dropped in order to obtain in the 3x factor. In any case, DPR's use of a 10x interspecies factor for acute toxicity, with its assumption of the 3x pharmacodynamic and 3x pharmacokinetic factors, was likely to be health protective since neither factor may be formally necessary to estimate risk if death occurs through direct interaction with lung tisssue (in other words, the 10x interspecies factor may not be necessary at all). But since there was little detailed understanding of phosphine's mechanism(s) of toxicity, both 3x factors were retained along with the intrahuman factor of 10. The total uncertainty factor will thus remain 100.

The subchronic / chronic RfC of 0.01 ppm in the draft RCD raises questions in this regard, as it was based on toxicologic endpoints that may have involved absorption and thus required calculation of a human equivalent NOEL. However, absent mechanistic evidence, we calculated this value in the same way that we calculated the acute value.

USEPA memo, p. 7, 1st bullet: "More detail needs to be provided (*eg*., p. 53) regarding the potential for exposure from ambient air and why it is not of concern. May want to cite any research plans associated with the TAC network, or other pertinent documents, where the potential for phosphine exposures would have been discussed. Also, if there are environmental fate characteristics which would minimize the potential for such exposures they should also be discussed..."

DPR response: The draft RCD simply summarized a brief treatment of the potential for ambient exposure that appeared in the draft EAD (pp. 96-97). The EAD concluded that there was little chance of such exposure. Any enhanced discussion of the potential for ambient exposure should be undertaken by the Worker Health and Safety Branch of DPR if they deem it necessary.

4. Risk characterization / Risk Assessment Findings (USEPA memo, page 7)

USEPA memo, p. 7, 6th bullet: "Please consider revising or removing 'Section VI. Issues Related to Food Quality Protection Act.' Of particular concern are the statements made in part C which discusses *in utero* effects based on epidemiological studies (*eg*., Garry et al. 2002 and O'Malley *et al.*, in press). EPA has several concerns over the interpretation of the epidemiological data presented in the RCD."

DPR response: In the absence of more defined objections, this section will remain intact in the revised RCD.

Department of Pesticide Regulation

Brian R. Leahy
Director

M E M O R A N D U M

Edmund G. Brown Jr.
Governor

TO: Sheryl Beauvais, Ph.D.
Senior Toxicologist
Worker Health and Safety Branch

FROM: Ian Reeve, Ph.D. *(original signed by I, Reeve)*
Staff Toxicologist
(916) 323-7617

DATE: June 12, 2014

SUBJECT: RESPONSE TO ENVIRONMENTAL PROTECTION AGENCY COMMENTS ON HS-1888: ESTIMATION OF EXPOSURE TO PERSONS IN CALIFORNIA TO PHOSPHINE

The draft exposure assessment document (EAD), for aluminum phosphide, magnesium phosphide, and phosphine was prepared on January 14, 2013 by the Worker Health and Safety (WHS) Branch of the Department of Pesticide Regulation (DPR). The EAD and the associated draft risk characterization document (RCD) were sent out for external review. The Environmental Protection Agency (EPA) provided comments on the information in the EAD and RCD in a memo dated April 24, 2013. DPR appreciates EPA's review. This memo contains responses to EPA's comments. The comments on the RCD will be addressed by the Medical Toxicology Branch.

Comment 1: The assessment is based on data generated by NIOSH and a registrant that are from the late 1980's and 2002, respectively. Characterization should be provided regarding the representativeness of these data relative to current fumigation practices and settings.

Additional language characterizing the representativeness of the exposure data relative to the current fumigation practices and settings was incorporated throughout the EAD.

Comment 2: Characterization should also reflect any evolution of permit conditions in California.

One permit condition was generated for the use of aluminum phosphide and magnesium phosphide in California. It pertains to the use of aluminum phosphide and magnesium phosphide and was described in the EAD: The permit conditions issued by DPR to the county agricultural commissioners contain the following requirements: "Use of aluminum and magnesium phosphide is strictly prohibited around all residential areas, including single and multi-family residential properties, nursing homes, schools (except athletic fields, where use may continue), day care facilities, and hospitals." (DPR, 2012). In the EAD, for burrowing pest fumigation, this condition led to the use of the buffer zone of 100 feet for the occupational and residential

bystander scenarios. As described in the EAD, due to this 100 foot buffer zone and the measured air concentrations of the registrant study, no exposure is anticipated for the residential bystander.

Comment 3: If data evaluation records are available for these studies it would aid in a review process. Perhaps a separate section in the document should be included to discuss the scientific credibility of each exposure data source used in the assessment. The overall quality of the assessment is difficult to understand without that type of discussion.

Evaluation of the data and its potential effects on the exposure estimates was presented in the exposure appraisal section of the EAD.

Comment 4: Label requirements for PPE and respirator recommendations were not verified by EPA.

Product label PPE requirements and recommendations were used by DPR to select protection factors.

Comment 5: The characterization of the potential for dermal exposure differs from the risk characterization document. The exposure assessment uses an analogy comparing phosphine penetration in cement and stored commodities to a potential for dermal absorption in workers. The risk assessment document says just that no data are available. EPA does not concur with the analogy because treatment concentrations and the time exposed are not the same as experienced by workers. Also, DPR should consider the discrepancy between the two documents.

The statement in the risk characterization document about there being no data available for assessing dermal exposure is true. This was also stated in the EAD, "No studies on the dermal absorption of phosphine, which is a gas with a vapor pressure of 29,300 mmHg at 25ºC (HDSB, 2011), were discovered." The description of other studies measuring the penetrating ability of phosphine, and the product label statement mentioning the ability of phosphine to penetrate concrete were included in the EAD to bring up the possibility of dermal absorption by workers. This information was not intended to be analogy. The potential for dermal absorption of active ingredients must be addressed in the EADs. In the case of phosphine, dermal absorption may occur and, since no data were available to quantitate absorbed amounts, the estimates generated may underestimate exposure.

Comment 6: Incidents were only considered from California but other incidents outside the state, especially those of a more severe nature, should be considered as they could be informative.

The incident descriptions obtained from the Pesticide Illness Surveillance Program database are the most recent recorded cases in California and are the most relevant to assessing the potential causes of excessive exposures in the state.

Comment 7: An inherent difference exists between CDPR and EPA risk assessments in that durations of exposure are defined differently between the two Agencies. This issue has been addressed before in other forums.

The durations used for the exposure estimates ranged from daily exposures to annual exposures. The daily exposures represent the full work day period. Shorter exposure period data (e.g., 5 min), were available but were not compatible with the associated toxicity studies.

Comment 8: Risk findings are made in some cases are based on exposure data which are very limited. For example, in Table 11 on page 34 there are two different subcategories of exposure both with very low numbers of monitoring units (as low as 3 in one of the two scenarios). Consider, as an alternative, possible combinations of like activities in order to base decisions on larger datasets.

The low number of monitoring units reduces our confidence in the exposure estimates. The air concentration data are grouped according to the sampling time and worker location. However, to consolidate data further (i.e., combining data for different sampling times and worker locations), would reduce the specificity of the estimates.

Comment 9: The DPR assessment cites the ANSI standard for respiratory protection factors that are outdated. EPA uses the OSHA protection factors available at http://www.osha.gov/Publications/3352-APF-respirators.pdf which alter the findings of the DPR assessment because ANSI used a PF of 100 for full faced respirators and OSHA has assigned a PF of 50 for these devices.

The outdated ANSI standard protection used in the EAD for the full face-piece air-purifying respirator is 99%. This type of respirator, equipped with a phosphine canister, is what would most likely, due to its portability, be used by the worker in phosphine air concentrations at or below 15 ppm. The OSHA assigned protection factor for this type of respiratory protection is 50 or 98%. Exposure estimates incorporating the protection factor for the full face-piece respirator phosphine canister combination were revised to reflect the OSHA protection factor.

Above 15 ppm, the full face-piece SCBA in pressure-demand mode would be used. This device has an OSHA assigned protection factor of 10,000 or 99.99%. This protection factor is the same as that used in the EAD for this device.

Comment 10: This is a general issue which may apply to both DPR and EPA risk assessments but it is worth noting. The protection factor for SCBA (Self Contained

Breathing Apparatus) varies depending upon how it's used. For full face pieces, in demand mode SCBAs have a protection factor of 50 and in continuous flow mode they have a protection factor of 1000. On page 18 and in Table 7 (pg 19) of the document the PF 50 is cited which seems appropriate given how SCBAs are used for routine tasks. However, in Table 13 (pg 38) it appears the protection factor used in the calculations is 1000. The document should be checked for consistency.

Based upon language in the product labels and the NIOSH Pocket Guide to Chemical Hazards, for estimated phosphine concentrations above 15 ppm, the SCBA in pressure-demand mode was utilized for estimating exposure in the EAD. The OSHA assigned protection factor for this device is 10,000. This value is expressed by DPR as 99.99%.

Table 7 contains NIOSH respiratory protection guidelines. No protection factors are listed in the table. However, recommended phosphine air concentrations for various levels of respiratory protection are listed.

Comment 11: Community based exposures from ambient air should be discussed in more detail in the document especially in light of recent efforts focused on environmental justice related issues. More details should also be provided from the Han (2000) citation. Phosphine is not in the TAC network, nor does it appear to have been included in any special monitoring studies outside of a CARB study conducted in 2008.

Phosphine is not included in the list of pesticidal active ingredients monitored by DPR in its Air Monitoring Network, which is only able to monitor a finite set of chemicals. A total of 34 chemicals included in the Air Monitoring Network list were prioritized based on criteria that included high use, volatility, high priority for risk assessment, and the feasibility of inclusion in a multi-residue monitoring method. Phosphine did not meet the last criterion.

However, exposures to phosphine in ambient air away from applications are anticipated to be equal to or less than bystander exposures, as the highest pesticide concentrations in air occur adjacent to an application. Bystander exposure estimates are thus health-protective estimates for airborne phosphine exposures both adjacent to and away from applications. This information was added to the EAD. Han (2000) was cited because its results suggested a potential non-pesticidal source for phosphine in California; however, the study was conducted in China and for that reason was not discussed in detail in the EAD.

Comment 12: There should be a better cross walk between related tables such as those presenting data (e.g., Table 8 and Table 12).

Footnotes in tables containing exposure estimates (such as Table 12) mention tables summarizing the studies on which the estimates are based.

Comment 13: More discussions should be provided regarding the uncertainties associated with adjusting occupational exposure data for fumigants by application rate since exposures can occur based on the characteristics of a particular facility, how well a treated area is sealed, or how aeration takes place. Given these factors, exposures may not be expected to be as proportional to treatment rates (i.e., concentration x time) as conventional pesticides.

Discussion concerning uncertainties associated with adjusting the phosphine air concentration to either the estimated seasonal application rate or the maximum product label application rate was added to the appraisal section of the EAD. In addition, a table comparing the exposure study application rates and the estimated seasonal and product label maximum application rates was added to the appraisal section.

Comment 14: The PEL was used as the basis for estimating residential bystander exposure for all durations of exposure and it was adjusted for number of months of typical treatments when estimating annual exposures. This approach did not utilize modeling to define peak emission values for other shorter exposure periods which historically have been the major risk concern for fumigants. EPA will model residential bystander exposure using PERFUM when it completes its registration review risk assessment.

Although PERFUM modeling can be performed by the Environmental Modeling Branch of DPR, the resources are limited and, as a result, no modeling was performed to define peak emission values for short exposure periods. However, short-term exposures cannot legally exceed the 15-min TWA STEL of 1 ppm. In addition, for the exposure study to be useful, extremely short-duration exposure toxicity studies which have a clear toxic endpoint would be necessary.

Comment 15: This is a general issue which may apply to both DPR and EPA risk assessments but it is worth noting. EPA is looking into the legality of regulations for ship holds, particularly if vessels are not of United States registry.

Comment noted. No response needed.

Comment 16: More details should be provided regarding the dermal monitoring discussion on page 89 of the document.

This portion of the EAD is not a discussion of dermal exposure monitoring, but a summary of a study considered for use in estimating exposure. The workers' clothes in the study were contaminated with aluminum phosphide dust. However, these types of workers are located outdoors. Hence, the phosphine which is generated would likely volatilize off of the clothing and away from the skin. The phosphine from the contaminated clothing would probably be more of an inhalation exposure issue in this scenario. Dermal absorption would potentially be more of an

issue for workers in enclosed environments containing persistent levels of phosphine, especially if effective respiratory protection reduces inhalation exposures.

Comment 17: More details of the origin of the 100 foot buffer specified for occupational bystanders for burrowing pest application (pg 96) should be provided.

Details of the origin of the 100 foot buffer-zone were added to the EAD. This buffer zone for burrowing pest applications was a requirement instituted by EPA in 2010.

Reference

DPR (2012). Pesticide Use Enforcement Program Standards Compendium: Vol. 3, Restricted Materials and Permitting. Department of Pesticide Regulation, California Environmental Protection Agency, 1001 I St., P.O. Box 4015, Sacramento, CA 95812-4015. http://www.cdpr.ca.gov/docs/enforce/compend/vol_3/rstrct_mat.htm

cc: Ann Hanger, Senior Environmental Scientist (Specialist), Registration Branch

PHOSPHINE PRODUCERS ASSOCIATION

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19 April 2013

California Department of Pesticide Regulation
Risk Assessment (Phosphine)
Attn: Ms. Ann Hanger
Pesticide Registration Branch
Department of Pesticide Regulation
1001 I Street
P. O. Box 4015
Sacramento, CA 95812- 4015

Re: 2013 Phosphine Risk Assessment Documents

Dear Ms. Hanger:

This letter is in response to the 2013 Phosphine Risk Assessment documents presented to D&D Holdings, Inc., United Phosphorus, Inc., Cytec Industries, Inc. and Bernardo Chemicals, Inc. The comments are being submitted by the Phosphine Producers Association (PPA) and are as follows:

RISK CHARACTERIZATION DOCUMENT

1. Sub-Chronic NOEL (No Observed Effect Level)

California Department of Pesticide Regulation (CDPR) selected the NOEL for sub-chronic toxicity to be 1 ppm due to findings of "palpebral closure, slowed respiration and decreased body temperature" at 3 ppm.

The PPA disagrees with this selection of the sub-chronic NOEL at 1 ppm for the following reasons:

a. In the Schaefer's study, observations of total palpebral closure (sleeping behavior) were also noted prior to exposure in animals assigned to both control (female) and treated groups. Therefore, suggesting that this finding is a treatment-related effect is questionable.

b. The finding of palpebral closure was sporadic, i.e., the only statistical significant increase in incidence (%) was noted at week 4 and in males only. If this is a treatment-related effect, both males and females would be affected and the effect would persist to the end of the study (week 13).

c. Slowed respiration was noted at weeks 8 and 13, but only in males with no statistical difference detected. The fact that this finding was noted only in one sex and only occasionally suggests that this is not a treatment related effect. Further, observation of slowed respiration is very subjective.

d. Decrease in body temperature was noted but only in one sex (male) at week 13 and the decrease is within the normal body temperature range found in rats.

e. The findings of palpebral closure, slowed respiration and lower body temperature are not uncommon in an inhalation study. The biological and toxicological significance of these findings are questionable.

f. The findings of palpebral closure, slowed respiration and decreased body temperature are incidental and sporadic; they are not treatment related effects since they are observed only in one study (Schaefer). Indeed, no similar findings were noted in a 2-year inhalation study in rats (Newton, 1989) at 3 ppm or in other sub-chronic studies.

Using a weight of evidence approach, the PPA requests CDPR to reconsider the NOEL for sub-chronic at 3 ppm. The sub-chronic NOEL of 3 ppm is supported by the developmental toxicity NOEL of 4.9 ppm in rats.

2. Chronic NOEL

The chronic NOEL suggested by CDPR is 1 ppm.

The PPA disagrees with CDPR's establishment of the chronic NOEL at 1 ppm based on a sub-chronic study for the following reasons:

a. A sub-chronic NOEL could be used in lieu of a chronic NOEL only when chronic data are not available. For phosphine, CDPR has reviewed and evaluated a chronic 2-year inhalation study in rats

(Newton 1989), which was classified as "acceptable" with a NOEL established by CDPR at 3 ppm.

b. The 2-year inhalation study in rats (Newton, 1989) follows Guidelines and is in compliance with all Good Laboratory Practices (GLP) requirements. In the study, there were no treatment related effects (body weight, feed consumption, clinical laboratories, ophthalmoscopy, gross pathology, organ weights, histopathology and tumor incidence). Therefore, the NOEL of 3 ppm from this "acceptable" study should be used as the NOEL for chronic toxicity.

c. The sub-chronic NOEL of 1 ppm was established based on sporadic palpebral closure, incidental slower respiration and questionable lower body temperature in males at week 13. These findings should not be considered as treatment related effects since none of these findings was found in the 2-year chronic inhalation study or in other sub-chronic studies. The validity of the sub-chronic NOEL at 1 ppm is disputable and, therefore, should not be used as either sub-chronic or chronic NOEL.

3. Determination of Reference Doses (RfDs)

The PPA disagrees with CDPR's selection of the sub-chronic NOEL at 1 ppm and the chronic NOEL at 1 ppm based on sub-chronic data. The PPA feels the following RfDs are more appropriate:

Acute RfC = Critical acute NOEL ÷ 100 = 5 ppm ÷ 100 = 0.05 ppm
Seasonal RfC – Critical subchronic NOEL ÷ 100 = 3 ppm ÷ 100 = 0.03 ppm
Annual RfC – Critical chronic NOEL ÷ 100 = 3 ppm ÷ 100 = 0.03 ppm

4. Risk Characterization

a. The PPA agrees with CDPR's approach in calculating the margin of exposure (MOE), which is the ratio of the critical NOEL value (acute; sub-chronic and chronic) divided by the estimated human exposure value. The CDPR concludes that many seasonal and annual use scenarios produced MOEs of under 100, indicating insufficient health protection for workers and bystanders under those scenarios.

However, the PPA disagrees with CDPR's conclusion since many MOEs should be re-calculated using the suggested NOELs of 3 ppm for both sub-chronic and chronic endpoints instead of 1 ppm as selected by CDPR. Re-calculation of MOEs using the NOEL of 3 ppm may result in adequate MOEs in some exposure scenarios.

b. **Regulatory History**
The following incorrect information was found on page 5. Neither ECO_2FUME® Fumigant Gas nor VAPORPH_3OS® Phosphine Fumigant are labeled for use in burrows. The following phrase should be deleted from the first paragraph: "preharvest treatment of pest burrows in agricultural and non-agricultural areas".

CALIFORNIA EXPOSURE ASSESSMENT DOCUMENT (EAD)

1. This EAD deals with exposure to phosphine, aluminum phosphide, and magnesium phosphide. The exposure estimates generated in this document are organized according to the type of fumigation or aeration followed by the type of structure, if applicable, and the exposure scenario (e.g., applicator, aerator, occupational bystander, or residential bystander). The author generated short term exposure limits (STEL), permissible exposure limit (PEL), and time-weighted average (TWA) for an 8-hour working day for different exposure scenarios (i.e., short term, seasonal, full year, etc.), and via different methods of fumigation applications in upright bins of grain elevators, box cars, train cars, warehouses, etc.

   The exposure estimates were associated with commodity fumigation (8 different types of structures). Exposure estimates were also generated for scenarios associated with spot fumigation, burrowing pest fumigation, etc. The MOE's (margins of exposure) were generated for short-term, intermediate term, and chronic term exposures. The highest measured air concentration of the registrant study for a given scenario was used to generate the short-term MOE, while the mean of the measured air concentrations was used to generate the intermediate and chronic MOE's. These inhalation air concentrations were expressed in mg/L. The air concentrations were converted from mg/L to ppm (at 25 degrees C) for ease of comparison to the EAD exposure estimates.

Registrants' review: Application levels used in this EAD were taken from registrants' submissions or calculated by Cal EPA. The PPA does not have sufficient resource on industrial hygiene to comment on the exposure estimates mentioned in this EAD.

2. The Exposure Assessment Document states that there are contradictory statements in the labeling for ECO_2FUME® Fumigant Gas and $VAPORPH_3OS$® Phosphine Fumigant that create uncertainty in estimating applicator exposure (the statement, found on p.112, is reproduced below).

   Granular and Cylinderized Gas Formulations
   Two primary sources of uncertainty in the exposure estimates used for the cylinderized gas and granular formulations are contradictory product label statements and lack of data. Three of the product labels for these formulations have contradictory statements about the proper location of the applicator during fumigation of a structure. The product label for EcoFume® contains the statement that the gas cylinder containing phosphine must be placed outside of the structures to be fumigated. However, the label also has the statement that the handler should, "never work alone when applying the fumigant from within the storage structure..." This type of contradictory language is also seen on the product label for $VAPORPH_3OS$®.

   These statements create uncertainty in estimating exposure for the applicator since the handler's location may be inside or outside of the structure during fumigation. However, for exposure assessment purposes, the applicator was assumed to be outside of the structure during fumigation. This seemed like a logical assumption since the interior levels of a fumigated structure could reach a sustained phosphine air concentration of 1000 ppm at the maximum application rate.

This language was part of the Risk Mitigation Measures required by U.S. EPA to be added to application manuals in response to the 1998 Reregistration Eligibility Decision (RED) for Aluminum and Magnesium Phosphide. In spite of Cytec's objections at the time, this language was required by U.S. EPA so that the language on cylinderized phosphine labels would be the same as language on metal phosphide labels.

The Phosphine Producers Association would like to thank CDPR for considering our position in the above listed comments. We certainly welcome any questions or an opportunity to discuss these specifics. You may contact me at 540-234-9281 or via e-mail snichols@degeschamerica.com.

Sincerely,

Susan Nichols

Susan Nichols, Chairman
Phosphine Producers Association

/sn

Brian R. Leahy
Director

Department of Pesticide Regulation

Edmund G. Brown Jr.
Governor

M E M O R A N D U M

TO: Tom Moore, Ph.D.
Acting Branch Chief
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

FROM: Andrew Rubin, Ph.D., D.A.B.T.
Staff Toxicologist, Health Assessment Group
Medical Toxicology Branch
Dept. of Pesticide Regulation, Cal-EPA

DATE: June 11, 2014

SUBJECT: RESPONSE TO THE PHOSPHINE PRODUCER'S ASSOCIATION COMMENTS ON THE PHOSPHINE RISK CHARACTERIZATION DOCUMENT

In a letter dated April 19, 2013, the Phosphine Producers Association (PPA) provided commentary on DPR's phophine risk characterization document (RCD draft of February 15, 2013). PPA made specific recommendations on both the RCD and the exposure assessment document. DPR's responses to the comments directed at the RCD appear in the following paragraphs. Citations are identified in the References section of the RCD.

1. Subchronic NOEL (PPA memo, pages 1-2)

PPA disagreed with the selection of the subchronic NOEL at 1 ppm from the study of Schaefer (1998b) for several reasons, including (a) total palpebral closure was "noted prior to exposure in both control (female) and treated groups"; (b) palpebral closure was sporadic, with the only statistically significant increase occurring among males at week 4; (c) increased incidence of slowed respiration was noted "only occasionally" (weeks 8 and 13) and only in males, suggesting that it was not a treatment effect; (d) decrease in body temperature occurred "only in one sex (male) at week 13 and the decrease is within the normal body temperature range found in rats"; (e) "the findings of palpebral closure, slowed respiration and lower body temperature are not uncommon in an inhalation study"; and (f) palpebral closure, slowed respiration and decreased body temperature were incidental and sporadic findings.

DPR response: PPA made reasonable points regarding the selection of the critical subchronic NOEL, several of which have now been added to the Risk Appraisal section of the RCD (section V.A.1.b.). However, the subchronic NOEL designation will remain at 1 ppm due to the dose dependence of all three signs (for palpebral closure particularly among males, but also among high-dose females), the proximity of the critical value to NOELs and LOELs suggested in three other subchronic studies (Omae *et al.*, 1996; Waritz and Brown, 1975; and Barbosa *et al.,* 1994), and the proximity of the NOEL to an acute lethal dose.

2. Chronic NOEL (PPA memo, pages 2-3)

PPA disagreed with DPR's use of the critical subchronic NOEL of 1 ppm to establish the critical chronic NOEL for several reasons, including (a and b) the existence of an acceptable chronic inhalation study with a NOEL established at the high dose of 3 ppm based on an absence of effects at that dose (Newton, 1998—incorrectly identified in the PPA memo as "Newton, 1989"); and (b) the weakness of the 1-ppm subchronic NOEL.

DPR response: With the establishment of 1 ppm as the critical subchronic NOEL (see #1 above), DPR felt it prudent for health-protective reasons not to assign a separate chronic NOEL that was greater than that value.

3. Determination of reference doses (PPA memo, page 3)

Because PPA disagreed with DPR's subchronic / chronic NOEL designations, they also disagreed with the resultant reference dose calculations for those exposure scenarios.

DPR response: DPR will continue to use 1 ppm for the subchronic and chronic critical NOELs (see responses to items 1 and 2 above) and thus stands by the reference dose calculations in the draft RCD.

4. Risk characterization (PPA memo, page 3)

PPA holds (a) that since the subchronic / chronic NOEL designations were, in their view, incorrect, the resultant MOEs were also incorrect for those scenarios; and (b) "Neither ECO_2FUME® nor $VAPORPH_3OS$® Phosphine Fumigant are labeled for use in burrows. The following phrase should be deleted from the first paragraph: 'preharvest treatment of pest burrows in agricultural and non-agricultural areas'.

DPR response: (a) DPR will continue to use 1 ppm for the subchronic and chronic critical NOELs (see responses to items 1 and 2 above) and thus stands by the MOE calculations in the draft RCD; and (b) The entire passage reads: "Food tolerances for phosphine residues were necessitated by the following practices: post-harvest fumigation with phosphine gas *or with compounds that produce phosphine gas* [emphasis added], preharvest treatment of pest burrows in agricultural and non-agricultural areas, and fumigation of processed foods and animal feed." It should thus be clear that it was not referring only to ECO_2FUME® and $VAPORPH_3OS$®, but included phosphine generating compounds, as well. However, for greater clarity, this passage has

been isolated in its own paragraph in the revised RCD, minimizing the possibility of concluding that it referred only to ECO_2FUME® and VAPORPH_3OS®.

Brian R. Leahy
Director

Department of Pesticide Regulation

Edmund G. Brown Jr.
Governor

M E M O R A N D U M

TO: Lisa Ross
Environmental Program Manager II
Worker Health and Safety Branch

FROM: Sheryl Beauvais *(original signed by S. Beauvais)*
Senior Toxicologist
916-445-4268

DATE: June 12, 2014

SUBJECT: REGISTRANT COMMENTS ON PHOSPHINE EXPOSURE ASSESSMENT DOCUMENT – HS1888

In April 2013, the Phosphine Producers Association sent comments on the California Department of Pesticide Regulation's draft Risk Characterization Document (RCD) and draft Exposure Assessment Document. Comments on the RCD will be addressed separately by the Medical Toxicology Branch.

Two comments were made regarding the EAD:

Comment 1: Application levels used in this EAD were taken from registrants' submissions or calculated by Cal EPA. The PPA does not have sufficient resource on industrial hygiene to comment on the exposure estimates mentioned in this EAD.

No response to this comment is required.

Comment 2: The Exposure Assessment Document states that there are contradictory statements in the labeling for EC02FUME® Fumigant Gas and VAPORPH30S® Phosphine Fumigant that create uncertainty in estimating applicator exposure…This language was part of the Risk Mitigation Measures required by U.S. EPA to be added to application manuals in response to the 1998 Reregistration Eligibility Decision (RED) for Aluminum and Magnesium Phosphide. In spite of Cytec's objections at the time, this language was required by U.S. EPA so that the language on cylinderized phosphine labels would be the same as language on metal phosphide labels.

No response to this comment is required.

cc: Ian Reeve, Staff Toxicologist (Specialist), Worker Health and Safety Branch
Ann Hanger, Senior Environmental Scientist (Specialist), Registration Branch