CHRONIC TOXICITY SUMMARY

PHOSPHINE

(hydrogen phosphide; phosphorus trihydride; Celphos; Phostoxin)

CAS Registry Number: 7803-51-2

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.8 μg/m^3** (0.6 ppb)
Critical effect(s)	Decreased body weight gain in mice
Hazard index target(s)	Respiratory system; alimentary system; nervous system; kidney; hematopoietic system

II. Chemical Property Summary (HSDB, 1995, except as noted)

Description	Colorless gas
Molecular formula	PH_3
Molecular weight	34 g/mol
Vapor density	1.17 (air = 1)
Boiling point	–87.7°C
Vapor pressure	20 atm @ –3°C (Weast, 1980)
Solubility	0.26 volumes in water @ 20°C; soluble in alcohol, ether (Sax and Lewis, 1989)
Conversion factor	1.39 mg/m^3 per ppm at 25ºC

III. Major Uses and Sources

Phosphine is used as an agricultural fumigant against insects and is among the most acutely toxic of the fumigant gases (HSDB, 1995). In its use as a fumigant, application of aluminum, magnesium, or zinc phosphide pellets generates phosphine gas upon exposure to moisture. Because of high volatility, phosphine residue dissipates from treated material upon ventilation. Inadequate sealing of materials during the course of treatment can result in unplanned environmental exposure.

Phosphine is also used by the semiconductor industry as a chemical doping agent for electronic components (n-type semiconductors) (HSDB, 1995). Other minor sources/uses of phosphine are in chemical syntheses: specifically, in preparations of phosphonium halides, for polymerization initiation, and as condensation catalysts. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 3312 pounds of phosphine (CARB, 1999). In 2000, more than 120,000 pounds of phosphide compounds (including 119,519 pounds of aluminum phosphide and 1607 pounds of zinc phosphide) were applied in California agriculture (CDPR, 2001). In the

presence of water these phosphides break down to phosphine. However, the fraction emitted as phosphine is not known.

IV. Effects of Exposures to Humans

Toxicity among 22 workers intermittently exposed to phosphine levels of 0.17-2.11 ppm in air from fumigation activity ranging over 0.5 to 29 years (mean = 11.1 years) was evaluated (Misra *et al.*, 1988). The subjects were interviewed within one day of fumigation activity and reported that symptoms subsided when phosphine was not in use. The most frequently reported symptoms include dyspnea (31.8%), headache (31.8%), chest tightness (27.3%), cough (18.2%), anorexia and epigastric pain (18.2%), finger paresthesia and numbness (13.6%), and giddiness, numbness, and lethargy (13.6%). No change in motor or sensory nerve conduction velocity was found.

A similar spectrum of toxic effects among workers involved in grain storage at a seaboard terminal has been reported (Jones *et al.*, 1964). Among 69 men exposed to breathing zone phosphine levels of 0-35 ppm for as long as 16 hours per day, the authors report symptoms of multiple origins. These include gastrointestinal (diarrhea, nausea, epigastric pain, vomiting), cardio-respiratory (chest tightness, dyspnea, pain in chest, palpitations, retrospinal pain), and central nervous (headache, dizziness, staggering gait) systems. Symptoms were reported to appear only at the time of exposure and apparently were reversible.

In another report of chronic occupational exposure, authors cited the appearance of chronic bronchitis, anemia, and digestive disorders (Eichler, 1934).

Most literature reports of human toxic health effects of phosphine, however, come from case reports of acute exposures. Some are suggestive of potential chronic toxicity endpoints because of the irreversible nature of the effect. In a case report of phosphine poisoning of 29 people exposed by inhalation on a grain freighter, pathological findings included evidence of urinary tract injury (occult blood), liver damage (bilirubinuria and increased SGPT, GGPT, and LDH), and myocardial damage (increased MB fraction of CPK, abnormal ECG) (Wilson *et al.*, 1980). A-two-year old child who died as a result of the exposure showed myocardial necrosis with mononuclear infiltrates, pulmonary edema with damaged epithelia, pleural effusion, and an enlarged spleen. In another case report exposure of a 7-months pregnant, 24-year-old woman to aluminum phosphide from a nearby grain storage site was lethal (Garry *et al.*, 1993). There was evidence of severe pulmonary edema, necrosis of individual hepatic cells, and anoxic change in Purkinje cells of the cerebellum. These reported deaths of a small child and a pregnant woman exposed together with individuals who survived exposure to phosphine suggest that there may be sensitive human subpopulations. In another case report of acute phosphine poisoning by inhalation, Schoonbroodt *et al.*, (1992) observed necrosis of the nasal mucosa, delayed onset of pulmonary edema, and myocardial injury. Chopra *et al*. (1986) treated sixteen patients with aluminium phosphide poisoning during 1985. Findings included mucosal necrosis and cardiac abnormalities (due to hypoxemia). Renal failure (1/16), proteinuria (1/16), and increased blood transaminases (2/16) resulted from oral exposure to phosphine. The multi-organ involvement in toxicity suggests that phosphine is a broad-spectrum toxicant.

In a 1994 two deaths and three illnesses were reported due to phosphine fumigation of agricultural products in railroad cars (Perrotta *et al*., 1994). The annual report for the year 2000 of the American Association of Poison Control Centers' Toxic Exposure Surveillance System does not list fumigants as a separate category of pesticides (Litovitz *et al*., 2001). However, two of the case reports of fatalities, that were presented in abstract form, were due to aluminum phosphide.

V. Effects of Exposures to Animals

A subchronic inhalation toxicity study of phosphine was conducted in Balb-c mice (Barbosa *et al.*, 1994). Twelve animals/sex/dose group were exposed for 6 hours/day, 5 days/week for 13 weeks to 0, 0.3, 1.0, or 4.5 ppm phosphine. Non-cancer toxicity endpoints included reduction in weight gain and changes in relative organ weights of kidneys, lungs, liver, heart, brain and spleen. In the highest dose group, itching and scratching of the eyes, feet and tail, and decreased overall activity were observed. No diarrhea, loss of equilibrium, convulsions, seizures, or other neurological disturbances were noted. A dose-dependent decrease in total body weight gain was observed at all exposure levels with a greater effect observed in females ($p<0.0001$). Statistically significant decreases in relative organ weights (kidney, heart, and brain) were observed in males only at the 0.3 ppm exposure level ($p<0.001$). On the other hand, female mice showed increased relative organ weights (lungs, heart, and spleen) predominantly at higher doses (1.0 and 4.5 ppm; $p<0.001$). At 4.5 ppm phosphine absolute kidney and spleen weights were significantly increased in females ($p<0.01$). Increased frequencies of micronuclei in polychromatic erythrocytes from bone marrow and spleen were also seen at 4.5 ppm. This group also conducted a short-term repeated dose experiment. Six mice/sex/group were exposed to 5.5 ppm phosphine for 2 weeks (6 hrs/day, 5 days/wk). No statistically significant changes in weight gain were observed at the end of this exposure period.

In another subchronic inhalation toxicity study, male and female Fischer 344 rats (10/sex/group) were exposed to levels of 0, 0.37, 1.0, and 3.1 ppm phosphine for 6 hours per day, 5 days per week, for 13 weeks (Newton *et al.*, 1993). A higher dose group at 10 ppm was terminated prematurely (at 3 days) because of high mortality. A satellite group exposed to 5.1 ppm for 2 weeks was terminated after 13 days recovery. Observations of overt toxicity and viability were made at the time of each exposure; body weight and food consumption were monitored weekly; ophthalmic examination was done the day before termination; and hematological and clinical chemistry indices were measured after 4 and 13 weeks. Postmortem examination included gross necropsy, with particular attention to orifices, the cranial cavity, surfaces of the brain and spinal cord, nasal cavity and sinuses, the thoracic, abdominal, and pelvic cavities and viscera, and the cervical tissue and organs. Histopathology was performed on 10% buffered formalin-fixed/hematoxylin-eosin-stained tissues. Significant observations after 13 weeks of phosphine exposure included decreased hemoglobin, hematocrit, and erythrocytes in males in the 3.1 ppm dose group. Male rats in the 1 ppm dose group showed decreased weight gain. Increased incidence of small seminal vesicles was noted at 1 and 3.1 ppm, although no histological correlate was observed. Absolute and relative decreases in liver weight were observed in all exposed groups, but there was no evidence that this effect was dose-related. A significant

decrease in serum glutamic pyruvic transaminase (SGPT) was observed at 3.1 ppm, although the authors noted unusually high control levels. None of these effects were observed after the 4 week recovery period. Other effects of a transient nature noted during the exposure include decreased weight gain in female rats at 1 ppm, decreased food consumption at 0.37 ppm in males and females, and increased blood urea nitrogen (BUN) at 3.1 ppm. Observations in the 10 ppm group necropsied after 3 days of exposure included decreased erythrocytes, increased alkaline phosphatase, and increased kidney weight with coagulative necrosis of the tubular epithelium of the outer cortex. In a subchronic study of CD male and female rats under similar conditions (exposure to 0, 0.3, 1, or 3 ppm phosphine 6 h/day, 5 days/week for 13 weeks), no neurotoxicity was observed (Schaefer *et al*., 1998).

Newton *et al.* (1993) also examined developmental toxicity by exposing 24 pregnant female CD^R rats per group to 0, 0.03, 0.33, 2.8, 4.9, and 7.0 ppm phosphine. The highest dose group was terminated prematurely because of high mortality; all other animals were necropsied after 20 days for evaluation of maternal and fetal toxicity. Maternal toxicity endpoints included weight of ovaries and uteri, number of corpora lutea, pregnancy, and implantation rate. Fetal toxicity was evaluated by weight, number, and location of fetuses and resorptions, visceral malformations and variations, and skeletal changes after alizarin staining. No statistically significant differences from control animals were observed for any parameter at any dose, with the exception of a change in mean number of resorption sites ($p \leq 0.01$), mean resorption/implant ratio ($p \leq 0.05$), and incidence of females with resorption ($p \leq 0.05$), all at 0.03 ppm only. In the absence of this effect at higher dose levels, these observations are not considered useful in establishing a low adverse effect level.

A 35-day phosphine inhalation study was conducted exposing rats continuously to 0, 0.05, 0.2, 1.5, and 8.0 mg/m^3 phosphine (0, 0.036, 0.14, 1.1, and 5.8 ppm) in which hematological endpoints and histopathological changes of the lungs and kidneys were examined (Pazynich *et al.*, 1984). Observations include a statistically significant change in erythrocytes (increase followed by a decrease at day 35) and decreased hemoglobin at the 0.05 and 0.2 mg/m^3 dose levels, although the 1.5 mg/m^3 dose group did not show this change. Other significant changes, noted in the lowest dose group, included decreased peroxidase activity after 35 days exposure, decreased sulfhydryl group content in blood after 27 days, and decreased phagocytotic index after 21 days. Some histological changes were noted in the lungs, kidneys, and to a lesser extent, the liver, particularly in the higher dose groups, although the exact nature of the degenerative change is not well described. Unclear dose-response relationships and temporal aspects of the endpoints also make establishment of a low adverse effect level unreliable.

Two rats were exposed to 20 ppm phosphine for 14 days (4 hours/day) (Waritz and Brown, 1975). Animals were monitored for weight gain, and organs/tissues fixed in Bouin's solution and stained with trichrome were examined histopathologically. There were no reported histopathological effects, although there was slightly reduced weight gain in the exposed animals.

In a chronic study of phosphine (Newton *et al*., 1999), 60 male and female F344 rats per group were exposed via whole-body inhalation for 6 h/day, 5 days/wk for up to 104 wk to mean concentrations of 0, 0.3, 1, or 3 ppm phosphine. Three ppm (4.17 mg/m^3) was the maximum

exposure level because of lethality seen at the high exposure level (7 ppm = 9.73 mg/m^3) in previous repeat dose studies (Newton *et al*., 1993). Ten rats per sex per group were killed after 52 weeks of exposure. Survivors were killed after 104 weeks of exposure. There were no phosphine-related effects seen on clinical observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, or ophthalmology. There were no phosphine-related macroscopic findings or effect on absolute or relative organ weights. No histologic or morphologic alterations attributable to phosphine exposure were seen in the more than 40 organs and tissues examined. Under the conditions of this study, the authors found no treatment-related changes suggestive of a toxic or carcinogenic effect in rats following 52 weeks or 2 years of whole-body inhalation exposure to 0.3, 1, or 3 ppm phosphine. Thus 3 ppm is a chronic NOAEL for rats.

VI. Derivation of Chronic Reference Exposure Level

Study	Barbosa *et al*., 1994
Study population	Balb-c mice (12 animals/sex/group)
Exposure method	Discontinuous whole body inhalation exposure (0, 0.3, 1, or 4.5 ppm)
Critical effects	Decrease in body weight gain, increase in relative organ weights; increase in micronuclei
LOAEL	4.5 ppm
NOAEL	1 ppm
Exposure continuity	6 hr/day, 5 days/ week
Average experimental exposure	0.178 ppm for NOAEL group (1 x 6/24 x 5/7)
Human equivalent concentration	0.178 ppm for NOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	13 weeks
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Reference exposure level	0.0006 ppm (0.6 ppb; 0.0008 mg/m^3; 0.8 μg/m^3)

Supportive study	Newton *et al*., 1999
Study population	Rats (60 animals/sex/exposure level)
Exposure method	Discontinuous whole body inhalation exposure (0, 0.3, 1, or 3 ppm)
Critical effects	None
LOAEL	None detected
NOAEL	3 ppm
Exposure continuity	6 hours/day, 5 days/week
Average experimental exposure	0.53 ppm (3 x 6/24 x 5/7)
Human equivalent concentration	0.53 ppm (gas with systemic effects, based on RGDR = 1.0 using default assumption that lambda (a) = lambda (h))
Exposure duration	2 years
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	10 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference exposure level	0.005 ppm (5 ppb, 0.007 mg/m^3, 7 μg/m^3)

Newton *et al*. (1999) found no treatment-related changes suggestive of a toxic effect in F344 rats following 52 weeks or 2 years of whole-body inhalation exposure to 0.3, 1, or 3 ppm phosphine. Thus in this study 3 ppm is a chronic NOAEL for rats. Three ppm was set as the maximum level because in an earlier subchronic study in rats Newton *et al*. (1993) found lethality at 7 ppm. However, the chronic results of Newton *et al*. (1999) differ from the subchronic results of Newton *et al*. (1993), in which at least transient effects were seen in the hematopoietic system after 13 weeks at 3.1 ppm. In a subchronic study in mice (Barbosa *et al*., 1994), 4.5 ppm phosphine was a LOAEL and 1 ppm was a NOAEL for decrease in body weight gain. The results of Barbosa *et al*. (1994) indicated that mice may be more sensitive than rats. Thus, it was selected as the key study, and decrease in body weight gain was selected as the critical effect.

OEHHA has applied a subchronic uncertainty factor of 3 to account for the short duration of the Barbosa *et al*. (1994) study and an intraspecies uncertainty factor of 10 to account for human variability. Due to the general inconsistencies among the various studies in the database on phosphine, and in particular with the observation of mortality at 7 ppm in a short-term developmental study in rats (Newton *et al.,* 1993), it was considered prudent to include the full interspecies uncertainty factor of 10 (even though the HEC adjustment procedure could be applied) to acknowledge the severity of effect in at least one comparison study, and the additional uncertainty associated with the apparent wide and unpredictable variability between species and between different studies in the same species (rats). This results in a cumulative uncertainty factor of 100 to be applied to the NOAEL of 1 ppm in the subchronic study by Barbosa *et al*. (1994) and a chronic REL for phosphine of 0.8 μg/m^3 (0.6 ppb).

The U.S. EPA based its RfC of 0.3 μg/m^3 on the Barbosa *et al.* (1994) study, an adequate subchronic animal study for the derivation of a REL, and included a Modifying Factor (MF) of 3

for database deficiencies (lack of multigenerational reproduction studies). The criteria for use of modifying factors are not well specified by U.S. EPA. USEPA used its default interspecies uncertainty factor of 10 for a 13 week study.

The lack of adequate data on levels of chronic phosphine exposure to humans precludes development of a REL from human studies. The endpoint used in the determination of the REL (total body weight gain) showed a dose-related decrease with phosphine exposure in Balb-c mice. This endpoint is also consistent with that found by Newton *et al.* (1993), who noted dose-dependent decreases in body weight gain in Fischer 344 rats after a 13 week exposure regimen at 1 ppm, and Waritz and Brown (1975), who reported slightly decreased weight gain in rats exposed for 14 days to 20 ppm. Surprisingly Newton *et al*. (1999) did not find differences in body weight gain at either 1 ppm or 3 ppm and they did not comment on the discrepancy between their 2 reports. Although body weight changes or changes in food consumption were not addressed in human studies, the scant human data do relate phosphine exposure to a broad spectrum of toxic effects (gastrointestinal, cardio-respiratory, CNS). The decrease in weight gain found in the animal studies and reported changes in some relative organ weights (Barbosa *et al.*, 1994) suggest systemic toxicity.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for phosphine include the availability of data on multiple inhalation exposure concentrations and the observation of a NOAEL in a lifetime animal study. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the inconsistency of the dose-response relationship across rodent studies.

VIII. Potential for Differential Impacts on Children's Health

Based on the lack of a dose-response in developmental toxicity caused by exposing pregnant female rats to 4.9 ppm phosphine (Newton *et al*., 1993) , the proposed REL of 0.8 $\mu g/m^3$ (0.6 ppb) is likely to be protective of developing humans in utero. However, there is no direct evidence in the literature to quantify a differential effect of phosphine on infants and children.

IX. References

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