

Phosphine; CASRN 7803-51-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Phosphine

File First On-Line 01/31/1987

| Category (section) | Assessment Available? | Last Revised |
|---|-----------------------|--------------|
| Oral RfD (I.A.) | yes | 01/31/1987 |
| Inhalation RfC (I.B.) | yes | 07/01/1995 |
| Carcinogenicity Assessment (II.) | yes | 09/01/1992 |

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Phosphine

CASRN — 7803-51-2

Last Revised — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

| Critical Effect | Experimental Doses* | UF | MF | RfD |
|--|--|-----|----|----------------|
| Body weight and clinical parameters | NOEL: 0.51 mg/kg food converted to 0.026 mg/kg/day | 100 | 1 | 3E-4 mg/kg/day |
| Rat Chronic Oral Study | LOAEL: none | | | |
| Hackenburg, 1972 | | | | |

*Dose Conversion Factors & Assumptions: Food consumption of 5% bw/day; thus, 0.51 mg/kg of diet x 0.05 kg of diet/kg bw/day = 0.026 mg/kg bw/day

I.A.2. Principal and Supporting Studies (Oral RfD)

Hackenburg, U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. *Toxicol. Appl. Pharmacol.* 23(1): 147-153.

This study reported a no effects dose level for rats fed diet fumigated with phastoxin over a 2-year period. The mean phosphine concentration during that time period was 0.51 mg/kg of feed. Based on an average 5% food consumption and average rat body weight of 610.4 g (reported in the study), the phosphine dose can be calculated as 0.026 mg/kg bw/day. Hackenburg (1972) found a slight, statistically insignificant tendency for test females to gain weight faster than their control counterparts. There were no other differences between controls and treated rats in hemoglobin content, hematocrit, differential white blood cell count, glucose levels, SGPT, serum urea, prothrombin time, organ weights, or tissue histopathology. Survival rates and tumor incidences were similar between controls and experimental animals.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — Application of an uncertainty factor of 100 (10 for intraspecies extrapolation and 10 for sensitive population) to the rat NOEL of 0.026 mg/kg yields an RfD of 0.02 mg/day.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

The ACGIH (1984) has recommended a TLV of 0.3 ppm (0.42 mg/cu.m) for phosphine, based principally on an epidemiologic study by Jones et al. (1964). In this study, workers exposed intermittently to about 10 ppm phosphine gas experienced gastrointestinal, cardiorespiratory, and central nervous system symptomatology. Based on the TLV, an RfD of 0.021 mg/kg/day can be recommended. However, the Hackenburg (1972) study was a 2-year study in rats which explored a number of functional and morphologic endpoints. This study forms a better basis for an RfD.

I.A.5. Confidence in the Oral RfD

Study — Medium

Database — Medium

RfD — Medium

Confidence in the study can be considered medium to low because only a moderate number of animals/dose and one dose group was used, but an extensive methodology was employed to assure proper administration of the test compound and an extensive number of parameters were measured. The database can be considered medium to low because the effectiveness and safety of this chemical has long been reported, but few experimental oral studies are available. Thus, the overall rating for the RfD can be considered medium to low.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 08/19/1985

Verification Date — 08/19/1985

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for phosphine conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Phosphine

CASRN — 7803-51-2

Last Revised — 07/01/1995

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

| Critical Effect | Exposures* | UF | MF | RfC |
|--------------------------------------|--|------|----|-----------------|
| Decreased body weight | NOAEL: 1.4 mg/cu.m (1.0 ppm) | 1000 | 1 | 3E-4 mg/cu.m |
| Mouse Subchronic Inhalation Study | NOAEL(ADJ): 0.25 mg/cu.m NOAEL(HEC): 0.25 mg/cu.m | | | |
| Barbosa et al., 1994 | LOAEL: 6.3 mg/cu.m (4.5 ppm) LOAEL(ADJ): 1.12 mg/cu.m LOAEL(HEC): 1.12 mg/cu.m | | | |

*Conversion Factors and Assumptions: MW = 34. Assuming 25 C and 760 mmHg, NOAEL (mg/cu.m) = NOAEL (ppm) x MW/24.45 = 1.4. NOAEL(ADJ) = 1.4 mg/cu.m x (6 hours/24 hours) x (5 days/7 days) = 0.25 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarrespiratory effect, assuming periodicity was attained. Because the lambda values are unknown for the experimental animal species (a) and humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x lambda(a)/(h) = 0.25 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Barbosa, A., E. Rosinova, J. Dempsey and A.M. Bonin. 1994. Determination of genotoxic and other effects in mice following short-term, repeated-dose, and subchronic inhalation exposure to phosphine. *Environ. Molec. Mutagenesis*. 24: 81-88.

Four groups of 24 Balb-c mice each (12/sex) were exposed to either air (control), 0.3, 1.0, or 4.5 ppm phosphine, 6 hours/day, 5 days/week for 13 weeks. After duration adjustment and conversion, these concentrations corresponded to 0.00, 0.07, 0.25, and 1.12 mg/cu.m, respectively. Exposures were conducted by diluting concentrated phosphine gas with ambient air and metering the appropriate mixture into the individual cages. Endpoints evaluated were body weight and organ weights. Mice exposed to the highest concentration showed signs of itching around the face, tail, and feet during exposure and were less active at the end of each exposure than were other groups. No neurological disturbances were noted in this group. At the end of the exposure, there was a statistically significant inverse linear relationship between body weight and concentration, independent of sex. Biological significance, however, was attained only among females at the highest exposure, where the average body weight following the 13-week exposure period was 10% less than that of the corresponding control. Alterations in some organ

weights were noted, but they were not clearly related to dose and could have been due to the variability in body weights. No other noncancer endpoints were investigated or reported. A LOAEL of 4.5 ppm and a NOAEL of 1 ppm are designated based on this 10% decrease in final body weight, in comparison with controls.

It is assumed that phosphine is an *in vivo* inhibitor of oxidative phosphorylation. This designation is not meant to imply a direct causal relationship between the observed alteration in body weight and inhibition of oxidative phosphorylation. It is, however, well established that the chronic toxicity of other inhibitors of oxidative phosphorylation, such as cyanide (Philbrick et al., 1979), dinitrophenol (Horner, 1942), pentachlorophenol (Schwetz et al., 1978), and rotenone (U.S. Fish and Wildlife Service, 1983), does include alterations in body weights. Thus, although the effects of chronic phosphine exposure are still unknown, the actual adverse effects reasonably may be expected to include body weight alterations such as those observed in this subchronic study in mice and in the subchronic study of Newton et al. (1993) with rats.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — Full factors of 10 each are used for sensitive human subpopulations and the use of a subchronic study. A partial factor of 3 is applied for deficiencies in the database (i.e., lack of multigenerational reproduction studies). Newton et al. (1993) reported an absence of effects in respiratory tract tissues subchronically exposed to phosphine. A partial factor of 3 also is used for interspecies extrapolation due to the use of dosimetric adjustments. The total uncertainty factor is 1000.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Acute exposure to phosphine can result in neurological, gastrointestinal, and respiratory effects in humans (Price and Chambers, 1990; WHO, 1988; Gupta et al., 1995). Twenty-two workers (mean age of 48 years) were examined after fumigating with aluminum phosphide (Misra et al., 1988). Mean phosphine concentration in the breathing zone of six workers during fumigation ranged from 0.78-0.98 ppm (1.1-1.4 mg/cu.m, respectively). Respiratory symptoms included suffocation, breathing difficulty, and chest tightness lasting from 15 minutes to 3 hours. Neurological symptoms, most commonly headaches (31.8% of the workers), and gastrointestinal effects also were reported. After touching the tablets, numbness and paraesthesia in the fingers were reported in 13.6% of the workers. Alcohol consumption and smoking was reported in 50 and 68% of workers, respectively. These results are difficult to interpret because no information regarding control groups, if any were employed, was given.

Crew members aboard a grain freighter were exposed to phosphine gas (Wilson et al., 1980). Symptoms that were prevalent in the exposed crew included shortness of breath, cough, vomiting, fatigue, headache, drowsiness, paresthesias, and tremor. The levels of phosphine in the ship ranged from 0.5-30 ppm. Gastrointestinal findings also were reported following phosphine exposure. Platelet and erythrocyte count were reduced in an individual poisoned by phosphine [Verga and Belloni, 1958 (cited in WHO, 1988)]. The hemoglobin concentration was 55%. The patient recovered, and the hematological levels returned to normal. Interpretation of these studies is limited due to experimental protocol deficiencies. Also, the exposures in these case studies are not to pure phosphine gas, but to reaction products of metal phosphides that have not been chemically or toxicologically characterized.

Barbosa and Bonin (1994) examined a small cohort of 31 fumigators who had worked with phosphine for a mean of 11.6 years (range = 1.5-32 years). Phosphine concentration in the breathing zone of fumigators was recorded during eight fumigations, with the highest level recorded being 2.4 ppm/hour (3.3 mg/cu.m/hour), although more typical concentrations were <0.1 ppm/hour. These workers and 21 controls matched by sex, age, and smoking habit had hematological profiles, whole serum and blood cholinesterase activities, and several clinical biochemistry measures monitored. No significant effects were seen in any parameter monitored, including genotoxic endpoints. These results show no association between exposure and toxic effects at adjusted phosphine concentrations of up to 0.2 mg/cu.m (3.3 mg/cu.m divided by 8 hours and factored by 10/20 cu.m of air).

Newton et al. (1993) exposed Fischer 344 rats (30/sex/group) to either 0, 0.3, 1.0 or 3.0 ppm phosphine for 6 hours/day, 5 days/week (converted and duration adjusted to 0, 0.07, 0.25, or 0.75 mg/cu.m, respectively), for 13 weeks. Ten animals/sex/group were sacrificed at the following intervals: 4 weeks (interim sacrifice), 13 weeks (terminal sacrifice), and 18 weeks (recovery period). Because no major effects were observed in the 3-ppm group, additional groups (10/sex/group) exposed to 5 or 10 ppm (1.75 or 3.50 mg/cu.m, respectively, converted and duration adjusted) were included with corresponding control groups. Animals were monitored for cage-side observations, weight gain, and food consumption. Hematology and clinical chemistry were performed. Histopathology was performed only in animals exposed to 3, 5, or 10 ppm phosphine. Tissues examined included all major organs, bone (sternum and femur), spleen, bone marrow, and the entire respiratory tract, including the nasopharyngeal region (number of sections not specified). Death came to 4/10 females on the third day of exposure to 10 ppm; the remaining six animals were sacrificed on this day. There were no deaths in the other exposed groups, including the males exposed to 10 ppm phosphine. Mortality exhibited an extremely sharp concentration response, animals exposed to 10 ppm for 18 hours died, whereas others exposed to 3 ppm for 13 weeks exhibited few toxicological consequences. This sharp response has been documented by Klimmer (1969) in rats and several other species. The animals exposed to 5 ppm phosphine were exposed for only 13 days, with a 4-week recovery period. Renal

tubular necrosis was noted in animals but only those exposed at the lethal concentration of 10 ppm. Congested lungs were noted in the four females that died of exposure to 10 ppm phosphine. Hemoglobin concentration, hematocrit, and erythrocyte count were decreased in male rats, but the changes were slight (<10%) and, under these exposure conditions, were not considered toxicologically significant. There were no biologically significant effects on organ weights in any exposure group. Minor effects that were of questionable toxicological significance and not concentration related were noted in the nasopharynx (submucosal glandular concretions) of both treated and control animals. Minor decreases in body weight gain (relative to controls) were noted in both sexes. The decrease noted at the highest concentration was approximately 7% for males and 4% for females. Although these alterations did not achieve biological significance, they do support the decreased body weight gain reported in the Barbosa et al. (1994) study. The histopathology performed on the nasal tract tissues provides the minimum database requirements for the derivation of an RfC.

In a series of inhalation experiments with widely ranging durations and concentrations of phosphine exposures, Klimmer (1969) elucidated a sharp concentration response for phosphine-related mortality, proposed and presented data for a concentration (C) x time (T) relationship for mortality, and demonstrated this relationship to apply across a number of species. Exposure of rats to either 25 ppm phosphine for a single 8-hour exposure or to 403 ppm for 0.6 hour resulted in death; the C x T relationship being a parts per million per hour value of 200 for the lower and 242 for the higher concentration. This relationship was shown to closely predict mortality to elevated concentrations of phosphine (5 ppm or greater) in other species including cats, rabbits, and guinea pigs. When the phosphine concentration was <5 ppm, however, mortality was not observed, despite extended exposure periods. No mortality occurred in either cats, guinea pigs, or rats exposed to 2.5 ppm phosphine for a parts per million per hour composite of 820, or around fifty-five 6-hour exposures. Only minor toxicity was observed in animals exposed to <5 ppm phosphine, although a number of endpoints, including urine, blood, and liver function tests (cats only) were performed before, at the midpoint, and at the end of the exposure periods. Gross and microscopic histopathology is generally described for all major organs, including lungs and brain. Mild, isolated cloudy swelling of renal tubular epithelium is described in general for rats exposed to 2.5 ppm for a composite of 820 hours, and mention is made of fatty liver in cats that also were exposed to this regime. The general nature in which the results are presented in this study precludes its selection as the principal study. The information provided on mortality corroborates that reported by Newton et al. (1993).

Morgan et al. (1995) exposed groups of male and female B6C3F1 mice and Fischer 344 rats (18/sex/group) to either 0 (air), 1.25, 2.50, or 5.00 ppm phosphine gas for 6 hours/day, 5 days/week for up to 2 weeks (10 exposures). When converted and duration adjusted, these concentrations correspond to 0, 0.31, 0.62, or 1.24 mg/cu.m. phosphine, respectively. Hematological and clinical chemistry and body and organ weights were monitored.

Histopathology, including the nasal passages, larynx, and lung, was evaluated, but only in animals exposed to the highest concentration. No mortality was noted. After 10 exposures, urea nitrogen levels were elevated slightly over control values (13.2 mg/dL) at 1.25 ppm (20.2 mg/dL) and 5 ppm (21.1 mg/dL), but not at the middle concentration. Lung weights of male rats and mice were significantly decreased (21-29%), and heart weights of female rats and mice were significantly increased (16-27%) after 10 exposures at the highest concentration. Histopathology showed cardiomyopathy in controls (2/6 males, 1/6 females) and in the animals exposed to the highest concentration (1/6 males, 4/6 females), the only exposed group examined. The severity of this lesion was minimal in all instances except for mild severity in one exposed female. Based on an increase in heart weight and the severity of cardiomyopathy in female rats, this study indicates a LOAEL of 1.24 mg/cu.m and a probable NOAEL of 0.62 mg/cu.m.

In a study reported by Pazynich et al. (1984), male white rats (16/group) were exposed either to air, 0.05, 0.20, 1.50, or 8.00 mg/cu.m phosphine for 1.5 months. The duration of the daily exposure is not stated. No other experimental details are available. The authors claimed significant decreases occurred in erythrocyte count and hemoglobin content at all concentration levels, although no data are presented. A number of other endpoints of questionable toxicological significance are examined and reported. No scientific conclusions could be made from this report.

Waritz and Brown (1975) exposed six male Charles River-CD rats to 4 ppm (5.6 mg/cu.m) phosphine, 4 hours/day for a total of 12 exposures over two weeks. Pathology was performed and included histological examination of the lungs, trachea, eyes, and kidneys. Mild respiratory irritation and piloerection was observed in the exposed animals. No gross or histopathologic effects were observed. Weight gain curves demonstrated an approximate 8% decrease in body weight relative to controls that was followed by a normal rate of weight gain during a 14-day recovery period.

Pregnant Sprague-Dawley rats (24/group) inhaled 0.03, 0.30, 3.00, 5.00, or 7.50 ppm (0.04, 0.40, 4.20, 7.00, and 10.40 mg/cu.m, respectively) phosphine during gestational days 6-15 for 6 hours/day (Newton et al., 1993). Control animals were exposed to room air only. Dams were sacrificed on gestational day 20. Because of excessive mortality in the high-concentration group, this concentration level was eliminated. Changes to body weight, food consumption, and clinical signs were not found in any of the exposed groups. An increase in dilated renal pelvises were reported in all groups, but this effect does not appear to be concentration related. There was an increase in the total resorptions per dam in animals exposed to 0.03 mg/cu.m (1.3) as compared with controls (0.5) but not at any other higher concentration. No major treatment-related fetal malformations were observed. A NOAEL of 5 ppm (7 mg/cu.m) phosphine is determined for maternal, reproductive, or developmental toxicity. The high incidence of maternal deaths at 7.5 ppm designates this level to be an FEL. The proximity of the NOAEL and the FEL

concentrations indicates that this compound has an extremely steep concentration-response curve and provides further corroboration for the results of Klimmer (1969) and the other portions of the Newton et al. (1993) study.

To evaluate effects of inhaled phosphine on male germ cells, Kligerman et al. (1994) exposed 50 male B6C3F1 mice for 6 hours/day for 10 days over a 12- day period to 5 ppm (7 mg/cu.m) phosphine. These male mice were then mated to groups of untreated female mice on each of six consecutive 4-day mating intervals. None of the six groups of females exhibited a significant increase in percent resorptions or implants/female, nor were any differences noted in the percent of females impregnated by control or exposed males.

Phosphine is a reductant and, predictably, reacts with heavy metals such as the iron in heme and the metals of metal-dependent enzymes present in cells (Price and Chambers, 1990). In vitro experimental evidence has elucidated extensive and specific information on the capability of phosphine to inhibit mitochondrial respiration, apparently through this reductive capacity (Price and Chambers, 1990). In studies with isolated mitochondria, Chefurka et al. (1976) identified cytochrome c oxidase as the site in the electron transport chain at which ATP synthesis is inhibited by phosphine. In vitro, phosphine has been shown to react with the heme moiety of human hemoglobin in the presence of oxygen (Potter et al., 1991). These authors reported that Heinz bodies (aggregations of denatured hemoglobin) developed in human erythrocytes following exposure to 1.25 ppm phosphine for 4 hours, with hemolysis observed at 3 ppm. In vivo corroboration of these effects, however, is limited. Inhibitory effects on mitochondrial respiration were not detected in insects receiving a lethal dose of phosphine (Price and Chambers, 1990). No biologically significant hematological alterations were noted in the in vivo study of Biodynamics (1990). Klimmer (1969) noted marked decreases in blood elements, but only at high (5 ppm) concentrations, and no effects at lower concentrations in exposures extending for 24 weeks. Thus, the in vitro effects on blood demonstrated by Potter et al. (1991) may not be manifest under chronic in vivo exposure conditions. Isolated case reports have cited red cell hemolysis. In a postmortem examination of a child poisoned by phosphine, Wilson et al. (1980) reported hemolysis in conjunction with other major pathology. Unstable hemoglobins are present in the human population (Winterbourn, 1990), and there are no in vivo data to rule out a hypothesis that these individuals would be at increased risk for adverse hematological effects as a result of exposure to phosphine. The absence of a true chronic study prevents evaluation of blood as a target tissue.

I.B.5. Confidence in the Inhalation RfC

Study — Medium

Database — Low

RfC -- Low

The principal study was performed and reported in a thorough manner and provided both a NOAEL and a LOAEL for an effect that was consistent with other studies of phosphine (Newton et al., 1993) and with the effects of other known inhibitors of oxidative phosphorylation. This analogy with other inhibitors points out the potential for fallacy in relying solely on body weight alterations to predict the array of toxicity that may actually occur in response to chronic exposure. Other effects of chronic exposure to these inhibitors included cataract formation for dinitrophenol, liver pathology for pentachlorophenol, and myelin degeneration and thyroid effects for cyanide. Confidence in the principal study is therefore no more than medium. The data base is rated low because of the absence of chronic studies. Also, there exist no multigenerational reproductive studies for this compound. It should be noted that the experimental exposures on which this RfC is based are to pure phosphine gas. Actual exposures, however, would most likely be to reaction products of metal phosphides, which have not been chemically or toxicologically characterized. A low confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

This assessment was peer reviewed by external scientists. This review was completed on 03/29/1995. Their comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is included in the IRIS documentation files.

Other EPA Documentation — U.S. EPA, 1990

Agency Work Group Review — 02/09/1993, 09/22/1993, 05/10/1995

Verification Date — 05/10/1995

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for phosphine conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Phosphine

CASRN — 7803-51-2

Last Revised — 09/01/1992

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as to human carcinogenicity

Basis — Based on inadequate data in animals and no tumor data in humans. While phosphine has not been associated with cancer in humans, there is some evidence of chromosomal damage (transient chromatid deletions, gaps and breaks, persistent chromosomal translocations). A relationship between these genetic effects and the development of cancer in humans is sometimes postulated.

II.A.2. Human Carcinogenicity Data

None.

II.A.3. Animal Carcinogenicity Data

Inadequate. Hackenberg (1972) fed 30 Wistar rats/sex an aluminum phosphide-fumigated diet, equivalent to 0.27 mg phosphine/kg (a range of 0.167 to 0.377 mg/kg was fed in several feed preparations), for weeks 1-16; and for weeks 17-104, the feed contained 0.51 mg/kg (a range of 0.205 to 7.5 mg/kg was fed in several feed preparations). Untreated control groups (30 Wistar rats/sex) were fed a basal diet that was not fumigated. Fifteen rats/sex/group were used at various interim time points for hematological, blood-glucose, and urine analyses. Tissues from all rats that died during the study and at least five treated rats/sex that were killed at termination (24 months) were examined macroscopically and microscopically for neoplasms. Tumors were reported to occur infrequently at multiple sites in all groups of rats. The authors reported no differences between tumor incidences in control and treated rats. Adverse effects were not observed in this study, indicating that the MTD had not been reached.

Cabrol Telle et al. (1985) provided 30 Sprague-Dawley rats/sex feed that was fumigated with phosphine (average residue levels of 5 ppb dietary phosphine) for less than or equal to 2 years. It is not clear if the investigators estimated or measured the level of residual phosphine. After 1 year, 19-20 rats/sex/group were sacrificed for gross examination; histopathologic examination was performed on approximately 10 rats/sex/group. The investigators conducted similar examination of the 10 remaining rats/sex/group that were sacrificed after 2 years. Survival appeared to be similar in all groups. No tumors occurred in any group of rats sacrificed after 1 year. Although a number of tumors were reported in treated and control groups at termination, no significant differences in incidence were observed. An MTD was not achieved in this study. U.S. EPA (1989) determined that this study was inadequate for predicting the carcinogenicity of phosphine to rats since only one dose level was evaluated and too few rats remained after the interim sacrifice for potentially low excess tumor incidences to achieve statistical significance.

II.A.4. Supporting Data for Carcinogenicity

Garry et al. (1989) reported that pesticide applicators exposed to phosphine may have increased levels of genetic aberrations. The exposed groups consisted of 9 men who were exposed to phosphine alone, 11 to phosphine and other pesticides, and 4 who did not use phosphine. Two control groups included 15 state grain workers and 24 community control subjects. As a group, the pesticide applicators exhibited 3.58 times more total chromosome aberrations (excluding gaps) than the controls ($p < 0.001$). Phosphine-exposed workers had a 5-fold increase in deletions compared with controls ($p < 0.001$) and a significant increase in gaps ($p < 0.02$) and breaks ($p < 0.01$). No increase in sister chromatid exchanges was observed. Human lymphocytes exposed to phosphine in vitro demonstrated similar patterns of chromosome damage in a dose-related manner. However, when the human subjects were studied 6 weeks to 3 months after fumigation with phosphine had ceased, there was no difference in the number of chromosome gaps,

deletions or breaks between men exposed to phosphine and control subjects. The only persistent change was that of increased chromosome rearrangements ($p < 0.05$) in the exposed group. The authors were unable to state conclusively whether the chromosome rearrangements were directly attributed to phosphine exposure but expressed this as a distinct possibility.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

None.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1989

The 1989 Health and Environmental Effects Document for Phosphine has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 03/31/1992

Verification Date — 03/31/1992

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for phosphine conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Phosphine
CASRN — 7803-51-2

VI.A. Oral RfD References

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1984-1985. Cincinnati, OH. p. 27.

Hackenburg, U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. *Toxicol. Appl. Pharmacol.* 23(1): 147-158.

Jones, A.T., R.C. Jones and E.O. Longley 1964. Environmental and clinical aspects of bulk wheat fumigation with aluminum phosphide. *Am. Ind. Hyg. Assn. J.* 25: 376-379.

VI.B. Inhalation RfC References

Barbosa, A., E. Rosinova, J. Dempsey and A.M. Bonin. 1994. Determination of genotoxic and other effects in mice following short-term, repeated-dose, and subchronic inhalation exposure to phosphine. *Environ. Molec. Mutagenesis*. 24: 81-88.

Barbosa, A. and A.M. Bonin. 1994. Evaluation of phosphine genotoxicity at occupational levels of exposure in New South Wales, Australia. *Occup. Environ. Med.* 51(10): 700-705.

Bio/dynamics, Inc. 1989. MRID No. 413770-02. Available from EPA. Write to FOI, EPA, Washington, DC 20460. (Also reported in Newton et. al., 1993.)

Bio/dynamics, Inc. 1990. MRID No. 414131-01. Available from EPA. Write to FOI, EPA, Washington, DC 20460. (Also reported in Newton et al., 1993.)

Chefurka, W., K.P. Kashi and E.J. Bond. 1976. The effect of phosphine on electron transport in mitochondria. *Pest. Biochem. Physiol.* 6: 65-84.

Gupta, S., K. Sushil and K. Ahlawat. 1995. Aluminum phosphide poisoning - A review. *Clin. Toxicol.* 33(1): 19-24.

Horner, W.D. 1942. Dinitrophenol and its relation to formation of cataracts. *Arch. Ophthal.* 27: 1097-1112.

Kligerman, A.D., J.B. Bishop, G.L. Erexson, et al. 1994. Cytogenetic and germ cell effects of phosphine inhalation by rodents: II. Subacute exposures to rats and mice. *Environ. Molec. Mutagen.* 24: 301-306.

Klimmer, O. 1969. Study of action of phosphine (PH₃). Chronic phosphine poisoning. *Arch Toxicol.* 24: 164-187. (German trans.)

Misra, U., S. Bhargava, D. Nag, M. Kidwai and M. Lal. 1988. Occupational phosphine exposure in Indian workers. *Toxicol. Lett.* 42(3): 257-263.

Morgan D.L., M.P. Moorman, M.R. Elwell, et al. 1995. Inhalation toxicity of phosphine for Fisher 344 rats and B6C3F1 mice. *Inhal. Toxicol.* 7: 225-238.

Newton, P.E., R.E. Schroeder, J.B. Sullivan, W.M. Busey and D.A. Banas. 1993. Inhalation toxicity of phosphine in the rat: Acute, subchronic, and developmental. *Inhal. Toxicol.* 5(2): 223-239. (Also reported as Bio/dynamics, Inc., 1989 and 1990.)

Pazynich, V.M., I.A. Mazur, A.V. Podloznyi, et al. 1984. Experimental substantiation and prediction of marginally acceptable concentrations, differentiated in time, of phosphine in atmospheric air. *Gig. i. Sanit.* 1: 13-15. (Russian trans.)

Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander, and R.G. Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. *J. Toxicol. Environ. Health.* 5: 579-592.

Potter, W.T., S. Rong, J. Griffith, J. White and V.F. Garry. 1991. Phosphine-mediated Heinz body formation and hemoglobin oxidation in human erythrocytes. *Toxicol. Lett.* 57(1): 37-45.

Price, N.R. and J. Chambers. 1990. Biochemistry of phosphines. In: *The Chemistry of Organophosphorus Compounds, Volume 1*, F.R. Hartley, ed. p. 643-661.

Schwetz, B.A., J.F. Quast, P.A. Keeler, C.G. Humiston and R.J. Kociba. 1978. Results of a 2-year toxicity and reproduction studies on pentachlorophenol in rats. In: *Pentachlorophenol: Chemistry, Pharmacology and Environmental Toxicology*, K.R. Rao, ed. Plenum Press, NY. p. 301-309.

U.S. EPA. 1990. Health and Environmental Effects Document for Phosphine. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, Ohio, for the Office of Solid Waste and Emergency Response, Washington, DC. EPA No. 600/8-90/001.

U.S. Fish and Wildlife Service. 1983. MRID No. 00141408. Available from EPA. Write to FOI, U.S. EPA, Washington, DC 20460.

Waritz, R.S. and R.M. Brown. 1975. Acute and subacute inhalation toxicities of phosphine, phenylphosphine, and triphenylphosphine. *Am. Ind. Hyg. Assoc. J.* 36: 452-458.

Wilson, R., F. Lovejoy, R. Jaeger and P. Landrigan. 1980. Acute phosphine poisoning aboard a grain freighter. Epidemiologic, clinical, and pathological findings. *JAMA.* 244(2): 148-150.

Winterbourn, C.C. 1990. Oxidative denaturation in congenital hemolytic anemias: The unstable hemoglobins. *Seminars in Hematology.* 27(1): 41-50.

WHO (World Health Organization). 1988. Environmental Health Criteria 73: Phosphine and selected metal phosphides. World Health Organization: Distribution and Sales Service, 1211 Geneva 27, Switzerland. 100 p.

VI.C. Carcinogenicity Assessment References

Cabrol Telle, A.-M., G. De Saint Blanquat, R. Derache, E. Hollande, B. Periquet and J.P. Thouvenot. 1985. Nutritional and toxicological effects of long-term ingestion of phosphine-fumigated diet by the rat. *Food Chem. Toxicol.* 23(11): 1001-1009.

Garry, V.F., J. Griffith, T.J. Danzl, et al. 1989. Human genotoxicity: Pesticide applicators and phosphine. *Science.* 246: 251-255.

Hackenberg, U. 1972. Chronic ingestion by rats of standard diet treated with aluminum phosphide. *Toxicol. Appl. Pharmacol.* 23(1): 147-158.

U.S. EPA. 1989. Health and Environmental Effects Document for Phosphine. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

VII. Revision History

Substance Name — Phosphine
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| Date | Section | Description |
|------------|-------------------------|--|
| 09/01/1992 | II. | Carcinogenicity assessment on-line |
| 07/01/1995 | I.B. | Inhalation RfC summary on-line |
| 10/28/2003 | I.A.6, I.B.6, II.D.2 | Screening-Level Literature Review Findings message has been added. |

VIII. Synonyms

Substance Name — Phosphine

CASRN — 7803-51-2

Last Revised — 01/31/1987

- 7803-51-2
- CELPHOS
- DELICIA
- DETIA
- DETIA GAS EX-B
- FOSFOROWODOR
- HYDROGEN PHOSPHIDE
- Phosphine
- PHOSPHORUS TRIHYDRIDE
- PHOSPHORWASSERSTOFF
- RCRA WASTE NUMBER P096
- UN 2199