Phosphoric acid; CASRN 7664-38-2

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 Phosphoric acid

File First On-Line 08/01/1995

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	08/01/1995*
Carcinogenicity Assessment (II.)	not evaluated	

*A comprehensive review of toxicological studies was completed 01/11/05 - please see section I.B.6 for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Phosphoric acid
CASRN — 7664-38-2

Not available at this time.

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

Substance Name — Phosphoric acid
CASRN — 7664-38-2
Last Revised — 08/01/1995

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.

NOTE: ****SEE BENCHMARK CONCENTRATION IN DISCUSSION. Discussion of the benchmark dose can be found in the Discussion of Principal and Supporting Studies Section.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Bronchiolar fibrosis **13-Week Rat Inhalation Study** **Aranyi et al., 1988a**	Benchmark Concentration: See Conversion Factors and Assumptions and Principal and Supporting Studies	300	1	1E-2 mg/cu.m

*Conversion Factors and Assumptions: MW = 82. The Benchmark Concentration (BMC) associated with a 10% increase in incidence in the critical effect relative to controls (BMC10)

was determined to be 100 mg/cu.m (see Principal and Supporting Studies). BMC10(ADJ) = 100 mg/cu.m (2.25 hours/24 hours x 4 days/7 days) = 5.4 mg/cu.m. The BMC10(HEC) was calculated for a particle:respiratory effect in the tracheobronchial (TB) region. Information on the growth of hygroscopic phosphoric acid aerosols (Martonen and Clark, 1983) was used to estimate the nonaerodynamic diameter of the aerosol particles at the lesion site to be approximately 2.5 microns (0.49 microns x 5); the lower value for the sigma g given in the study (1.56) was assumed for the distribution of hydrated particles. Based on the default weight of 267 g for a male Sprague-Dawley rat, the RDDR for an effect in the TB area is 0.64; BMC10(HEC) = 5.4 mg/cu.m x 0.64 = 3.4 mg/cu.m.

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

Aranyi, C., M.C. Henry, S.C. Vana, R.D. Gibbons and W.O. Iverson. 1988a. Effects of multiple intermittent inhalation exposures to red phosphorus/butyl rubber obscurant smokes in Sprague-Dawley rats. Inhalation Toxicology, Premier Issue. p. 65-78.

In two parallel 13-week inhalation studies, groups of Sprague-Dawley rats were exposed for 2.25 hours/day on 4 consecutive days/week to either filtered air (controls) or an aerosol of combustion products from burning 95% red phosphorus and 5% butyl rubber. In the first study, male Sprague-Dawley rats were exposed to filtered air (control) or 300, 750, or 1200 mg/cu.m of combustion products. In the second study, male Sprague-Dawley rats (40/group) were exposed to either filtered air (control) or 50, 180, or 300 mg/cu.m of these same combustion products. The combustion products were mixed and diluted with filtered air and introduced into 1-cu.m exposure chambers. The aerosol mass concentration was monitored continuously by optical methods and periodically by gravimetric filter sampling. Aerosol particle size was determined once a day with MMADs ranging from 0.49-0.65 microns and sigma g's of 1.56-1.83. The percent of the aerosols that were phosphorus acids ranged from 71-79% (apparently based on gravimetric analysis). The duration-adjusted values for the second, lower concentration study were 2.7, 9.6, and 16.7 mg/cu.m. In the first study, the number of rats in the control and high- and mid-exposure groups was 176, and 84 rats were in the group exposed to 300 mg/cu.m. Agent-related mortality (19/176 animals) was observed among the animals exposed to the two highest concentrations in the first study, 19/176 at 1200 mg/cu.m and 1/176 at 750 mg/cu.m. Decreases in body weight gain also were observed, but only in the two groups exposed to the highest concentrations. No deaths were noted in the second study. In the first study, all major organs and respiratory tract tissues were examined histologically in a portion of the animals (n = 12) from each exposure group. Neurobehavioral studies also were performed in the first study. The focus of the second, lower concentration study was the respiratory tract; tissues examined in this study included the turbinates (two sections), trachea, and five lobes of the lung from 20 animals in each exposure group and controls. Concentration-related decreases in pulmonary

bactericidal activity was observed for all exposure groups only in the first study, although no significant effects were noted in the second study.

Both studies clearly indicated the target organ to be the respiratory tract, specifically the terminal bronchioles. Pathological examination of a portion of those animals that died revealed extensive involvement of bronchiolar and laryngeal mucosa, the latter probably being contributory to death. Terminal bronchiolar fibrosis (minimal to severe) with no or minimal involvement of pulmonary tissues was the only concentration-dependent lesion noted in the respiratory tract of animals surviving repeated exposures. This lesion was present in all animals examined that had been exposed to 750 or 1200 mg/cu.m, including those necropsied after an 8-week recovery period, and was judged predominately as moderate and severe. In the second study, this lesion was present with minimal severity in 9/20 animals exposed to 300 mg/cu.m, 4/20 animals exposed to 180 mg/cu.m, and 0/20 animals exposed to 50 mg/cu.m. Based on the histologic lesions in the tracheobronchiolar region, 180 mg/cu.m is the LOAEL, and 50 mg/cu.m is the NOAEL.

DERIVATION OF A BENCHMARK CONCENTRATION (BMC): The data for bronchiolar fibrosis were combined from both studies for BMC analyses. Estimates of the 1, 5, and 10% incidence levels [extra risk; P(d)-P(0)/P(0)] were obtained using both Weibull and linear models. The Weibull model (no threshold) gave the better goodness-of-fit to the data. The maximum likelihood estimate (MLE) of the 10% incidence level was 150 mg/cu.m, with the lower 95% confidence level bound of the MLE at 100 mg/cu.m = BMC10. The corresponding estimates for the 5% incidence level were 112 mg/cu.m for the MLE and 64 mg/cu.m = BMC05. These estimates were nearly the same with the linear model. As there is some evidence suggesting that a 10% incidence level correlates with a NOAEL for one type of noncancer endpoint (Faustman et al., 1994; Allen et al., 1994) and, because both the BMC05 and BMC10 were below the empirical LOAEL of 180 mg/cu.m, the BMC10 of 100 mg/cu.m was chosen for further quantitative analysis. This practice is in general concordance with the RfC methodology (U.S. EPA, 1990a, 1994) in choosing the highest NOAEL with the lowest LOAEL.

Calculation of an RDDR for this study is made with specific information about the behavior of hygroscopic phosphoric acid particles in the airways of humans and with information indicating that similar effects at similar sites are observed in both rodents and in monkeys exposed to another acid aerosol. Pathology in the respiratory tract (terminal bronchioles) was noted in both monkeys (Alarie et al., 1973) and rodents (U.S. EPA, 1989) exposed to sulfuric acid aerosols of approximately the same MMAD and size distribution as that reported in the principal study. The work of Martonen and Clark (1983) provides specific quantitative information on the growth characteristics of phosphoric acid aerosols in human airways, based on the fact that growth of hygroscopic particles depends on the degree of humidification and the transit time of the particle. Based on the assumptions that growth and deposition processes are similar between rodents and

humans and between sulfuric and phosphoric acids, alterations in diameter (geometric) were calculated for the approximate site of the lesion (terminal bronchioles) from the initial airborne MMAD of the aerosol and found to be approximately 2.5 microns. A sigma g not of the same multiple as the MMAD (fivefold) was designated due to the fact that hygroscopic particles of different sizes grow at differing rates (Martonen and Clark, 1983), the end result possibly being a more uniform distribution. The lowest sigma g cited in the study, 1.56, is maintained for purposes of computing an RDDR.

It should be noted that hygroscopic particle growth in airways is a complex issue that is not fully understood. In addition to the assumptions already stated above, others have been made in applying this RDDR. Some others are that alterations for hygroscopic changes are based on alterations in geometric diameter, which is not fully predictive of aerodynamic diameter; that the lesion site, the terminal bronchioles, is also the site of deposition for acid aerosols of this particular MMAD; that growth characteristics of a polydisperse hygroscopic aerosol become more uniform on humidification; that the characteristics for particle growth (such as humidification at different levels in the airways) are similar between rodents and humans. Calculation of the RDDR for an effect in the tracheobronchial area is undertaken in full light of these assumptions and limitations and found to be 0.64 for an effect in the tracheobronchial area, the BMD10(HEC) is 3.4 mg/cu.m. The RDDR for the thoracic region is 0.61 and could be used because the location of the lesion is somewhat ambiguous. The decision to calculate the RDDR based on the tracheobronchial region is based on the occurrence of lesions in this region after sulfuric acid inhalation.

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

UF — A factor of 3 was used for interspecies extrapolation as dosimetric considerations were partially accounted for by calculation of an RDDR. Although the model used to estimate the RDDR, as given in U.S. EPA (1990b), is for insoluble and nonhygroscopic particles, sufficient information is available on this acid aerosol (Martonen and Clark, 1983) to address hygroscopicity and to identify the critical assumptions made in application of the RDDR calculation. A factor of 10 is used to protect sensitive human subpopulations. A full factor of 10 also is applied for the use of a subchronic study. The total uncertainty factor is 300. Because toxicity was limited to the site of deposition, and the principal chemical species absorbed and generated, phosphorus acid anions, are present in normal human tissues, concern for systemic toxicity is ameliorated.

MF — None

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

Due to its high reactivity, exposure to airborne phosphorus would be to the oxidized and hydrolyzed forms (i.e., phosphoric acids) rather than to elemental phosphorus. Bohl and Kaelble (1973) examined elemental phosphorus levels in the air at five different production plants, documenting a high level of around only 0.2 mg/cu.m, with all other values being less than 0.05 mg/cu.m. Elemental phosphorus occurs in three allotropic forms: white (or yellow), red, and black. Red phosphorus is produced by heating white phosphorus in an inert atmosphere. Although both the red and white forms are reactive; the white is more reactive. Under production conditions, white phosphorus spontaneously ignites in air yielding phosphorus oxides (such as phosphorus pentoxide) that hydrolyze to phosphoric acids (U.S. EPA, 1990a). Phosphoric oxides/acids also were shown to be the principal constituent of smokes produced from the combustion of red phosphorus (Burton et al., 1982; U.S. DOD, 1981).

The main constituents of airborne phosphorus (phosphoric acids and oxides) would exist as acid aerosols. As phosphoric acid is a strong acid and hygroscopic, it has chemical and physical similarities to the acid aerosol of sulfuric acid. The latter acid aerosol has been studied extensively for both its physical and toxicologic properties (U.S. EPA, 1989). Experimental inhalation studies of acid aerosols have established several points. Among these are that acid aerosols in general have effects in the respiratory tract, that their toxicity is due to direct irritant action of the hydrogen ion, that the effects are dependent not only on concentration but also on particle size and duration of exposure, and that the hygroscopic nature of the acid particles alters their size once within the humid conditions of the respiratory tract. It is therefore defensible to consider the effects of the acidic oxidation products of phosphorus in light of what is known about other acid aerosols. Mortality resulting from exposure to either sulfuric or phosphoric acid aerosols are attributable to laryngeal and tracheal involvement (U.S. EPA, 1989; U.S. DOD, 1981). Similarly, bronchiolar lesions with minimal or no involvement of gas exchange tissues were noted in the studies by U.S. DOD (1981) and Aranyi et al. (1988a,b) and in both long- and short-term studies with sulfuric acid aerosols (U.S. EPA, 1989). In a nearly continuous 78-week exposure of sulfuric acid aerosols to cynomolgus monkeys, Alarie et al. (1973) documented bronchiolar histopathology that was accompanied by pulmonary functional deficits at higher aerosol concentrations. These results are parallel to those of U.S. DOD (1981) where bronchiolar histopathology and marginal deficits in pulmonary function (marginal changes in estimated pulmonary resistance and tidal volume) also were documented. Slight but detectable pulmonary function changes were noted in monkeys exposed by Alarie and co-workers to 0.48 mg/cu.m of sulfuric acid mist with an MMAD in ambient air of 0.54 and a geometric standard deviation of 1.5-1.8; mists of similar concentration (0.38 mg/cu.m) but containing particles of larger size (2.15 microns) produced slight histopathology but no detectable pulmonary deficits. Aerosols of a larger size (3.6 microns), however, did produce histopathology lower in the lung (increases in thickness of alveolar walls). Alarie and colleagues also exposed guinea pigs for 52 weeks to

sulfuric acid mists at around 0.1 mg/cu.m and noted no adverse effects regardless of particle sizes, which ranged from 0.8-2.78 microns.

Historically, phosphorus workers were noted to be particularly susceptible to a severe and debilitating necrosis of the jaw often described as "phossy" jaw (U.S. EPA, 1990a). This affliction was associated with production of matches from white phosphorus, a process banned internationally over a century ago. There exist, however, several more recent case studies of early stages of "phossy" jaw, predominantly among phosphorus production workers. Hughes et al. (1962) describes several such reports. These authors also describe a study on a group of 48 phosphorus plant workers whose exposure to phosphorus ranged from 1 to 17 years. No differences were noted in leukocyte count among the exposed workers, a persistent finding in acute elemental phosphorus poisoning. Also, no differences in bone density were noted between the workers and the controls (28 individuals not exposed to phosphorus) in radiographs of both hands. In no case are exposure values causal of these effects given or estimated. Bone effects have been noted in animals exposed to phosphorus. Inuzuka (1956) reported that exposure of rats (strain and numbers unspecified) apparently to elemental phosphorus at 150-160 mg/cu.m, 0.5 hours/day for 60 days caused bone (femur and humerus) abnormalities, including insufficient ossification, widened epiphyseal line, and disordered axial development. Acute poisonings with elemental phosphorus in humans are reported to involve primarily the liver (Fahim et al., 1990). These studies give indications that humans have a wide range of susceptibility to the toxic effects of phosphorus, and that elemental phosphorus is probably causal of these toxicities. Relevance of these studies to this RfC is limited because exposures will be almost exclusively to oxidation products of phosphorus, not elemental phosphorus.

The occupational study of Dutton et al. (1993) does have some relevance to this RfC because levels of phosphorus oxidation products are reported. These authors examined lung function in a cohort of 131 workers involved in refining phosphorus rock to obtain elementary phosphorus. Years of exposure, which were estimated from work records based on where workers spent their entire working days, ranged from 0-46 years, with a mean of 11.4 years. The study indicates that the maximum levels of phosphorus oxidation products (as phosphorus pentoxide) was measured at 2.23 mg/cu.m. Pulmonary function tests (forced vital capacity, forced expiratory volume in 1 second, and forced expiratory flow) were conducted annually over an 8-year period in all workers. These data were analyzed longitudinally and cross-sectionally over the third through the seventh year of exposure. Neither analysis revealed any significant residual effect after adjusting for age and smoking. Although this study has several limitations, these data do indicate that long-term exposures to levels of airborne phosphorus oxidation products over twice the recommended ACGIH (1991) 8-hour TLV had no demonstrable effect on lung function.

Aranyi et al. (1988b) also determined that neither sex nor exposure duration and frequency to combustion products from burning 95% red phosphorus and 5% butyl rubber had significant

influence on pulmonary bactericidal activity. The respiratory tract was again the target organ where mild to moderate terminal bronchiolar fibrosis was found in both sexes of rats exposed to 750 mg/cu.m or more for as little as 2 weeks.

Groups of Sprague-Dawley rats (apparently from a local colony) were exposed for 15 minutes daily, 5 days a week for 13 weeks to smoke and combustion products generated from felt pellets impregnated with white phosphorus at 0, 192.5, 589, or 1161 mg/cu.m (U.S. DOD, 1981). The MMAD of the airborne particles was 0.5 micron (no sigma g value reported). Duration-adjusted values are 0, 1.43, 4.38, or 8.64 mg/cu.m, respectively. These concentrations represent the amount of material present on collecting filters that could be converted to phosphoric acid and are therefore phosphoric acid equivalent concentrations. The number of animals claimed in the body of the report to be exposed is inconsistent with those reported in the accompanying pathology tables. Based on the latter source, there were 34 males and 43 females in the highest exposure group, 24/sex in the intermediate exposure group, and 18/sex in the lowest exposure group. Groups of control animals (air only) equal to half the number in the exposed groups also were claimed to be included in the study. Hematologic profiles, clinical chemistry, and gross and microscopic pathology, the latter including the nasal turbinate (sectioning procedures not given), trachea, lung, and liver, were performed on most of the animals. Bone marrow but not bone tissue was examined. Some animals (n = 7-12) exposed to the low and high concentrations were administered physiological (ventilatory and electrocardiograph tests) and behavioral examinations. Animal sacrifices were performed at 6, 13, and 17 weeks (4 weeks postexposure). Mortality, attributed to asphyxiation from laryngeal/tracheal tissue swelling, occurred in 43/77 rats exposed to the highest concentration. No animals in the lower two exposure groups and only one control animal died. No concentration-related changes were noted in body or organ weights, hematology profiles, clinical chemistry, or behavioral tests in any exposed group examined. Histopathological examination of surviving animals showed effects limited to the respiratory tract. Tracheitis and laryngitis occurred in nearly all (28/31) animals examined that survived exposure from the highest concentration, including those examined 4 weeks postexposure. Bronchiolitis also was noted in the postexposure animals, occurring in 6/16 animals examined at the high concentration, in 5/24 animals at the middle concentration, and in 0/12 animals at the low concentration. This lesion indicates that lower portions of the respiratory tract were involved, which is partially corroborated by alterations in several of the physiological parameters (reductions in tidal volume and increases in estimated pulmonary resistance). The composite number of animals exposed to the intermediate concentration with either tracheitis or laryngitis was 32/47, and, for the low concentration, was 2/35. Both of the occurrences at the low concentration were judged as slight in severity, one occurring in a male examined at 6 weeks, the other in a female examined at 13 weeks. Based on these two occurrences of a respiratory tract pathology that is shown to increase in severity and to progress deeper into the tract with increasing concentrations, the low concentration, 192.5 mg of phosphoric acid equivalents/cu.m, is designated a LOAEL. The daily regime of 2.25-hour exposure was much longer in the

principal study than the 15-minute exposure used by U.S. DOD (1981). This acute exposure regime and other uncertainties about the study of U.S. DOD (1981) make the study of Aranyi et al. (1988a) a more scientifically robust choice for the principal study.

In a 13-week inhalation study by Marrs et al. (1989), female Wistar rats (50/group), Porton-strain mice (100/group), and guinea pigs (42-48/group) were exposed to smoke of oxidation products obtained by combustion of a pyrotechnic mixture of 95% amorphous oiled red phosphorus and 5% polyvinyl butyral BL18), at 0, 16, or 128 mg phosphorus content/cu.m, 1 hour/day, 5 days/week (duration adjusted to 0, 0.48, or 3.80 mg/cu.m). Mice received 180 exposures, and rats and guinea pigs received 200 exposures (equivalent to 40 weeks). The pyrotechnic mixture, in granular form, was ignited to maintain the desired concentration during the exposure period. The particle size of the smoke was not determined. Histopathology was performed 19 months after the start of the study or if animals appeared unhealthy. Tissues examined histologically included the trachea and lower respiratory tract tissues and all major organs, including the heart and liver. The nasal tract tissues were not examined. Mortality was excessively high in all three species, including the control groups. Many of the animals that died had microscopic appearances consistent with severe chronic murine pneumonia. Guinea pigs were the only species in which mortality seemed to be related to exposure concentration. Aside from mortality, few adverse effects were noted. In mice, alveolar aggregates of macrophages with granules were observed in 9/37 low-concentration (24%) and 9/22 high-concentration (41%) animals compared with 2/41 controls (5%). In the exposed rats, body weights relative to controls were decreased throughout the exposure period, although no weights are actually presented. This study demonstrated a marked species difference in tolerance to the smoke, with guinea pigs being especially sensitive. Due to the excessive mortality not related to the test substance and lack of data presented, no effect levels are assigned from this study. It should be noted, however, that no concentration- related effects were reported in the larynx, trachea, or bronchioles of any species.

Female New Zealand rabbits and Wistar rats (10/group) inhaled smoke produced by burning 95% red phosphorus and 5% butyl rubber (Smoke I) or 97% red phosphorus and 3% butadiene styrene (Smoke II) for 30 minutes (Marrs, 1984). The resulting smoke had a phosphorus content of 680 mg/cu.m for Smoke I and 670 mg/cu.m for Smoke II. Larynx, trachea, lung, liver, kidney, adrenal gland, spleen, and pancreas were examined at 24 hours or 14 days after exposure. In rabbits, epithelial necrosis, alveolitis, and inflammation of the larynx developed 24 hours after exposure to Smoke I. Some rabbits still exhibited effects 14 days after exposure. Rabbits in the control group appeared normal, except for two animals exhibiting a mild degree of alveolitis. In rats, laryngotracheal inflammatory changes and congested lungs were observed at 24 hours postexposure to Smoke I. Fourteen days after exposure, some rats still displayed mild to moderate laryngeal and tracheal inflammation. Smoke II appeared to be more toxic than Smoke I, especially in rats. Following exposure to Smoke II, tracheal inflammation (ranging from mild to severe) with exudate in the lumen developed in some of the rabbits. Several rats exposed to

Smoke II died; four died within 24 hours of exposure, and two died 4-5 hours after exposure. Mild laryngeal inflammation accompanied by severe pulmonary congestion and focal hemorrhage were observed in exposed rats. No other treatment-related findings were evident, except for congested livers in two of the rats that died. Although this is a single-dose study, the occurrence of tracheal and laryngeal inflammation support the effect noted in the longer term study of U.S. DOD (1981).

Burton et al. (1982) characterized aerosols generated by burning pellets consisting of red phosphorus and butyl rubber (95/5 by weight) to which 1% mineral oil was added. Samples of the combustion products were collected from the exposure chamber on glass fiber filters and submitted to GC/MS and thin- layer chromatography. The size and distribution of the resultant aerosols were 1.0-1.3 microns (MMAD) and 1.5-1.7 (sigma g). Particle size was not altered appreciably when relative humidity within the chamber was varied from 20-50%. Thin layer chromatography of samples showed a single intense spot corresponding to phosphoric acid with some plates suggesting the presence of a small amount of diphosphoric acid. GC analysis of air samples from a phosphorus smoke at 3940 mg/cu.m indicated the presence of 2 ppm phosphine, but no elemental phosphorus or other volatile low molecular phosphorus compounds were detected. In a series of acute (1-hour) exposures to these combustion products, Sprague-Dawley rats were observed to develop slight to mild epiglottal deformation at 3150 mg/cu.m, laryngeal edema at 5400 mg/cu.m, and laryngeal and tracheal lesions at 8500 mg/cu.m. Exposure to 1500 mg/cu.m for 4 hours resulted in blunted epiglottises, severe laryngeal edema, and some hemorrhaging. The nares, turbinates, and eyes appeared to unaffected at gross examination.

Pregnant AMRI:(SD x WI) rats (24/group) were exposed to 0, 589, or 1161 mg/cu.m of combustion products of white phosphorus and felt smoke for 15 minutes daily on gestational days 6-15 (U.S. DOD, 1981, 1982). The smoke was generated from ignition of felt pellets impregnated with white phosphorus. No effects on pregnancy or reproductive parameters were reported. In the fetuses of dams exposed to the highest concentration, visceral variations (reversed ductus arteriosus and ectopic testicles) were observed. Examination of the skeletal system of fetuses from dams exposed to the high concentration revealed a concentration-related increase in the incidence of hypoplasia of the xiphoid process. The total number of fetuses examined were not reported; therefore, incidence data could not be determined for the fetotoxic findings. Statistical significance also was not reported. A NOAEL of 589 mg/cu.m and a LOAEL of 1161 mg/cu.m were determined for developmental effects.

In a single-generation reproduction study, female rats were exposed to 0, 589, or 1161 mg/cu.m of combustion products of white phosphorus and felt smoke, 15 minutes/day, 5 days/week, for 3 weeks prior to mating (4-5 estrus cycles), then during gestation (21 days) and lactation (21 days) (U.S. DOD, 1981, 1982). Males were exposed to the same concentrations for 10 weeks prior to and during the mating period. Dams and pups appeared to be weakened (no specifics given) by

each exposure to the higher concentration. Body weights of the pups from dams exposed to the highest concentration were reduced (91- 92% of control pups). There were no effects on litter size or fetal abnormalities of the exposed groups. The 24-hour viability, lactation, and 21-day survival indices were all significantly lower in the dams exposed to the highest concentration. A NOAEL of 589 mg/cu.m combustion products and a LOAEL of 1161 mg/cu.m combustion products were determined for reproductive effects.

In a dominant lethal mutation study, 13-week-old male rats were exposed to 0, 589, or 1161 mg/cu.m of combustion products of white phosphorus and felt smoke, 15 minutes/day, 5 days/week, for 10 weeks prior to mating with unexposed female rats (U.S. DOD, 1981, 1982). The exposure period covered the complete cycle of spermatogenesis. There was an increase in the number of females with one or more resorptions for the group mated with the males exposed to the lower concentration. No other significant differences were reported.

In a study in which elemental phosphorus was the test agent, Condray (1985) performed an oral reproductive study in which Sprague-Dawley rats (15 males and 30 females/group) were exposed by gavage to elemental white phosphorus in corn oil at doses of 0, 0.005, 0.015, or 0.075 mg/kg/day for 80 days prior to mating until the onset of lactation. Because of low fertility in the first litter, the study was extended to two litters, and dosing continued throughout the study. Pups were sacrificed at weaning and parental animals were sacrificed after the weaning of the F1b litter. There were no statistically significant effects. The mean number of viable pups in the F1b litters exposed to 0.075 mg/kg/day was slightly lower than controls. No treatment-related gross or microscopic changes were seen in any of the generations. The most significant effect in this study was mortality, which occurred among pregnant females. Death came to 4 controls and 1 low-dose, 1 mid-dose, and 16 high-dose animals. The majority of the deaths in the dams exposed to the highest dose occurred near parturition (13/16). This report is provided in a condensed form with few details. The test substance (elemental phosphorus) and exposure route (gavage) used in this study make these results of marginal significance to this RfC. Other studies on development and reproduction (U.S. DOD, 1981, 1982) were by the inhalation route to combustion products of phosphorus and neither showed any indications of similar maternal effects.

Using elemental phosphorus, Dalhamn and Holma (1959) studied the distribution of red phosphorus in the mouse following acute inhalation exposure. Fifteen mice were exposed to 5 mg/cu.m red phosphorus (pulverized and radiolabeled) for 1 hour. Particles had a maximum size of 1 micron and a mean diameter of 0.46 +/- 0.28 microns. Autoradiography revealed high radioactivity in the gastrointestinal and respiratory tracts immediately after exposure and remained after 2 hours, except in the upper respiratory tract. At 2 and 10 days postexposure, radioactivity was found only in the lungs. The study indicated that inhalation of red phosphorus results in long retention in the lungs, and, therefore, toxic effects of elemental phosphorus are unlikely beyond the digestive and respiratory tracts.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

This RfC is for aerosols of phosphoric acid and phosphorus oxidation products and does not apply to elemental phosphorus or other forms of phosphorus, such as phosphorus salts. Because the site of deposition (and toxicity) of acid aerosol particulates is dependent on size, distribution, and character, this RfC would be most appropriate for phosphoric acid aerosols in the range of 0.4-1.0 microns. The principal study used a sufficient number of animals and was thorough in investigation of the target tissue. The confidence in this study is medium. The reactivity of elemental phosphorus to acids and oxides ameliorates concern for lack of more complete information on reproductive and developmental endpoints. However, the database cannot be rated higher than medium due to the lack of chronic data. It should be noted that chronic studies with another acid aerosol, sulfuric acid, resulted in the same respiratory tract pathology noted in the phosphorus smoke aerosols, although effect levels may be somewhat lower than for phosphorous (U.S. EPA, 1989; Alarie et al., 1973). The overall confidence in the RfC is medium.

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 04/11/1995. 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, 1989, 1990a,b, 1994

Agency Work Group Review — 09/24/1993, 05/09/1995

Verification Date — 05/09/1995

A comprehensive review of toxicological studies published through 2004 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfC for Phosphoric acid and a change in the RfC is not warranted at this time. For more information, IRIS users may contact 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 — Phosphoric acid
CASRN — 7664-38-2

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Phosphoric acid
CASRN — 7664-38-2

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Phosphoric acid
CASRN — 7664-38-2

Date	Section	Description
08/01/1995	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.
03/03/2005	I.B.6	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — Phosphoric acid
CASRN — 7664-38-2
Last Revised — 06/01/1995

- 7664-38-2
- Phosphoric acid
- Orthophosphoric acid
- ACIDE PHOSPHORIQUE [FRENCH]
- Acido fosforico [Spanish]
- Caswell No. 662
- EPA Pesticide Chemical Code 076001
- HSDB 1187
- WC-REINIGER