ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

PROPOSED

RED PHOSPHORUS (CAS Reg. No. 7723-14-0)

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels C AEGL-1, AEGL-2 and AEGL-3 C are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

> **AEGL-1** is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
>
> **AEGL-2** is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
>
> **AEGL-3** is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Red phosphorus consists of randomly arranged arrays of phosphorus tetrahedra in the form of connected chains and rings. Along with white phosphorus, it is an allotropic form of phosphorus. At normal temperature and humidity, red phosphorus reacts very slowly with water vapor and air to form phosphine and various phosphorus oxyacids. Red phosphorus smoke is used as a military screen. The smoke is generated by combustion of red phosphorus/butyl rubber (RP/BR) containing 5% BR, about 1.25% insulating oil, and about 1% talc or silica. Other uses include manufacturing of pyrotechnics, safety matches, and fertilizers.

Red phosphorus and red phosphorus/butyl rubber smoke have high phosphoric acid content. Ortho-phosphoric acid is a corrosive mineral acid and is likely the cause of the irritation and inflammation to the respiratory tract that occurs following inhalation of red phosphorus smoke while the cellular toxicity of red phosphorus is likely due to its activity as a reducing agent resulting in disruption of oxidative processes.

Reports of human exposure lack definitive exposure terms. Acute inhalation exposure (duration not specified) to 1000 mg red phosphorus/m^3 was considered intolerable. Another report noted that workers experienced significant but reversible symptoms of respiratory distress and irritation of the eyes and mucous membranes following exposure to red phosphorus smoke at concentrations of 100 - 700 mg/m^3 for less than 15 minutes. Other reports described concentrations greater than 100 mg/m^3 to be intolerable.

Acute inhalation toxicity data are available for rats, mice, dogs, guinea pigs, and rabbits. Regardless of the species, inhalation exposure to red phosphorus smoke or smoke from red phosphorus/butyl rubber formulations consistently produced irritation and inflammation of the respiratory tract and, at higher concentrations, was lethal. Where histopathologic analysis was performed, lethality in rats, mice, and rabbits was associated with severe necrotic and inflammatory lesions in the larynx and trachea, and pulmonary congestion and edema. Considerable species variability in the response severity to inhaled red phosphorus or red phosphorus butyl rubber formulations was reported. The guinea pig was generally considered a uniquely sensitive species and not appropriate for human health risk assessment. The toxic responses to red phosphorus and red phosphorus/butyl rubber smoke are generally attributed to the high phosphoric acid content.

Acute inhalation toxicity studies were primarily lethality bioassays with little focus on assessing exposure-response relationships for nonlethal effects. Histopathological assessments provided insight into mode of action, and for animals surviving the test exposures, identified critical effects for nonlethal exposures. However, identification of thresholds for nonlethal toxicity were poorly defined.

Data were unavailable with which to directly derive AEGL-1 values for red phosphorus. A 3-fold reduction of the AEGL-2 values was considered a justified approach for deriving the AEGL-1 values because the progression of effects from AEGL-1 severity to AEGL-2 severity represents a continuum of the same mode of action (contact irritation) and effect. Comparison

of the AEGL-1 values to the limited human exposure data indicates that notable effects (greater than those characterizing the AEGL-1 tier) would be unlikely following exposure to AEGL-1 concentrations.

Information regarding the response of humans to red phosphorus or red phosphorus/butyl rubber smoke lacked definitive exposure terms and was not considered sufficient for development of AEGL-2 values. The AEGL-2 severity effects in animals (necrosis, hemorrhage, and edema in the respiratory tract) were consistently associated with exposures that also caused deaths. Necropsies of animals surviving through the post-exposure observation period generally revealed only minor signs of toxicity that were not consistent with AEGL-2 severity but clearly showed the respiratory tract as a target of toxicity. Results from the multispecies study by Ballantyne (1998), showed no lethality and only pulmonary congestion in mice exposed one hour to smoke of unformulated red phosphorus (111 mg/m^3). The data reported by Ballantyne (1998) were also considered the most relevant for deriving AEGL values for red phosphorus because pure unformulated red phosphorus was used rather than the butyl rubber formulations. Mice appeared to be more sensitive than rabbits, dogs, or rats. The 1-hour exposure of mice to 111 mg red phosphorus/m^3 that resulted in pulmonary congestion was considered an appropriate point-of-departure (POD) for AEGL-2 derivation with a total uncertainty factor application of 10 (3 for intraspecies variability and 3 for interspecies variability).

Red phosphorus is a direct-contact irritant which is primarily due to the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics which justifies an intraspecies uncertainty factor of 3. Because the mouse appeared to be a sensitive species and the critical effect associated with the POD are of minimal severity for the AEGL-2 tier, the interspecies uncertainty factor of 3 is considered adequate. Further reduction of the AEGL-2 values by additional uncertainty adjustment would result in AEGL-2 values inconsistent with the limited information available for humans. Data were unavailable with which to empirically derive a time scaling exponent, n, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

For AEGL-3 development, human data lacked definitive exposure terms but served as supporting data. As for AEGL-2, the Ballantyne (1998) study was considered more relevant for deriving AEGL values for red phosphorus due to its use of pure unformulated red phosphorus rather than the butyl rubber formulations. The 1-hour $BMLC_{05}$ of 469 mg/m^3 for rats exposed to red phosphorus smoke was used as the POD for AEGL-3 derivation. Although results of the Ballantyne (1998) study indicated the mouse is a more sensitive species, the BMC analyses of the mouse data showed the BMC model to be a poor fit (p=0.09 for the mouse data vs p=0.66 for the rat data). Furthermore, overall data in rats are more robust. The lethality benchmark values from the Ballantyne data are lower than those from other studies.

Animal lethality data exhibited considerable variability that would normally warrant an interspecies uncertainty factor of 10. However, this would result in AEGL-3 values inconsistent with human occupational data. The interspecies variability is primarily the result of the extreme sensitivity of guinea pigs which the investigators and the NRC (1997a) considered uniquely susceptible and inappropriate for human health risk assessment. Therefore, the interspecies uncertainty factor was limited to 3. Red phosphorus is a direct-contact irritant which is a function of the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus was considered a greater determinant of the toxic response than toxicokinetics, thereby justifying an intraspecies uncertainty factor of 3. As previously noted, greater uncertainty application would result in AEGL-3 values inconsistent with the human experience data. Time scaling was performed as described for AEGL-2.

The AEGL values for red phosphorus are summarized in Table S-1.

TABLE S 1. AEGL Values For Red Phosphorus (mg/m^3)

Classification	10-min	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	6.7	4.7	3.7	0.93	0.47	3-fold reduction of the AEGL-2 values as a protective estimate of AEGL-1 severity
AEGL-2 (Disabling)	20	14	11	2.8	1.4	Mild pulmonary congestion in mice; 1-hr exposure to 111 mg/m^3 (Ballantyne, 1998); UF= 3 x 3; n=1 or 3
AEGL-3 (Lethality)	85	59	47	12	5.9	Rat 1-hr $BMCL_{05}$ of 469 mg/m^3 (Ballantyne, 1998); UF= 3 x 3; n=1 or 3

References

Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech. 17:251-266.

NRC (National Research Council). 1997a. Guidelines for developing community emergency exposure levels for hazardous substances. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

1. INTRODUCTION

Red phosphorus consists of randomly arranged arrays of phosphorus tetrahedra in the form of connected chains and rings. Along with white phosphorus, it is an allotropic form of phosphorus. It is produced by closed system heating of white phosphorus to 400°C for several hours (Berkowitz et al., 1981). The properties of red phosphorus are intermediate between those of white and black phosphorus (O'Neil, et al., 2001). Red phosphorus is more stable than white phosphorus and considered less toxic (Dalhamn and Holma, 1959). At normal temperature and humidity, red phosphorus reacts very slowly with water vapor and air to form phosphine and various phosphorus oxyacids (Ballou 1991). It may be ignited by friction, static electricity, heating or by oxidizing agents (Bingham, 2001).

Red phosphorus smoke is used as a military screen. The smoke is generated by combustion of red phosphorus/butyl rubber (RP/BR) containing 5% BR, about 1.25% insulating oil, and about 1% talc or silica (NRC, 1997b). The butyl rubber alters the dispersion characteristics of the smoke. The organic components reportedly comprise less than 0.04% of the particulate phase of the smoke, while the remainder is a complex mixture of ortho-phosphoric, pyrophosphoric, tripolyphosphoric, tetrapolyphosphoric and higher phosphoric acids in varying percentages depending on the combustion conditions (Brazell et al., 1984, 1986, Mitchell and Burrows, 1990). The composition of RP/BR smoke generated under experimental and field conditions was qualitatively and quantitatively similar with the exception that higher polymeric forms were generally absent under field conditions (Brazell et al., 1984). Other uses include manufacturing of pyrotechnics, safety matches, and fertilizers (Mitchell and Burrows, 1990).

TABLE 1. Chemical and Physical Data for Red Phosphorus

Parameter	Value	Reference
Synonyms	Yellow phosphorus; white phosphorus; tetraphosphorus	Mitchell and Burrows (1990)
Chemical formula	Polymeric $(P_4)_n$	Mitchell and Burrows (1990)
Molecular weight	$(123.9)_n$	Mitchell and Burrows (1990)
CAS Registry No.	7723-14-0	Mitchell and Burrows (1990)
Physical state	solid	Mitchell and Burrows (1990)
Solubility in water	Negligible	Mitchell and Burrows (1990)
Vapor pressure	0.05 mm Hg @ 25°C	Mitchell and Burrows (1990)
Density	2.34 g/cm^3	Mitchell and Burrows (1990)
Boiling point/Freezing point	280°C/	Mitchell and Burrows (1990)

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Dalhamn and Holma (1959) reported four cases of acute, atypical sudden-onset pneumonia (verified by x-ray) in a factory where red phosphorus was produced via sublimation of white phosphorus. One death occurred. Because red phosphorus concentrations up to 40 mg/m^3 were detected, it was considered a possible cause. However, the workers also were

exposed to white phosphorus.

Mitchell and Burrows (1990) estimated that death may occur in humans exposed to 2,000 mg/m^3 of RP/BR smoke for more than 15 minutes but no details regarding this assessment were provided.

2.2. Nonlethal Toxicity

Mitchell and Burrows (1990) considered that acute exposure (specific duration not specified) to 1000 mg red phosphorus/m^3 would be intolerable. Uhrmacher et al. (1985) reported that workers experienced significant but reversible symptoms of respiratory distress and irritation of the eyes and mucous membranes following exposure to red phosphorus smoke at concentrations of 100 - 700 mg/m^3 for less than 15 minutes. Exposure to red phosphorus concentrations greater than 100 mg/m^3 were considered intolerable for workers, although accommodation to some effects was implied (ACGIH, 1991); additional information was unavailable regarding this report.

2.3. Developmental/Reproductive Effects

Data on developmental/reproductive toxicity of red phosphorus in humans were not available.

2.4. Genotoxicity

No information regarding potential genotoxicity of red phosphorus in humans was available.

2.5. Carcinogenicity

No information regarding the carcinogenic potential of red phosphorus in humans was available.

2.6. Summary

No definitive exposure-response data are available regarding the toxicity of red phosphorus in humans following inhalation exposure. Acute exposure to 40 mg/m^3 was associated with chemical pneumonia and exposure to 100-700 mg/m^3 was reportedly intolerable and resulted in reversible respiratory distress and ocular irritation.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Rats

Weimer et al. (1977) examined the effects of red phosphorus/butyl rubber (360 g)/black powder (15 g) mixture smoke on rats. Groups of five male and five female Sprague-Dawley albino rats were exposed in a static chamber to 1128-1882 mg/m^3 for 60-240 minutes

(Ct = 67,685-451,680 mg≅min/m^3) and observed for 2 weeks post exposure. A red phosphorus/butyl rubber (360 g) and black powder (15 g) mixture was ignited in the chambers and specific exposure concentrations maintained for specified durations. The exposure concentrations were monitored by measuring the total particulate matter and phosphoric acid content. The MMAD was reported as 1.1 µm. Respiratory distress was observed in rats of all treatment groups (Table 2). As the total Ct exposure product increased, respiratory distress became more severe, leading to prostration and death in some rats. In addition to respiratory effects, transient hypoactivity, salivation, and conjunctivitis were observed in rats of the 1813 and 1882 mg/m^3 treatment groups. There were no treatment-related effects on body weight, hematologic or clinical chemistry indices, organ weights, or gross or microscopic lesions. Most of the deaths occurred during exposure, but latency of 1 to 13 days was also observed.

TABLE 2. Mortality in Rats Following Acute Inhalation Exposure to Red Phosphorus/Butyl Rubber Smoke

Concentration (mg/m^3)	Duration (minutes)	Ct (mg≅min/m^3)	Mortality[a]
1128	60	67685	0/10
1537	60	92225	1/10
1846	90	166180	0/10
1676	120	201085	4/10
1625	150	148813	5/10
1572	180	283000	8/10
1813	180	326340	9/10
1882	240	451680	10/10

Weimer et al., 1977
[a] no. of deaths/no. exposed

In a study by Burton et al. (1982; also reported by Ballou, 1981) groups of five male and five female Sprague-Dawley rats were exposed to an to aerosol generated by combustion of red phosphorus/butyl rubber (95% red phosphorus and 5% butyl rubber with 1% mineral oil added as a die extruder lubricant and 1% talc powder as a coating). Nominal exposure concentrations were 3.15, 4.33 (only ten males tested at this exposure), 5.36, or 8.46 mg/L for 1 hour or 1.53 mg/L for 4 hours (equivalent to 3150, 4330, 5360, and 8460 mg/m^3 for 1 hour and 1530 mg/m^3 for 4 hours). Analytical concentrations (as phosphoric acid) were 2720 mg/m^3, 4030, 4410, and 6420 mg/m^3, respectively, for the 1-hour study and 1210 mg/m^3 for the 4-hour study. Analysis of the chamber atmosphere (gravimetric analysis followed by gas chromatographic analysis) showed a mixture of phosphorus pentoxide, phosphoric acid, and other hydrolysis products including trace amounts of phosphine, but no white phosphorus or other volatiles. The MMAD of the aerosols ranged from 1.0-1.4 µm (1.5 – 1.7 geometric standard deviation) for the 1-hour exposure and 0.9 µm for the 4-hour exposure. Post exposure observation was 14 days. All rats were subjected to gross examination.

Mortality ratios for rats in the Burton et al. (1982) study was 2/10, 5/10, 7/10, and 9/10 for the 1-hour exposure to 3150, 4330, 5360, or 8460 mg/L, respectively. Rats died at 1 to 11 days postexposure (Table 3). The 1-hour LC_{50} calculated using the method of Litchfield and

Wilcoxon (1949) was 4597 mg/m^3 (as red phosphorus/butyl rubber smoke; see Appendix E). Two rats died after a 4-hour exposure to 1.53 mg/L; one during exposure and one at 7 days post exposure. There were gross findings in the larynx and epiglottis of animals in all groups, and in the trachea of rats in the 8460 mg/m^3 group. In rats of the 1-hour exposure groups and the 4-hour 1530 mg/m^3 group, the epiglottis was slightly to moderately deformed, blunted on the tip, or partially to virtually absent; this was accompanied by ulceration and edema. Laryngeal lesions consisted of severe ulceration and edema with a fibrin substance on the mucosal surface of the ventral larynx. Moderate to severe pulmonary congestion, edema, and hemorrhage were observed in some rats exposed for 1 hour to 5360 and 8460 mg/m^3 but no further details were provided. No histopathological lesions were observed in the eyes, nares, or turbinates.

TABLE 3. Mortality of Rats Exposed to Red Phosphorus/Butyl Rubber Smoke

Exposure time (hrs)	Exposure concentration (mg/m^3)	Lethality	Time of death
1	3150	2/10	post-exposure day 6 and 10
1	4330	5/10	2 during exposure; 3 at 7-10 days post exposure
1	5360	7/10	1 at end of exposure; 1 at day 7, 2 at day 8; 3 at day 9
1	8460	9/10	6 at end of exposure; 3 within 2 days post exposure
4	1530	2/10	1 during exposure; 1 at day 7 post exposure

1-hr LC_{50} = 4597mg/m^3
Burton et al.,1982

Groups of five female Porton Wistar-derived rats (170-190g) were exposed for 30 minutes to combustion aerosols of two red phosphorus compositions (Marrs, 1984). Surviving rats were sacrificed at 24 hours and 14 days after exposure. Groups of five female rats served as controls. The test aerosols were generated by combustion of 95% red phosphorus and 5% butyl rubber (composition I) or 97% red phosphorus and 3% butadiene styrene (composition II). Exposure duration for all tests was 30 minutes. Air was drawn through filter paper and the impacted material weighed. The chamber atmosphere for composition I and II was 3.2 and 3.1 g/m^3 (3200 and 3100 mg/m^3, respectively) as solid material and 0.68 and 0.67 g/m^3 (680 and 670 mg/m^3, respectively) as phosphorus. All rats were necropsied and microscopic examination was conducted on the larynx, trachea, lungs, liver, kidney, adrenals, spleen, and pancreas. One rat exposed to composition I died during exposure and four rats exposed to composition II died within the first 24 hours. Necropsy findings in rats that died as a result of treatment included laryngeal inflammation, blood in the tracheal lumen, severe pulmonary congestion, pulmonary edema, and hepatic congestion. With the exception of pulmonary edema, similar findings were seen in the four remaining rats in the composition I group and in the one surviving rat (killed at 24 hours) of the composition II group. The rats surviving 14 days after exposure to composition I exhibited mild to moderate laryngeal inflammation and severe pulmonary congestion. The rats surviving 14 days after exposure to composition II exhibited laryngeal inflammation, mild alveolitis, and pulmonary congestion. The 30-minute exposure of rats to aerosols from either test composition resulted in severe damage to the respiratory tract and death.

Aranyi (1983) conducted acute and repeated inhalation exposure experiments in rats exposed to combustion aerosols of red phosphorus/butyl rubber. A standardized protocol was

established such that homogeneity of the chamber atmosphere could be maintained within ∀20% both within and between chambers (Aranyi, 1983). Chamber temperatures were 24-27°C, 40-60% relative humidity, and oxygen content about 21%. The median aerodynamic diameter of the aerosol ranged from 0.3 to 0.6 μm. A series of range-finding inhalation studies with red phosphorus/butyl rubber aerosol was conducted. In one experiment, male and female rats (10-20 per group) were exposed to red phosphorus/butyl rubber combustion aerosol at concentrations of 2.00, 2.22, 2.62, 3.09, or 3.15 mg/L (2000, 2200, 2620, 3090, or 3150 mg/m^3) for 1 hour (1.2 hours at 3.15 mg/L) or 8.8 mg/L (880 mg/m^3) for 4 hours, and observed for 14 days. No animals died after exposure to 2000 or 2220 mg/m^3, 6% (1/18) died after exposure to 2620 mg/m^3, and 20% (5/20) died after exposure to 3090 and 20% (2/10) died in the 3150 mg/m^3 exposure group (Table 4). Because no animals died after a single 4-hour exposure to 880 mg/m^3 (a cumulative exposure similar to a 1-hour exposure to 3090 or 3150 mg/m^3), the investigators concluded that exposure concentration rather than duration was the determining factor for lethality. There did not appear to be gender-related variability in the inhalation toxicity of red phosphorus aerosol.

TABLE 4. Mortality and Mean Survival Time of Rats Exposed to Red Phosphorus/Butyl Rubber Aerosol[a]

Exposure conc. (mg/m^3)	Exposure duration (hrs)	Mortality[b]	Survival time (days)
2,000	1.0	0/20	15.0
2220	1.1	0/18	15.0
2620	1.0	1/18	14.6
3090	1.0	5/20	11.6
3150	1.2	2/10	12.7
880	4.0	0/8	15.0

[a] Whole-body exposure, males and females combined; 14-day post exposure observation
[b] No dead/no. exposed
Aranyi, 1983

In an acute inhalation study, Ballantyne (1998) exposed groups of 12, 10, 9, and 12 Porton-strain rats to unformulated pure red phosphorus smoke at concentrations of 1422, 2749, 5056, or 6731 mg/m^3 (as ortho-phosphoric acid) or 450, 870, 1600, or 2130 mg/m^3, respectively, as phosphorus for 1 hour (Table 5). The study used the unformulated pure red phosphorus to avoid the presence of combustion products from formulated red phosphorus compounds. Exposure was whole body in a 10 m^3 chamber. The post exposure observation period was 14 days. The smoke was generated by combustion of unformulated pure red phosphorus by electrical heating via a resistance wire. The resulting atmosphere distributed by a fan was sampled and analyzed (spectrophotometric analysis of material trapped in filters) every 5 minutes to determine chamber ortho-phosphoric acid and phosphorus concentration. Homogeneous distribution of the smoke was confirmed (±5%) in preliminary tests without animals in the chamber. The animals were observed 14 days and all animals including those that died were subjected to necropsy and the larynx, trachea, lungs, liver, and kidneys were processed for microscopic examination. The effects of inhalation exposure to unformulated red phosphorus smoke are presented in Table 5. Damage to the respiratory tract (necrosis and inflammation in the larynx and trachea, pulmonary congestion, hemorrhage, edema, and pneumonitis) were detected in rats of all treatment groups. There was necrosis in the subepithelial layer of the

larynx and trachea at the higher concentrations but only in the epithelial layer at the lower concentrations. Deaths occurred in all treatment groups except the 450-mg/m^3 exposure group. The LC_{50} for a 1-hour exposure to red phosphorus aerosol was 1217 mg/m^3 as phosphorus (1422 mg/m^3 as ortho-phosphoric acid). No clinical observations were reported. Except for the liver and kidney, microscopic effects were limited to the respiratory tract of exposed animals.

TABLE 5. Mortality and Histopathology in Rats Following 1-Hour Exposure to Red Phosphorus Smoke

Parameter	Concentration (mg/m^3 as phosphorus)			
	450	**870**	**1600**	**2130**
No. animals/group	12	10	9	12
No. dead	0	2	6	12
LC_{50} & LCt_{50} (expressed as ortho phosphoric acid)	LC_{50} = 3846 mg/m^3 ; LCt_{50} = 231,429 mg•min/m^3			
LC_{50} & LCt_{50} (expressed as phosphorus)	LC_{50} = 1217 mg/m^3 ; LCt_{50} = 73,237mg•min/m^3			
Histopathology[a]				
Larynx				
Necrosis	0	2 (++,+++)	4 (+, ++)	11 (+,++)
Inflammation	1 (+)	2 (+, +++)	7 (+,++)	7 (+, ++, +++)
Trachea				
Necrosis	0	1 (++)	6 (+, ++)	9 (+)
Inflammation	1 (+)	2 (+, ++)	7 (+, ++)	2 (+, ++)
Lungs				
Congestion	5 (+)	5 (+, +++)	5 (+, ++)	11 (+, ++)
Hemorrhage	0	2 (++)	1 (++)	10 (+, ++)
Edema	0	1 (+)	2 (+, ++)	5 (+, ++)
Pneumonitis	0	1 (+++)	3 (++, +++)	10 (+, ++)
Liver				
Congestion	0	1 (+)	5 (++, +++)	11 (++, +++)
Kidney				
Congestion	0	0	0	2 (+)

Ballantyne, 1998.
[a]Severity grade: + mild, ++ moderate, +++ severe

3.1.2 Mice

Ballantyne (1998) exposed Porton-strain mice (20, 50, 50, 20, and 20/group) to aerosols of unformulated pure red phosphorus (351, 430, 695, 1422, or 2749 mg/m^3 as ortho-phosphoric acid; 111, 136, 220, 450, 870 mg/m^3 as phosphorus. The exposure system was as described for rats (section 3.1.1). The post exposure observation period was 14 days. The LC_{50} for a 1-hour exposure to red phosphorus smoke was 856 mg/m^3 (as ortho-phosphoric acid). None of the mice exposed to 111 mg/m^3 died, 1 of 50 (2%) exposed to 136 mg/m^3 died, and 44-100% died after exposure to 220-870 mg/m^3. The effects of exposure are summarized in Table 6. The incidence and severity of tracheal and laryngeal necrosis, and inflammation increased with exposure concentration.

TABLE 6. Mortality and Histopathologic Findings in Mice Following 1-Hour Inhalation Exposure to Red Phosphorus Smoke

Parameter	Concentration (mg/m^3 as phosphorus)				
	111	**136**	**220**	**450**	**870**
No. animals/group	20	50	50	20	20
No. Dead (%)	0	1 (2)	22 (44)	15 (75)	20 (100)
LC_{50} & LCt_{50} (expressed as ortho phosphoric acid eq.)	LC_{50} = 856 mg/m^3 ; LCt_{50} = 51,944 mg•min/m^3				
LC_{50} & LCt_{50} values (expressed as phosphorus)	LC_{50} = 271 mg/m^3 ; LCt_{50} =16,438 mg•min/m^3				
Histopathology[a]					
Larynx					
Necrosis	0	4 (+, ++)[c]	24 (+, ++, +++)	13 (+, ++)	19(+, ++)
Inflammation	0	5 (+, ++)	26 (+, ++, +++)	8 (+, ++, +++)	17 (+, ++, +++)
Trachea					
Necrosis	0	6 (+, ++)	24 (+, ++)	5 (+, ++)	14 (+, ++)
Inflammation	0	6 (+, ++)	28 (+, ++)	7 (+, ++)	14 (+, ++)
Lungs					
Congestion	6 (+)	50 (++, +++)	50 (++, +++)	17 (+, ++)	20 (+, ++)
Hemorrhage	0	1 (+)	20 (++, +++)	0	3 (+)
Edema	0	0	4 (+)	0	4 (+)
Pneumonitis	0	0	1 (+)	0	2 (+)
Liver					
Congestion	0	1 (+)	14 (+, ++)	0	8 (++)
Kidney					
Congestion	0	0	6 (+)	0	8 (+)
Cortical necrosis	0	0	7 (+, ++)		

Source: Ballantyne, 1998.
[a]Severity grade: + mild, ++ moderate, +++ severe

3.1.3 Rabbits

Ballantyne (1998) reported on the effects of red phosphorus smoke on groups of 10 New Zealand White rabbits exposed for 1 hour to concentrations of 1422, 2749, 5056, or 6731 mg/m^3 (as ortho-phosphoric acid) (450, 870, 1600, or 2130 mg/m^3, as phosphorus). The post exposure observation period was 14 days. The results of this experiment are summarized in Table 7. The 1-hr LC_{50} was 5337 mg/m^3 expressed as ortho-phosphoric acid and 1689 mg/m^3 expressed as phosphorus. Deaths occurred in all exposure groups. Clinical observations were not reported. With the exception of the mild to moderate congestion in the liver (observed only in rabbits that died), and mild congestion and cortical neurosis in the kidney, microscopic effects were limited to the respiratory tract.

TABLE 7. Mortality and Histopathology in Rabbits Exposed to Red Phosphorus Smoke for 1 Hour				
Parameter	**Concentration (mg/m^3 as phosphorus)**			
	450	**870**	**1600**	**2130**
No. animals/group	10	10	10	10
No. dead (%)	1 (10)	1 (10)	3 (30)	8 (80)
LC_{50} & LCt_{50} (expressed as ortho phosphoric acid eq.)	LC_{50} = 5337 mg/m^3 ; LCt_{50} = 321,906 mg•min/m^3			
LC_{50} & LCt_{50} (expressed as phosphorus)	LC_{50} = 1689 mg/m^3 ; LCt_{50} = 101,869 mg•min/m^3			
Histopathology[a]				
Larynx				
Necrosis	0	0	3 (++, +++)	8 (+, ++, +++)
Inflammation	1 (++)	0	10 (+. +++)	10 (+, ++, +++)
Trachea				
Necrosis	0	2 (+, ++)	5 (+, +++)	7 (+, ++)
Inflammation	1 (++)	1 (++)	9 (+, +++)	9 (+, +++)
Lungs				
Congestion	2 (+)	3 (+, ++,+++)	7 (+, ++, +++)	10 (+, ++, +++)
Hemorrhage	0	2 (++, +++)	2 (++)	8 (+, ++)
Edema	0	1 (+)	4 (+. ++, +++)	7 (+, ++, +++)
Pneumonitis	2 (++)	0	2 (+++)	7 (+, ++)
Liver				
Congestion	0	0	1 (++)	8 (+)
Kidney				
Congestion	0	0	0	8 (+)

Ballantyne, 1998.
[a]Severity grade: + mild, ++ moderate, +++ severe

3.1.4 Guinea Pigs

Weimer et al. (1977) exposed (see section 3.1.1 for experimental protocol) groups of five male and five female Hartley albino guinea pigs to red phosphorus/butyl rubber smoke at the concentrations 120-2277 mg/m^3 for 5-150 minutes (Ct = 600-222,415 mg≅min/m^3). A majority of the deaths occurred during exposure with the remaining deaths occurring within 1 day after exposure (Table 8). The primary sign of toxicity, similar to rats and dogs, was respiratory distress at all concentrations and durations, and which became more severe as the Ct product increased.

TABLE 8. Mortality in Guinea Pigs Following Acute Exposure to Red Phosphorus/Butyl Rubber Smoke

Concentration (mg/m^3)	Duration (minutes)	C×t ($mg \cong min/m^3$)	Mortality[a]
120	5	600	0/10
352	10	3,520	4/10
485	15	7,275	7/10
797	10	7,970	9/10
737	30	22,123	10/10
1,576	30	47,280	8/10
2,277	30	68,313	9/10
1,479	60	88,748	9/10
1,846	90	166,180	8/10
1,483	150	222,415	10/10

Weimer et al., 1977
[a]Incidence: no. of deaths/no. exposed

Ballantyne (1998) exposed groups of 20, 20, 10, and 10 Dunkin-Hartley guinea pigs to unformulated pure red phosphorus smoke at concentrations of 114, 164, 351, or 1422 mg/m^3 (as ortho-phosphoric acid) (36, 52, 111, or 450 mg/m^3, respectively, as phosphorus). The animals were observed 14 days post exposure. Necropsies was performed on all animals, and the larynx, trachea, lungs, liver, and kidneys were examined microscopically. The 1-hour LC_{50} expressed as ortho-phosphoric acid was 193 mg/m^3 and the 1-hour LC_{50} expressed phosphorus was 61 mg/m^3. Results of this experiment are summarized in Table 9. Respiratory tract lesions were less severe in guinea pigs than in other species tested; all lesions observed in guinea pigs were mild to moderate in severity. Those that died exhibited few or no tracheal or laryngeal lesions but did show notable pulmonary congestion. Mild liver and kidney congestion was observed in one to three guinea pigs exposed to 52-450 mg/m^3. Toxicity was observed in guinea pigs of all test groups. Based upon the histopathologic findings, the investigators considered the guinea pig deaths a consequence of asphyxia secondary to laryngospasm.

TABLE 9. Mortality and Histopathology in Guinea Pigs Exposed to Red Phosphorus Smoke for 1 Hour				
Parameter	**Concentration (mg/m^3)**			
	36	**52**	**111**	**450**
Animals/group	20	20	10	10
Number dead (%)	0	9 (45)	9 (90)	10 (100)
LC_{50} & LCt_{50} values (expressed as ortho phosphoric acid eq.)	LC_{50} = 193 mg/m^3 ; LCt_{50} = 11,506 mg•min/m^3			
LC_{50} & LCt_{50} values (expressed as phosphorus)	LC_{50} = 61 mg/m^3 ; LCt_{50} =3,641 mg•min/m^3			
Histopathology[a]				
Larynx				
Necrosis	4 (+)	5 (+)	0	0
Inflammation	4 (+)	7 (+, ++)	0	0
Trachea				
Necrosis	8 (+)	7 (+)	0	0
Inflammation	18 (+)	8 (+)	0	0
Lungs				
Congestion	20 (+, ++)	13 (+, ++)	10 (+)	3 (+)
Hemorrhage	2 (+)	1 (+)	0	0
Edema	4 (+)	0	0	0
Inflammation	0	2 (++)	0	0
Liver				
Congestion	0	3 (+)	1 (++)	1 (+)
Kidney				
Congestion	0	1 (++)	2 (+, ++)	2 (+)

Ballantyne, 1998.
[a]Severity grade: + mild, ++ moderate, +++ severe

3.2. Nonlethal Toxicity

3.2.1. Dogs

Beagle dogs (6/group; predominately males) were exposed in a static chamber to red phosphorus smoke at 1212-1882 mg/m^3 for 30-240 minutes (Ct = 45,580-451,680 mg≅min/m^3) and observed for 2 weeks following exposure (Weimer et al., 1977). A red phosphorus/butyl rubber (360 g) and black powder (15 g) mixture was ignited in the chambers and specific exposure concentrations maintained for specified durations. The exposure concentrations were monitored by measuring the total particulate matter and phosphoric acid content. The MMAD was 1.1 µm. Results of this experiment are summarized in Table 10. One dog in the1572 mg/m^3 (180-min) exposure group died 4 days after exposure but investigators did not consider it treatment related. The remaining dogs survived the duration of the study. Signs of toxicity were primarily those of respiratory distress although there were no exposure-related lesions in the respiratory tract. There were no treatment-related changes in body weight, hematologic or clinical indices, organ weights, or gross or microscopic lesions. Conjunctivitis was observed in dogs exposed to the highest ct product (451,680 mg·min/m^3) but this resolved by 3 days post exposure.

TABLE 10. Response of Beagle Dogs Following Acute Exposure to Red Phosphorus Smoke			
Concentration (mg/m^3)	**Duration (minutes)**	**Ct ($mg \cong min/m^3$)**	**Lethality[a]**
1519	30	45,570	0/6
1212	90	109,080	0/6
1483	150	222,415	0/6
1572	180	283,000	1/6 (4 days post exposure)
1813	180	326,340	0/6
1882	240	451,680	0/6 (reversible conjunctivitis)

Weimer et al., 1977
[a] no. of deaths/no. exposed

3.2.2. Rats

No deaths occurred in groups of 10 rats exposed for 60 minutes to red phosphorus smoke at a concentration of 1128 mg/m^3 (Section 3.1.1; Table 2). Weimer et al. (1977) noted that conjunctivitis was observed in rats exposed to ct products at or above 326,340 $mg \cdot min/m^3$. The conjunctivitis resolved by 3 days post exposure.

In a study by Aranyi (1983), male and female rats were exposed to red phosphorus/butyl rubber combustion aerosol at concentrations of 2.00, 2.22, 2.62, 3.09, or 3.15 mg/L (2000, 2200, 2620, 3090, or 3150 mg/m^3) for 1 hour and observed for 14 days (see Section 3.1.1; Table 4). No rats died after exposure to 2000 or 2220 mg/m^3 and there were no deaths after a single 4-hour exposure to 880 mg/m^3 (a cumulative exposure similar to that of a 1-hour exposure to 3090 or 3150 mg/m^3). Surviving rats, however, exhibited marked decreases in body weight immediately after the exposure with gradual recovery starting about 9 days later.

In an acute inhalation study, male Sprague-Dawley rats (number not reported) were exposed whole-body to 1000 mg/m^3 of red phosphorus/butyl rubber (95%/5%) aerosol for 3.5 hours (Aranyi et al., 1988). Controls were exposed to filtered air. The MMAD was 0.5 µm with a geometric standard deviation of 1.8. The mean concentration of red phosphorus/butyl rubber was reportedly within 5% of target. The phosphoric acid content was 70% and the oxygen concentration was 21%. Bactericidal activity in rats inhaling [^{35}S] *Klebsiella pneumoniae* was significantly decreased in RP/BR-exposed rats (~30% killed bacteria) compared with that of controls (~80% killed bacteria). Total cell count and macrophage 5'-nucleotidase activity were significantly decreased in rats exposed to 1000 mg/m^3, and the alveolar macrophage ATP was significantly increased in exposed rats.

In the acute inhalation study (see Section 3.1.1) reported by Ballantyne (1998), there were no deaths in a group of 12 Porton-strain rats exposed for 1 hour to red phosphorus smoke at concentrations of 1422 mg/m^3 as ortho-phosphoric acid (450 mg/m^3 as phosphorus). However, these rats did exhibit mild inflammation of the trachea and mild pulmonary congestion (Table 5).

3.2.3. Mice

In a 1-hour inhalation study there were no deaths among 20 Porton-strain mice exposed to aerosols of unformulated pure red phosphorus (351 mg/m^3 as ortho-phosphoric acid or 111 mg/m^3 as phosphorus) (Ballantyne, 1998). The exposure system was as described for rats (Section 3.1.1). The post exposure observation period was 14 days at which time necropsy revealed mild pulmonary congestion (Table 6).

3.2.4. Rabbits

Groups of five female New Zealand white rabbits (230-240 g) were exposed (whole body) to aerosols generated from red phosphorus/butyl rubber compositions I and II as described for rats in Section 3.1.1 (Marrs, 1984). The chamber concentrations were 3200 and 3100 mg/m^3 as solid material and 680 and 670 mg/m^3 as phosphorus for compositions I and II, respectively. A control group consisted of five female rabbits. There were no treatment-related deaths in either test group. Four rabbits exposed to composition I and sacrificed at 24 hours showed laryngeal inflammation with evidence of progression to epithelial necrosis. Tracheal inflammation was observed in these rabbits with three of five also exhibiting alveolitis, and one bronchopneumonia. Two of five rabbits killed on day 14 had laryngeal inflammation, three had tracheal inflammation, and all had alveolitis. For composition II, effects were qualitatively similar with the exception that one rabbit killed at 14 days post exposure exhibited pulmonary focal hemorrhage. Overall, severe respiratory damage was observed after a single 30-minute exposure to either composition.

3.2.5. Guinea Pigs

In the study by Weimer et al. (1977) (see section 3.1.1 for experimental protocol), there were no deaths among ten (5 male; 5 female) Hartley guinea pigs exposed for 5 minutes to red phosphorus/butyl rubber smoke at a concentration of 120 mg/m but the animals did exhibit signs of respiratory distress.

Ballantyne (1998) exposed groups of 20 Dunkin-Hartley guinea pigs to unformulated pure red phosphorus smoke at a concentration of 114 mg/m^3 (as ortho-phosphoric acid or 36 mg/m^3 as phosphorus). The animals were observed 14 days post exposure. Necropsy findings in guinea pigs surviving to the Day 14 termination included mild laryngeal inflammation and necrosis; mild tracheal inflammation and necrosis; and mild to moderate pulmonary congestion, hemorrhage and edema (Table 9).

3.3. Summary of Toxicity in Animals

The inhalation toxicity data for red phosphorus in animals is summarized in Tables 11 and 12. Regardless of the species, inhalation exposure to red phosphorus smoke or smoke from red phosphorus/butyl rubber consistently produced irritation and inflammation of the respiratory tract and, at higher concentrations, was lethal. Where histopathologic analysis was performed, lethality in rats, mice, and rabbits was associated with severe necrotic and inflammatory lesions in the larynx and trachea, and pulmonary congestion and edema. However, guinea pigs that died

exhibited only alveolar congestion in the lungs and no laryngeal or tracheal lesions. Ballantyne (1998) stated that minimal histopathologic findings in animals surviving potentially lethal exposures suggests that lesions may be reversible although they may predispose the animals to secondary infection. The toxic responses to red phosphorus and red phosphorus/butyl rubber smoke are generally attributed to the high phosphoric acid content (NRC, 1997b).

TABLE 11. Summary of Lethal Toxicity of Red Phosphorus or Red Phosphorus/Butyl Rubber Smoke in Animals

Species	Exposure	Effects	Reference
Rat	Ct of 67685-451680 mg/m^3; 60-240 min[a]	NOAEL: 1128 mg/m^3; 60 min LOAEL: 1537 mg/m^3; 60 min (10% lethality)	Weimer et al., 1977
	2720-6420 mg/m^3;1 hr[a]	NOAEL: not identified LOAEL : 2720 mg/m^3; 1 hr (20% lethality) LC_{50}: 4597 mg/m^3	Ballou, 1981; Burton et al., 1982
	1210 mg/m^3; 4 hrs[a]	20% lethality	Ballou, 1981; Burton et al., 1982
	680 mg/m^3; 30 min[a] 670 mg/m^3; 30 min[a]	20% lethality 80% lethality	Marrs, 1984
	2000-3150 mg/m^3; 1 hr[a]	NOAEL: 2200 mg/m^3; 1 hr LOAEL: 2620 mg/m^3; 1 hr (6% lethality)	Aranyi, 1983
	450-2130 mg/m^3; 1 hr[b]	NOAEL: 450 mg/m^3; 1 hr LOAEL: 870 mg/m^3; 1 hr (20% lethality) LC_{50}: 1217 mg/m^3 (as phosphorus) LC_{50}: 3846 mg/m^3 (as phosphoric acid)	Ballantyne, 1998
Mouse	111-870 mg/m^3; 1 hr[b]	NOAEL: 111 mg/m^3; 1 hr LOAEL: 136 mg/m^3; 1 hr (2% lethality) LC_{50}: 271 mg/m^3 (as phosphorus) LC_{50}: 856 mg/m^3 (as phosphoric acid)	Ballantyne, 1998
Rabbit	450-2130 mg/m^3; 1 hr[b]	NOAEL: - LOAEL: 450 mg/m^3; 1 hr (10% lethality) LC_{50}: 1689 mg/m^3 (as phosphorus) LC_{50}: 5337 mg/m^3 (as phosphoric acid)	Ballantyne, 1998
Guinea pig	Ct of 600-222,415[a] mg/m^3; 5-150 min	NOAEL: 120 mg/m^3; 5 min LOAEL 352 mg/m^3; 10 min (40% lethality)	Weimer et al., 1977
	36-450 mg/m^3; 1 hr[b]	NOAEL: 36 mg/m^3; 1 hr LOAEL:52 mg/m^3; 1 hr (45% lethality) LC_{50}: 61 mg/m^3 (as phosphorus) LC_{50}: 193 mg/m^3 (as phosphoric acid)	Ballantyne, 1998

[a]Red phosphorus/butyl rubber smoke test atmosphere; [b]red phosphorus smoke test atmosphere
NOAEL and LOAEL values are for death

TABLE 12. Summary of Nonlethal Toxicity of Red Phosphorus or Red Phosphorus/Butyl Rubber Smoke in Animals

Species	Exposure	Effects	Reference
Dog	Ct of 45570—451,680 mg/m^3; 30-240 min[a]	NOAEL: not identified LOAEL:1519 mg/m^3; 30 min.(respiratory distress); 1882 mg/m^3; 240 min.(conjunctivitis)	Weimer et al., 1977
Rat	Ct of 67685-451680 mg/m^3; 60-240 min[a]	NOAEL: not identified LOAEL: 1128 mg/m^3; 60 min (respiratory distress) 1813 mg/m^3; 180 min. (conjunctivitis)	Weimer et al., 1977
	2000-3150 mg/m^3; 1 hr[a]	no deaths; no additional information	Aranyi, 1986
	1000 mg/m^3; 3.5 hrs[a]	compromised alveolar macrophage function	Aranyi et al, 1988
	450-2130 mg/m^3; 1 hr[b]	NOAEL: not identified LOAEL: 450 mg/m^3; 1 hr (laryngeal and tracheal inflammation)	Ballantyne, 1998
Mouse	11-870 mg/m^3; 1 hr[b]	NOAEL: not identified LOAEL: 111 mg/m^3; 1 hr (mild pulmonary congestion);	Ballantyne , 1998
Rabbit	450-2130 mg/m^3; 1 hr[b]	all exposure tested resulted in lethality	Ballantyne , 1998
	680 mg/m^3; 30 min[a] 670 mg/m^3; 30 min[a]	laryngeal inflammation with evidence of progression to epithelial necrosis at 12 hrs; laryngeal inflammation, tracheal inflammation, and alveolitis at 14 days post exposure; no deaths	Marrs, 1984
Guinea pig	120 mg/m^3; 5 min.[a]	no deaths (exposure to 352 mg/m^3 for 10 min. caused 40% lethality)	Weimer et al., 1977
	36 mg/m^3; 1 hr[b]	no deaths; mild to moderate histopathology in larynx, trachea, and lungs; 1-hr exposure to 52 mg/m^3 caused 45% lethality	Ballantyne, 1998

[a]Red phosphorus/butyl rubber smoke test atmosphere; [b]red phosphorus smoke test atmosphere
NOAEL and LOAEL value are for effects other than death.

3.4. Developmental/Reproductive Effects

There are no data suggesting that a single inhalation exposure to red phosphorus would cause developmental or reproductive toxicity. The NRC (1997b) and Ballantyne and Salem (2008) reviewed single generation reproductive and developmental studies in rats as well as gestational exposure studies in rats exposed to red phosphorus/butyl rubber smoke. No reproductive effects or dose-related malformations were observed.

3.5. Genotoxicity

Information regarding the potential genotoxicity of red phosphorus following inhalation exposure is limited to a study by Aranyi (1984) in which female rats were exposed to red phosphorus/butyl rubber at 1000 mg/m^3 over a 2-week period. It was concluded (Aranyi, 1984; NRC, 1997b; Ballantyne and Salem, 2008) that the formulation was a weak clastogen

3.6. Carcinogenicity

Information regarding the potential carcinogenicity of red phosphorus following inhalation exposure is not available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Information regarding the metabolism and disposition of red phosphorus following inhalation exposure was provided by an experiment by Dalhamn and Holma (1959) in which 15 mice were exposed for 1 hour to [^{32}P]-red phosphorus aerosol (5 mg/m^3; maximum particle size of 1 μm and mean diameter of 0.46±0.28 μm). Groups of three mice were killed immediately after exposure and at 20 minutes, 40 minutes, 2 hours, 48 hours, and 10 days post exposure. Whole body autoradiography showed radioactivity in the lungs and gastrointestinal tract immediately after exposure and at each interval up to 2 hours after exposure. Radioactivity remained in the lungs of mice examined at 48 hours and at 10 days after exposure. There was no radioactivity detected in the gastrointestinal tract or other organs.

4.2. Mechanism of Toxicity

Red phosphorus and red phosphorus/butyl rubber smoke have high phosphoric acid content. Ortho-phosphoric acid is a corrosive mineral acid and is likely the cause of the irritation and inflammation to the respiratory tract that occurs following inhalation of red phosphorus smoke (Marrs, 1984; NRC, 1997b). Bingham (2001) noted that the cellular toxicity of red phosphorus is likely due to its activity as a reducing agent, resulting in disruption of oxidative processes.

4.3. Structure-Activity Relationships

There are no structure-activity data available useful to developing AEGL values for red phosphorus. As noted in Section 1, red phosphorus is not toxicologically or chemically equivalent to white or black phosphorus. The formation of phosphoric acid combustion products vary sufficiently such that AEGL values for any one would not necessarily be reflective of the responses to red phosphorus or the red phosphorus/butyl rubber formulations. Although phosphine is a known degradation product of red phosphorus, its formation is considered too slow to be of toxicologic concern (Mitchell and Burrows, 1990).

4.4. Other Relevant Information

4.4.1. Species Variability

Ballantyne (1998) showed that the comparative sensitivity of four species exposed to red phosphorus smoke was guinea pig>mouse>rat>rabbit based upon 1-hr LC_{50} values (expressed as mg phosphorus) of 61, 271, 1217, and 1689 mg/m^3, respectively. Based upon these data, the variability in the lethal response to red phosphorus/butyl rubber smoke may up to 27-fold when considering the uniquely sensitive guinea pig, but only abut 4-fold between rats and mice. Signs of toxicity were primarily in the respiratory tract although some effects were observed in the

liver and kidney in all species. Ballantyne (1998) also noted that the histopathology findings in guinea pigs suggested this species to be uniquely sensitive (asphyxial death due to laryngospasm) to the effects of red phosphorus smoke. In development of Emergency Exposure Guideline Levels, the NRC (1997a) considered the guinea pig to be uniquely sensitive and inappropriate as a model for human health risk. Based upon the results reported by Weimer et al. (1977), dogs are notably less sensitive than rats. A comparison of Ct products and responses shows that the Ct product causing only reversible conjunctivitis in dogs considerably exceeds the LCt_{50} of all rodent species.

4.4.2. Susceptible Populations

No data were found regarding variability in individual responses to the inhalation of red phosphorus smoke or red phosphorus/butyl rubber smoke. The corrosive/irritating properties of these smokes would likely predispose individuals with preexisting respiratory problems to greater risk for adverse effects or more severe responses. Because red phosphorus smoke appears to act as direct-contact irritant, variability in the responses of most individuals would be more a function of dosimetric factors rather than toxicodynamic processes.

4.4.3. Concurrent Exposure Issues

Concurrent exposure to any chemical affecting the respiratory tract would logically exacerbate the affects of red phosphorus smoke.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

All reports regarding human exposure described effects of greater severity than the AEGL-1 tier. Furthermore, reported exposure parameters and responses were imprecise.

5.2. Animal Data Relevant to AEGL-1

There are no dose-response data for AEGL-1 severity effects in animals. In a study by Ballantyne (1998), histological examination of six of 20 mice exposed to unformulated red phosphorus smoke (111 mg/m^3) for one hour showed pulmonary congestion at the 14-day post exposure termination. The next higher exposure (136 mg/m^3) resulted in notable increases in number and severity of respiratory tract lesions as well as the death of one animal. For nonlethal exposure in other species (rats, rabbits, guinea pigs), similar lesions were reported even in exposures not producing a lethal response, or no information was provided regarding nonlethal effects. The available data were lacking in the reporting of clinical observations that might have been instrumental in developing AEGL-1 values.

5.3. Derivation of AEGL-1 Values

Data were unavailable with which to directly derive AEGL-1 values for red phosphorus. Alternately, a 3-fold reduction of the AEGL-2 values was considered a justified approach for deriving the AEGL-1 values because the progression of effects from AEGL-1 severity to AEGL-

2 severity represent a continuum of the same mode of action (contact irritation) and effect. Further, comparison of the AEGL-1 values to the limited human exposure data suggests that notable effects would be unlikely following exposure to AEGL-1 concentrations. The AEGL-1 values are shown in Table 13.

TABLE 13. AEGL-1 VALUES for Red Phosphorus

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	6.7	4.7	3.7	0.93	0.47

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Human data regarding serious but nonlethal effects of inhalation exposure to red phosphorus lack definitive exposure terms. Mitchell and Burrows (1990) reported that acute exposure (specific duration not specified) to 1000 mg red phosphorus/m^3 was "intolerable". Uhrmacher et al. (1985) reported that human volunteers experienced significant but reversible symptoms of respiratory distress and irritation of the eyes and mucous membranes following exposure to red phosphorus smoke at concentrations of 100 - 700 mg/m^3 for less than 15 minutes. Exposure to red phosphorus concentrations greater than 100 mg/m^3 reportedly are not tolerated by workers, although accommodation to some effects was implied (ACGIH, 1991). Additional information was unavailable regarding these human experience reports.

6.2. Animal Data Relevant to AEGL-2

Most of the lethality bioassays also provided some information about nonlethal effects in laboratory species following acute exposure to red phosphorus smoke or red phosphorus/butyl rubber smoke (Table 12). Irritation of the respiratory tract was consistently noted in all species tested and, with the exception of guinea pigs, was qualitatively similar across species. Where available, necropsy results for animals surviving the red phosphorus exposures were indicative of respiratory tract damage that was reversible. One-hour exposure of rats to red phosphorus or red phosphorus/butyl rubber smoke at concentrations of 450-2000 mg/m^3 caused effects such as respiratory distress and pulmonary congestion but no deaths, while pulmonary congestion was reported for mice exposed to only 111 mg/m^3 for one hour. Dogs exhibited only conjunctivitis after a 240-minute exposure to 1882 mg/m^3, or respiratory distress at 1519 mg/m^3 for 30 minutes.

6.3. Derivation of AEGL-2 Values

Information regarding the response of humans to red phosphorus or red phosphorus/butyl rubber smoke lacked definitive exposure terms and was not considered sufficient for development of AEGL-2 values. Based upon results from studies with laboratory species, AEGL-2 severity effects (necrosis, hemorrhage, and edema in the respiratory tract) were consistently associated with exposures that also caused deaths. Necropsies of animals surviving through the post-exposure observation period generally revealed only minor signs of toxicity that

were not consistent with AEGL-2 severity but clearly showed the respiratory tract as a target of toxicity. Results from the multispecies study by Ballantyne (1998), showed no lethality and only pulmonary congestion in mice exposed one hour to smoke of unformulated red phosphorus (111 mg/m^3). Mice appeared to be more sensitive than rabbits, dogs, or rats. Guinea pigs were considered uniquely sensitive species and not considered for AEGL development (see Section 4.4.1). The 1-hour exposure of mice to 111 mg red phosphorus/m^3 which resulted in pulmonary congestion was considered an appropriate POD for AEGL-2 derivation with a total uncertainty factor application of 10 (3 for intraspecies variability and 3 for interspecies variability).

Red phosphorus is a direct-contact irritant, primarily due to the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics, and justifies an intraspecies uncertainty factor of 3. Because the mouse appeared to be a sensitive species and the critical effects associated with the POD are of minimal severity for the AEGL-2 tier, the interspecies uncertainty factor of 3 is considered adequate. Further reduction of the AEGL-2 values by additional uncertainty adjustment would result in AEGL-2 values inconsistent with the limited information available for humans. Data were unavailable to empirically derive a time scaling exponent, n, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The AEGL-2 values for red phosphorus are presented in Table 14 and their derivation summarized in Appendices A and C.

TABLE 14. AEGL-2 VALUES for Red Phosphorus (mg/m3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	20	14	11	2.8	1.4

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were available for derivation of AEGL-3 values for red phosphorus. Reports of exposures associated with human lethality (or estimates of lethal exposures) were not verifiable.

7.2. Animal Data Relevant to AEGL-3

Several studies (Weimer et al., 1977; Burton et al., 1982; Marrs, 1984; Aranyi, 1984; Ballantyne, 1998) provided animal lethality data for red phosphorus/butyl rubber smoke or for the combustion aerosol of pure red phosphorus. Data in several species (rat, mouse, rabbit, guinea pig) revealed notable differences in susceptibility (up to 28-fold difference in 1-hour LC_{50} values) among these species. Rabbits and dogs appeared to be less sensitive than rodents while guinea pigs were considered by investigators to be uniquely sensitive. In evaluating these data,

the NRC (1997b) considered the guinea pig data inappropriate for assessing human health risk. Benchmark estimates of lethality thresholds were calculated (U.S. EPA, 2007) for rat data (Burton et al., 1982; Aranyi, 1984; Ballantyne, 1998) and mouse data (Ballantyne, 1998) and are shown in Appendix E. Rabbits were a notably less sensitive species (Ballantyne, 1998) and were not further considered.

7.3. Derivation of AEGL-3 Values

Information on the inhalation toxicity of red phosphorus in humans lacked definitive exposure terms and, therefore, was not used to define a POD for AEGL-3 derivation but served as supporting data. Lethality assays in laboratory species utilized both red phosphorus/butyl rubber smoke (Weimer et al., 1977; Marrs, 1984; Aranyi, 1984) and pure unformulated red phosphorus smoke (Ballantyne, 1998). The data reported by Ballantyne (1998) were the most relevant for deriving AEGL values for red phosphorus in that it used pure unformulated red phosphorus rather than the butyl rubber formulations. The 1-hour $BMLC_{05}$ of 469 mg/m^3 for rats exposed to red phosphorus smoke was the POD for AEGL-3 derivation (Appendix E). Although results of the Ballantyne (1998) study suggested the mouse to be a more sensitive species, the BMC analyses of the mouse data showed the BMC model to be a poor fit to the data from mice ($p=0.09$ for the mouse data vs $p=0.66$ for the rat data). Furthermore, data for rats are more robust. The lethality benchmark values from the Ballantyne data are lower than those from the Aranyi (1984) report (Appendix E).

Toxicity data for multiple species showed a wide range of susceptibility to red phosphorus and red phosphorus/butyl rubber smoke. However, the responses of the dog, rabbit and guinea pig represented extremes; dogs and rabbits were notably less sensitive and guinea pigs were the most sensitive species tested. Although such variability would normally warrant an interspecies uncertainty factor of 10, this would result in AEGL-3 values inconsistent with human data; 15-minute exposures to 100-700 mg/m^3 produced ocular and nasal irritation but no mortality (see Section 2.2). Further, the interspecies variability is primarily the result of the extreme sensitivity of guinea pigs (see Section 4.4.1). Therefore, the interspecies uncertainty factor was limited to 3. Red phosphorus is a direct-contact irritant which is primarily due to the formation of ortho-phosphoric acid. The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics thereby justifying an intraspecies uncertainty factor of 3. As previously noted, application of greater uncertainty factors would result in AEGL-3 values inconsistent with the human experience data. Time scaling was performed as described for AEGL-2.

TABLE 15. AEGL-3 VALUES for Red Phosphorus (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	85	59	47	12	5.9

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values for red phosphorus were derived by a 3-fold reduction of the AZEGL-2 values. This approach was considered justified because the progression of effects from AEGL-1 severity to AEGL-2 severity represents a continuum of the same mode of action (contact irritation) and effect. The AEGL-2 values were based upon reversible pulmonary congestion in mice which was considered a protective critical effect for AEGL-2 development. Although some studies in animals described effects more consistent with AEGL-2 tier severity (notable histopathologic findings in the respiratory tract), these exposures were also associated with lethality. The AEGL-3 values were based upon a $BMCL_{05}$ for lethality in rats following a 1-hour exposure to unformulated red phosphorus smoke. Considerable species variability was apparent with dogs and rabbits being less sensitive than rodent species. Guinea pigs were considered uniquely sensitive, and not further considered for AEGL development. The AEGL values for red phosphorus are summarized in Table 16

TABLE 16. AEGL Values for Red Phosphorus (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	6.7	4.7	3.7	0.93	0.47
AEGL-2 (Disabling)	20	14	11	2.8	1.4
AEGL-3 (Lethality)	85	59	47	12	5.9

8.2. Comparisons with Other Standards and Guidelines

A summary of currently available standards and guidelines for red phosphorus is in Table 17. The values other than AEGL values are based upon data for red phosphorus/butyl rubber smoke formulations (the analyses for developing these exposure values were conducted prior to the 1998 publication by Ballantyne).

TABLE 17. Extant Standards and Guidelines for Red Phosphorus (mg/m^3)

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	6.7	4.7	3.7	0.93	0.47
AEGL-2	20	14	11	2.8	1.4
AEGL-3	85	59	47	12	5.9
EEGL[a]	40 (15-min)		10	2 (6-hrs)	
PEGL					1.0[b]
SPEGL[c]	4.0 (15-min)		1.0	0.2 (6-hrs)	
PPEGL					0.1[d]

[a] EEGL (Emergency Exposure Guidance Level, National Research Council) (NRC, 1997b) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but

avoids death, other severe acute effects and long-term or chronic injury; established for 15-min. 1-hr, and 6-hr durations.
[b] PEGL (Permissible Emergency Guidance Level, National Research Council) (NRC, 1997b) is defined as a concentration (8 hrs/day, 5 days/week) that will protect specific populations (military personnel and workers) from adverse health effects.
[c] SPEGL (Short-term Public Exposure Guidance Level, National Research Council) (NRC, 1993) is defined as a suitable concentration for unpredicted, single, short-term emergency exposure of 1 to 24 hours of the general public. SPEGLs take into account the wide range of susceptibility of the general public and are generally estimated by applying an uncertainty factor of two to ten to the EEGL to account for sensitive groups.
[d] PPEGL (Permissible Public Exposure Guidance Level, National Research Council) (NRC, 1997b) is defined as an exposure concentration (8 hrs/day, 5 days/week for perhaps a lifetime) that will be without adverse health effects in the general public including sensitive individuals.

8.3. Data Adequacy and Research Needs

Data are adequate for deriving AEGL-2 and AEGL-3 values for red phosphorus although definitive exposure terms are lacking for the limited data regarding human exposures. A threshold for AEGL-2 tier effects was not clearly defined and assessment of an exposure-response relationship for AEGL-1 tier effects was not possible with the available data.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1991. Documentations of the Threshold Limit Values and Biological Exposure Indices, 6th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH. (cited in NRC, 1997b)

Aranyi, C. 1983. Research and development on inhalation toxicologic evaluation of red phosphorus/butyl rubber combustion products. Phase II Report. U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. ADA158323.

Aranyi, C. 1984. Research and development on inhalation toxicologic evaluation of red phosphorus/butyl rubber combustion products. Phase III Report. U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. AD-A173549.

Aranyi, C. 1986. Research and development on inhalation toxicologic evaluation of red phosphorus/butyl rubber combustion products. Final Report (Phase IV). U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. NTIS/AD-A189 254/6.

Aranyi, C., Vana, S.N., Bradof, J.N., Sherwood, R. 1988. Effects of inhalation of red phosphorus/butyl rubber combustion products on alveolar macrophage responses in rats. J. Appl. Toxicol. 8:393-398.

Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech. 17:251-266.

Ballantyne, B. Salem, H. 2008. Screening smokes: Applications, toxicology, clinical considerations, and medical management. In: J.A. Romano, Jr., B. Lukey, H. Salem, eds.

Chemical Warfare Agents; Chemistry, pharmacology, Toxicology, and Therapeutics. 2nd Ed. CRC Press, Boca, Raton, FL, pp. 469-500.

Ballou, J.E. 1981. Chemical characterization and toxicologic evaluation of airborne mixtures. Final Report. U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. NTIS/AD-A102 678.

Berkowitz, J.B., Young, G.S., Anderson, R.C., Colella, A.J., Lyman, W.J., Preston, A.L., Steber, W.D., Thomas, R.G., and Vranka, R.G. 1981. Research and development for health and environmental hazard assessment. Task Order 5. Occupational and environmental hazards associated with the formulation and use of white phosphorus-felt and red phosphorus-butyl rubber screening smokes. Final Report. U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. NTIS/AD-A116 956/4.

Bingham, E. 2001. Phosphorus, selenium, tellurium, and sulfur. In: Patty's Toxicology, 5th ed. Volume 3. E. Bingham, B. Cohrssen, and C.H. Powell, Eds. Wiley Interscience, New York. pp. 459-464.

Brazell, R.S., Holmberg, R.W., and Moneyhun, J.H. 1986. Chemical characterization of selected military obscurants. Oak Ridge National Laboratory, Oak Ridge, TN. NTIS: DE84003202.

Brazell, R.S., Moneyhun, J.H., and Holmberg, R.W. 1984. Chemical and physical characterization of phosphorus smokes for inhalation exposure and toxicology studies. Final Report. U. S. Army Medical Research and Development.

Burton, F.G., Clark, M.L., Miller, and R.A., Schirmer, R.E. 1982. Generation and characterization of red phosphorus smoke aerosols for inhalation exposure of laboratory animals. Am. Ind. Hyg. Assoc. J. 43:767-772.

Dalhamn, T., and Holma, B.O. 1959. Animal experiments on the spread of inhaled radioactive red phosphorus in the body. A.M.A. Arch. Ind. Health. 20: 429-431.

Haber, F.R. 1924. Zur geschichte des gaskrieges [On the history of the gas war]. In: Fuenf Vortraege aus den Jahren 1920-23 [Five lectures from the years 1920-1923]. Berlin, Germany: Verlag von Julius Springer; pp. 76-92.

Litchfield, J.T.; Wilcoxon, F. 1949. Simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. 96: 99-113.

Marrs, T.C. 1984. Histological changes produced by exposure of rabbits and rats to smokes produced from red phosphorus. Toxicol. Lett. 21:141-146

Mitchell, W.R. and Burrows, E.P. 1990. Assessment of red phosphorus in the environment. U. S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. NTIS/AD-A221704.

NRC (National Research Council). 1993. Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

NRC (National Research Council). 1997a. Guidelines for developing community emergency exposure levels for hazardous substances. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

NRC (National Research Council). 1997b. Toxicity of military smokes and obscurants. Volume 1. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

O'Neil, M.J., A.M. Smith, P.E. Heckelman, et al. 2001. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals. Thirteenth Ed., Merck & Co. Inc., Whitehouse Station, NJ.

Rinehart, W. E., Hatch, T. 1964. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. Ind. Hyg. J. 25: 545-553.

ten Berge, W.F., Zwart, A., Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Materials 13: 301-309.

Uhrmacher, J.C., Werschulz, P.P., Schultz, D.O., Weber, D.O. 1985. Red Phosphorus. A health and environmental effects data base assessment of U.S. Army waste material. Final Report. Pp. 49-1 – 49-9. U.S. Army Medical Research and Development command, Fort Detrick, Frederick, MD. AD-A175274.

U.S. EPA (U.S. Environmental Protection Agency). 2007. Benchmark Dose Software. Version 1.4.1 National Center for Environmental Assessment, Office of Research and Development. [Online]. Available: http://www.epa.gov/ncea/bmds.htm.

Weimer, J.T, Affleck, G. Preston, J., Lucey, J., and Manthei, J. 1977. The acute effects of single exposures to United Kingdom red phosphorus screening smoke in rats, guinea pigs, rabbits, and dogs. Army Armament Research and Development Command, Chemical Systems Lab, Aberdeen Proving Ground MD. AD-B020755. Limited Distribution.

APPENDIX A: DERIVATION OF AEGL VALUES

Derivation of AEGL-1 Values for Red phosphorus

Data were unavailable with which to directly derive AEGL-1 values for red phosphorus. A 3-fold reduction of the AEGL-2 values was considered a justified approach for deriving the AEGL-1 values because the progression of effects from AEGL-1 severity to AEGL-2 severity represent a continuum of the same mode of action (contact irritation) and effect. AEGL-2 uncertainty factors were considered appropriate for lesser severity effects consistent with the AEGL-1 tier. Further, comparison of the AEGL-1 values to the limited human exposure data suggests that notable effects would be unlikely following exposure to AEGL-1 concentrations.

10-min AEGL-1

$20\ mg/m^3 \div 3 = 6.7\ mg/m^3$

30-min AEGL-1

$14\ mg/m^3 \div 3 = 4.7\ mg/m^3$

1-hr AEGL-1

$11\ mg/m^3 \div 3 = 3.7\ mg/m^3$

4-hr AEGL-1

$2.8\ mg/m^3 \div 3 = 0.93\ mg/m^3$

8-hr AEGL-1

$1.4\ mg/m^3 \div 3 = 0.47\ mg/m^3$

Derivation of AEGL-2 Values for Red phosphorus

Key Study: Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech.17:251-266.

Critical effect: Pulmonary congestion in mice exposed one hour to smoke of unformulated red phosphorus (111 mg/m^3); 2% lethality at the next higher exposure level (136 mg/m^3).

Time scaling: Data were unavailable with which to empirically derive a time scaling exponent, *n*, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, *n*, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (*n*), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

Uncertainty factors: Total uncertainty factor of 10.

Interspecies: 3; Because the mouse is a sensitive species and the critical effect associated with the POD is of minimal severity for the AEGL-2 tier, the interspecies uncertainty factor of 3 is considered adequate. Further reduction of the AEGL-2 values by additional uncertainty adjustment would result in AEGL-2 values inconsistent with the limited information available for humans.

Intraspecies: 3; The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics, which justifies an intraspecies uncertainty factor of 3.

Modifying Factor: None applied

Calculation:

$(111 \text{ mg/m}^3)^1 \times 1 \text{ hr} = 111 \text{ mg} \cdot \text{hrs/m}^3$

$(111 \text{ mg/m}^3)^3 \times 1 \text{ hr} = 1{,}367{,}631 \text{ mg}^3 \cdot \text{hrs/m}^3$

10-min AEGL-2

$(C \text{ mg/m}^3)^3 \times 0.1167 \text{ hrs} = 1{,}367{,}631 \text{ mg}^3 \cdot \text{hrs/m}^3$

$(C \text{ mg/m}^3)^3 = 8{,}204{,}145 \text{ mg}^3 \cdot \text{hrs/m}^3$

$C = 201.69 \text{ mg/m}^3$

$C = 201.69 \text{ mg/m}^3 \div 10 = 20 \text{ mg/m}^3$

30-min AEGL-2

$(C\ mg/m^3)^3 \times 0.5\ hrs = 1{,}367{,}631\ mg^3 \cdot hrs/m^3$
$(C\ mg/m^3)^3 = 2{,}735{,}263\ mg^3 \cdot hrs/m^3$
$C = 139.85\ mg/m^3$
$C = 139.85\ mg/m^3 \div 10 = 14\ mg/m^3$

1-hr AEGL-2

$(C\ mg/m^3)^1 \times 1\ hr = 111\ mg^3 \cdot hrs/m^3$
$(C\ mg/m^3)^1 = 111\ mg^3 \cdot hrs/m^3$
$C = 111\ mg/m^3$
$C = 111\ mg/m^3 \div 10 = 11\ mg/m^3$

4-hr AEGL-2

$(C\ mg/m^3)^1 \times 4\ hrs = 111\ mg^3 \cdot hrs/m^3$
$(C\ mg/m^3)^1 = 27.75\ mg^3 \cdot hrs/m^3$
$C = 27.75\ mg/m^3 \div 10 = 2.8\ mg/m^3$

8-hr AEGL-2

$(C\ mg/m^3)^1 \times 8\ hrs = 111\ mg^3 \cdot hrs/m^3$
$(C\ mg/m^3)^1 = 13.88\ mg^3 \cdot hrs/m^3$
$C = 13.88\ mg/m^3 \div 10 = 1.4\ mg/m^3$

Derivation of AEGL-3 Values for Red phosphorus

Key Study: Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech.17:251-266.

Critical effect: A 1-hour $BMLC_{05}$ of 469 mg/m^3 for rats exposed to red phosphorus smoke was used as an estimate of the lethality threshold and POD for AEGL-3 derivation.

Time scaling: Data were unavailable with which to empirically derive a time scaling exponent, *n*, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, *n*, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (*n*), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

Uncertainty factors:

Total uncertainty factor of 10.

Interspecies: 3;. Toxicity data in multiple species showed a wide range of susceptibility to red phosphorus and red phosphorus/butyl rubber smoke. The responses of the dog, rabbit and guinea pig represented extremes; dogs and rabbits were notably less sensitive and guinea pigs were the most sensitive species tested. Although such variability would normally warrant an interspecies uncertainty factor of 10, this would result in AEGL-3 values inconsistent with human data; 15-minute exposures to 100-700 mg/m^3 produced ocular and nasal irritation but no lethalities (see Section 2.2). Further, the interspecies variability is primarily the result of the extreme sensitivity of guinea pigs (see Section 4.4.1). Therefore, the interspecies uncertainty factor was limited to 3.

Intraspecies: 3; The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics, which justifies an intraspecies uncertainty factor of 3.

Modifying Factor: None applied

Calculation: $(469 \text{ mg/m}^3)^1 \times 1 \text{ hr} = 469 \text{ mg} \cdot \text{hrs/m}^3$
$(469 \text{ mg/m}^3)^3 \times 1 \text{ hr} = 103{,}161{,}709 \text{ mg}^3 \cdot \text{hrs/m}^3$

10-min AEGL-3

$(C\ mg/m^3)^3 \times 0.1167\ hrs = 103{,}161{,}709\ mg^3\ hrs/m^3$

$(C\ mg/m^3)^3 = 618{,}846{,}485\ mg^3 \cdot hrs/m^3$

$C = 852\ mg/m^3$

$C = 852\ mg/m^3 \div 10 = 85\ mg/m^3$

30-min AEGL-3

$(C\ mg/m^3)^3 \times 0.5\ hrs = 103{,}161{,}709\ mg^3 \cdot hrs/m^3$

$(C\ mg/m^3)^3 = 206{,}323{,}418\ mg^3 \cdot hrs/m^3$

$C = 590.09\ mg/m^3$

$C = 590.09\ mg/m^3 \div 10 = 59\ mg/m^3$

1-hr AEGL-3

$(C\ mg/m^3)^1 \times 1\ hr = 469\ mg^3 \cdot hrs/m^3$

$(C\ mg/m^3) = 469\ mg/m^3$

$C = 469\ mg/m^3 \div 10 = 47\ mg/m^3$

4-hr AEGL-3

$(C\ mg/m^3)^1 \times 4\ hrs = 469\ mg^3 \cdot hrs/m^3$

$(C\ mg/m^3)^1 = 117.25\ mg^3 \cdot hrs/m^3$

$C = 117.25\ mg/m^3 \div 10 = 12\ mg/m^3$

8-hr AEGL-3

$(C\ mg/m^3)^1 \times 8\ hrs = 469\ mg^3 \cdot hrs/m^3$

$(C\ mg/m^3)^1 = 58.6\ mg^3 \cdot hrs/m^3$

$C = 58.6\ mg/m^3 \div 10 = 5.9\ mg/m^3$

APPENDIX B: TIME SCALING CALCULATIONS

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber=s Law or Haber=s Rule ($C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor (n) for red phosphorus. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, n, for the relationship $C^n \times t = k$ is not possible. In the absence of definitive data, temporal scaling default exponents of $n = 3$ are typically applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001).

APPENDIX C: DERIVATION SUMMARY TABLES

AEGL-1 VALUES FOR RED PHOSPHORUS (ppm)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
6.7	4.7	3.7	0.93	0.47
Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: NA				
Effects: NA				
Endpoint/Concentration/Rationale: a 3-fold reduction of the AEGL-2 values was considered a justified approach for deriving the AEGL-1 values because the progression of effects from AEGL-1 severity to AEGL-2 severity represent a continuum of the same mode of action (contact irritation) and effect.				
Uncertainty Factors/Rationale: 10 total; 3 for interspecies and 3 for intraspecies (see AEGL-2)				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: NA				
Data Adequacy: Data were unavailable with which to derive AEGL-1 values for red phosphorus				

1

AEGL-2 VALUES FOR RED PHOSPHORUS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
20	14	11	2.8	1.4

Reference: Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke. Toxic Subst. Mech.17:251-266.

Test Species/Strain/Number: mouse/Porton-strain/20 -50 per group

Exposure Route/Concentrations/Durations: whole-body inhalation/111,136,220,450,870 mg/m^3/1-hr

Effects: conc. (mg/m^3)	Effect
111*	**mild pulmonary congestion in 6 of 20 mice***
136	2% lethality (1/50); necrosis, inflammation, hemorrhage in resp. tract
220	44% lethality (22/50); mild- severe histopathologic changes in resp. tract
450	75% lethality (15/20); mild- severe histopathologic changes in resp. tract
870	100% lethality (20/20)

* POD for AEGL-2 development

Endpoint/Concentration/Rationale: 1-hr exposure to 111 mg/m^3 caused only mild pulmonary congestion

Uncertainty Factors/Rationale: 10

Interspecies: 3; Because the mouse is a sensitive species and the critical effect associated with the POD is of minimal severity for the AEGL-2 tier, the interspecies uncertainty factor of 3 is considered adequate. Further reduction of the AEGL-2 values by additional uncertainty adjustment would result in AEGL-2 values inconsistent with the limited information available for humans.

Intraspecies: 3; The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics which justifies an intraspecies uncertainty factor of 3.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Data were unavailable with which to empirically derive a time scaling exponent, n, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

Data Adequacy: Sufficient; the mouse was considered a sensitive species for assessment of AEGL-2 severity effects.

2

1

AEGL-3 VALUES RED PHOSPHORUS (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
85	59	47	12	5.9

Key Study: Ballantyne, B. 1998. Acute inhalation toxicity of red phosphorus smoke Toxic Subst. Mech.17:251-266.

Test Species/Strain/Sex/Number: rats/Porton strain/9-12 per group/

Exposure Route/Concentrations/Durations: 1-hr whole-body exposure to 450, 870, 1600, or 2130 mg/m^3

Effects:

conc. (mg/m^3)	Effect
450	mild inflammation (larynx, trachea) and pulmonary congestion in 1-5 rats
870	20% lethality (2/10); necrosis, inflammation, edema, pneumonitis hemorrhage resp. tract
1600	67% lethality (6/9); mild- severe histopathologic changes in resp. tract
2130	100% lethality (12/12)

* POD for AEGL-3 development was the 1-hr $BMCL_{05}$ of 469 mg/m^3

Endpoint/Concentration/Rationale: 1-hr $BMCL_{05}$ of 469 mg/m^3 used as estimated of lethality threshold in rats

Uncertainty Factors/Rationale: 10

Interspecies:3;. Toxicity data in multiple species showed a wide range of susceptibility to red phosphorus and red phosphorus/butyl rubber smoke. The responses of the dog, rabbit and guinea pig represented response extremes; dogs and rabbits were notably less sensitive and guinea pigs were the most sensitive species tested. Although such variability would normally warrant an interspecies uncertainty factor of 10, this would result in AEGL-3 values inconsistent with human data; 15-minute exposures to 100-700 mg/m^3 produced ocular and nasal irritation but no lethalities (see Section 2.2). Further, the interspecies variability is primarily the result of the extreme sensitivity of guinea pigs (see Section 4.4.1). Therefore, the interspecies uncertainty factor was limited to 3.

Intraspecies: 3; The toxicodynamic aspect of exposure to red phosphorus is a greater determinant of the toxic response than is toxicokinetics which justifies an intraspecies uncertainty factor of 3.

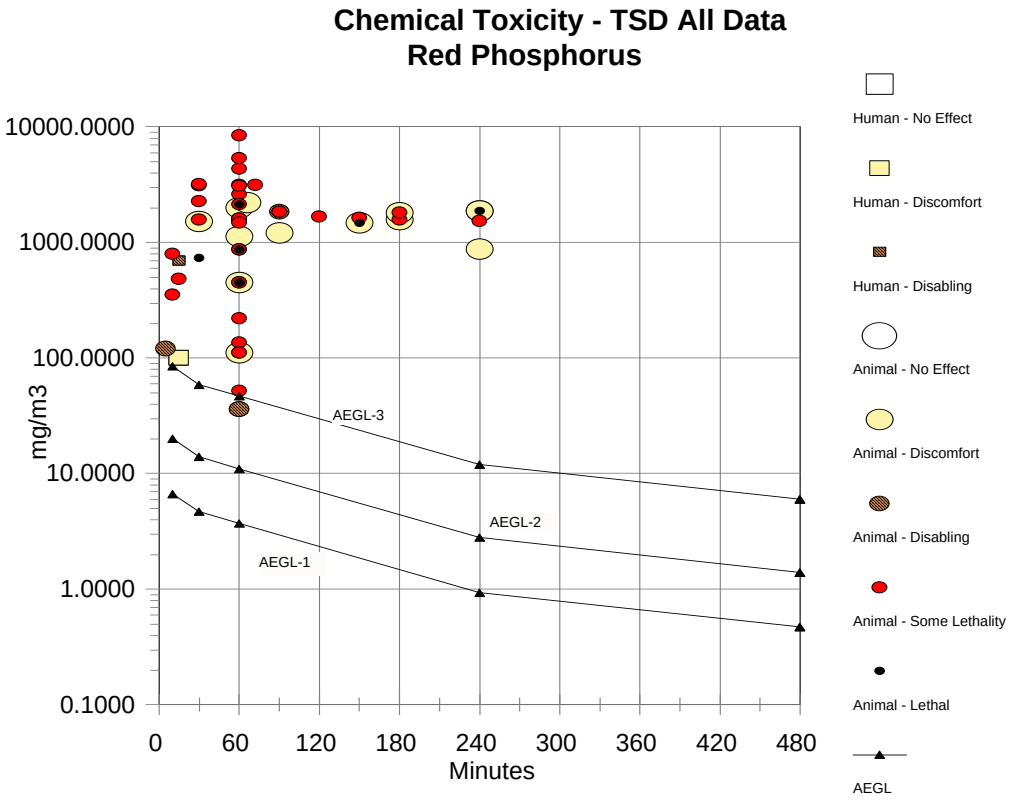
Modifying Factor: None applied

Animal to Human Dosimetric Adjustment:

Time Scaling: Data were unavailable with which to empirically derive a time scaling exponent, n, in the equation $C^n \times t = k$. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

Data Adequacy: Sufficient; exposure response data were sufficient for estimating a lethality threshold using U.S. EPA Benchmark Dose Software. Lethality bioassays were available in multiple species from multiple laboratories.

APPENDIX D: CATEGORY PLOT



1

Red
phosphorus

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal

Source	Species	Sex	# Expos.	mg/m^3	Min	Category	Comments
NAC/AEGL-1				6.7	10	AEGL	
NAC/AEGL-1				4.7	30	AEGL	
NAC/AEGL-1				3.7	60	AEGL	
NAC/AEGL-1				0.93	240	AEGL	
NAC/AEGL-1				0.47	480	AEGL	
NAC/AEGL-2				20	10	AEGL	
NAC/AEGL-2				14	30	AEGL	
NAC/AEGL-2				11	60	AEGL	
NAC/AEGL-2				2.8	240	AEGL	
NAC/AEGL-2				1.4	480	AEGL	
NAC/AEGL-3				85	10	AEGL	
NAC/AEGL-3				59	30	AEGL	
NAC/AEGL-3				47	60	AEGL	
NAC/AEGL-3				12	240	AEGL	
NAC/AEGL-3				5.9	480	AEGL	
	human		1	100	15	1	respiratory distress, ocular/nasal irritation (Uhrmacher et al., 1985)
	human		1	700	15	2	respiratory distress, ocular/nasal irritation (Uhrmacher et al., 1985)
	rat	m&f	1	1128	60	1	assumed mild respiratory tract/ocular effects (Weimer et al., 1977)*
	rat	m&f	1	1537	60	PL	10% lethality (Weimer et al., 1977)*
	rat	m&f	1	1846	90	2	assumed moderate respiratory tract/ocular effects (Weimer et al., 1977)*
	rat	m&f	1	1676	120	PL	40% lethality (Weimer et al., 1977)*
	rat	m&f	1	1625	150	PL	50% lethality (Weimer et al., 1977)8
	rat	m&f	1	1572	180	PL	80% lethality (Weimer et al., 1977)*
	rat	m&f	1	1813	180	PL	90% lethality (Weimer et al., 1977)*
	rat	m&f	1	1882	240	3	100% lethality (Weimer et al., 1977)*
	rat	m&f	1	3150	60	PL	20% lethality (Burton et al., 1982)*
	rat	m&f	1	4330	60	PL	50% lethality (Burton et al., 1982)*
	rat	m&f	1	5360	60	PL	70% lethality (Burton et al., 1982)*
	rat	m&f	1	8460	60	PL	90% lethality (Burton et al., 1982)*
	rat	m&f	1	1530	240	PL	20% lethality (Burton et al., 1982)*
	rat	f	1	3100	30	PL	20% lethality (Marrs, 1984)*
	rat	f	1	3200	30	PL	80% lethality (Marrs, 1984)*
	rat	m&f	1	2000	60	1	reversible body weight loss; no further details (Aranyi, 1983)*
	rat	m&f	1	2220	66	1	reversible body weight loss; no further details (Aranyi, 1983)*
	rat	m&f	1	2620	60	PL	1/18 dead at 14 days (Aranyi, 1983)*
	rat	m&f	1	3090	60	PL	5/20 dead at 11 days (Aranyi, 1983)*
	rat	m&f	1	3150	72	PL	2/10 dead at 13 days (Aranyi, 1983)*
	rat	m	1	880	240	1	assumed mild or reversible effects (Aranyi, 1983)*
	rat	m	1	450	60	1	mild pulmonary congestion (Ballantyne, 1998)
	rat	m	1	870	60	PL	20% lethality (2/10) (Ballantyne, 1998)

rat	m	1	1600	60	PL	66% lethality (6/9) (Ballantyne, 1998)
rat	m	1	2130	60	3	100% lethality (12/12) (Ballantyne, 1998)
mouse	m	1	111	60	1	mild pulmonary congestion (Ballantyne, 1998)
mouse	m	1	136	60	PL	2% lethality (1/50) (Ballantyne, 1998)
mouse	m	1	220	60	PL	44% lethality (22/50) (Ballantyne, 1998)
mouse	m	1	450	60	PL	75% lethality (15/20) (Ballantyne, 1998)
mouse	m	1	870	60	3	100% lethality (20/20) (Ballantyne, 1998)
rabbit	m	1	450	60	PL	10% lethality (1/10) (Ballantyne, 1998)
rabbit	m	1	870	60	PL	10% lethality (1/10) (Ballantyne, 1998)
rabbit	m	1	1600	60	PL	30% lethality (3/10) (Ballantyne, 1998)
rabbit	m	1	2130	60	PL	80% lethality (8/10) (Ballantyne, 1998)
guinea pig	m&f	1	120	5	2	respiratory distress (Weimer et al., 1977)*
guinea pig	m&f	1	352	10	PL	40% lethality (4/10) (Weimer et al., 1977)*
guinea pig	m&f	1	485	15	PL	70% lethality (7/10) (Weimer et al., 1977)*
guinea pig	m&f	1	797	10	PL	90% lethality (9/10) (Weimer et al., 1977)*
guinea pig	m&f	1	737	30	3	100% lethality (10/10) (Weimer et al., 1977)*
guinea pig	m&f	1	1576	30	PL	80% lethality (8/10) (Weimer et al., 1977)*
guinea pig	m&f	1	2277	30	PL	90% lethality (9/10) (Weimer et al., 1977)*
guinea pig	m&f	1	1479	60	PL	90% lethality (9/10) (Weimer et al., 1977)*
guinea pig	m&f	1	1846	90	PL	80% lethality (8/10) (Weimer et al., 1977)*
guinea pig	m&f	1	1483	150	3	100% lethality (10/10) (Weimer et al., 1977)*
guinea pig	m	1	36	60	2	mild to moderate histopath. throughout resp. tract (Ballantyne, 1998)
guinea pig	m	1	52	60	PL	45% lethality (9/20) (Ballantyne , 1998)
guinea pig	m	1	111	60	PL	90% lethality (9/10) (Ballantyne, 1998)
guinea pig	m	1	450	60	3	100% lethality (10/10) (Ballantyne, 1998)
dog	m&f	1	1519	30	1	respiratory distress without lesions (Weimer et al., 1977)*
dog	m&f	1	1212	90	1	respiratory distress without lesions (Weimer et al., 1977)*
dog	m&f	1	1483	150	1	respiratory distress without lesions (Weimer et al., 1977)*
dog	m&f	1	1572	180	1	respiratory distress without lesions (Weimer et al., 1977)*
dog	m&f	1	1813	180	1	respiratory distress without lesions (Weimer et al., 1977)*
dog	m&f	1	1882	240	1	respiratory distress, without lesions; conjunctivitis (Weimer et al., 1977)

* red phosphorus/butyl rubber formulation tested

APPENDIX E: BENCHMARK ANALYSES

Ballantyne (1998) Pure red phosphorus; rats; $BMCL_{05}$

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Wed Jun 17 10:10:33 2009
==========================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:
  P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background  =         0
              Intercept   =    -15.333
                 Slope    =    2.18725

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been specified
by the user,  and do not appear in the correlation matrix )

                  intercept      slope
 intercept            1             -1
    slope            -1              1

                              Parameter Estimates
                              95.0% Wald Confidence Interval
    Variable      Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
  background            0           NA
   intercept      -21.044       5.50834         -31.8402            -10.2479
       slope      2.96205      0.766325          1.46008             4.46402

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.

                          Analysis of Deviance Table
     Model          Log(likelihood)  # Param's          Deviance          Test d.f.   P-value
   Full model          -10.7327          5
  Fitted model         -11.7818          2               2.09835             3          0.5522
```

Reduced model	-36.0515	1	50.6377	4	<.0001
AIC:	27.5637				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	12	0.000
450.0000	0.0016	0.019	0	12	-0.139
870.0000	0.1598	1.598	2	10	0.347
1600.0000	0.7908	7.117	6	9	-0.916
2130.0000	0.9512	11.415	12	12	0.784

Chi^2 = 1.59 d.f. = 3 P-value = 0.6608

Benchmark Dose Computation

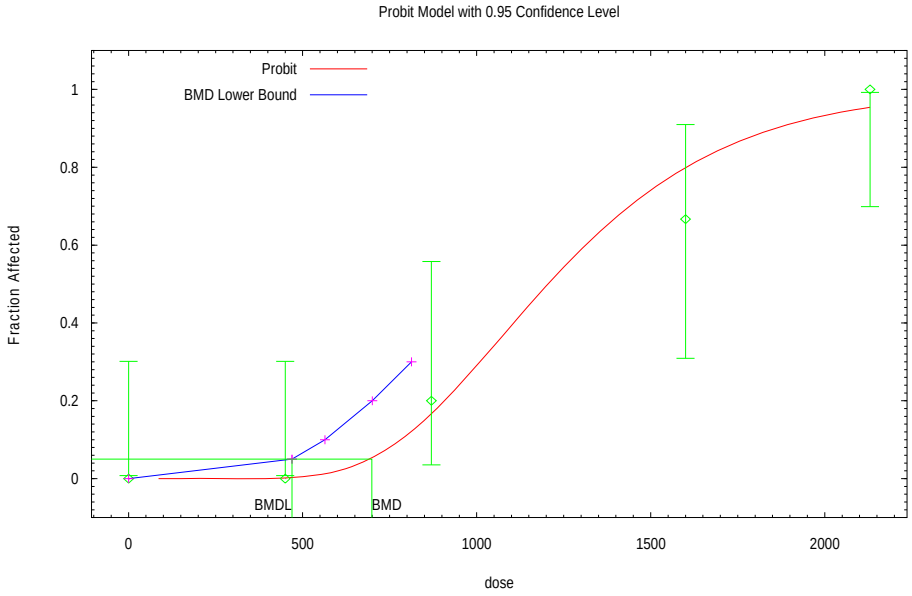
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC = 698.713

$BMCL_{05}$ = 469.332



10:10 06/17 2009

Ballantyne (1998); pure red phosphorus; rats; BMC_{01}

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Tue Jun 16 09:46:30 2009
==========================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:
  P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background  =         0
              Intercept   =    -15.333
                 Slope    =    2.18725

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been specified
by the user, and do not appear in the correlation matrix )

                  intercept       slope
 intercept            1              -1
    slope            -1               1

                              Parameter Estimates
                          95.0% Wald Confidence Interval
     Variable       Estimate       Std. Err.     Lower Conf. Limit   Upper Conf. Limit
   background             0             NA
    intercept       -21.044         5.50834          -31.8402           -10.2479
        slope        2.96205        0.766325           1.46008            4.46402

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.

                    Analysis of Deviance Table
      Model            Log(likelihood)  # Param's        Deviance  Test d.f.   P-value
    Full model           -10.7327           5
   Fitted model          -11.7818           2              2.09835     3         0.5522
  Reduced model          -36.0515           1              50.6377     4         <.0001
          AIC:        27.5637
```

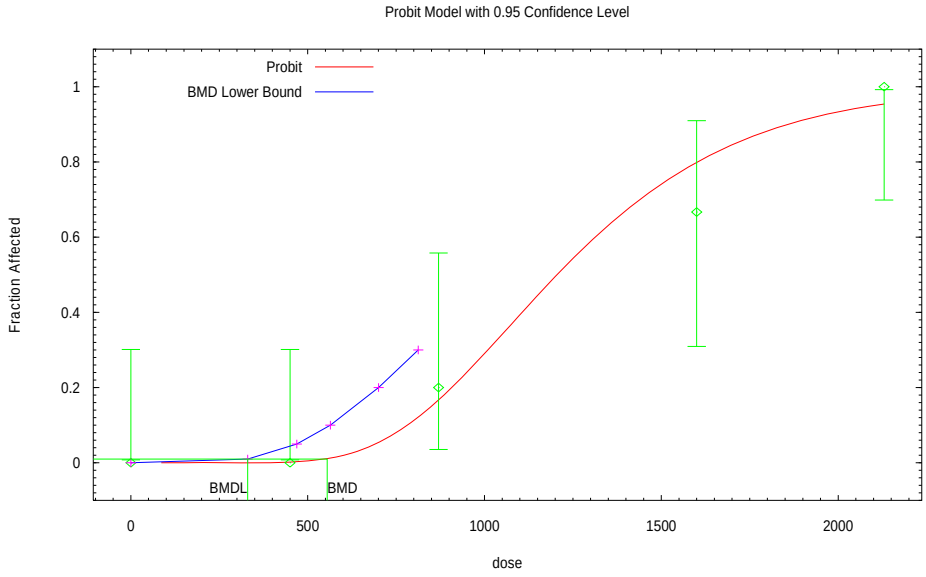
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	12	0.000
450.0000	0.0016	0.019	0	12	-0.139
870.0000	0.1598	1.598	2	10	0.347
1600.0000	0.7908	7.117	6	9	-0.916
2130.0000	0.9512	11.415	12	12	0.784

Chi^2 = 1.59 d.f. = 3 P-value = 0.6608

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC_{01} = 555.109
BMCL = 330.165



09:46 06/16 2009

Ballantyne (1998); pure red phosphorus; mice: $BMCL_{05}$

```
 ================================================================
            Probit Model. (Version: 2.8;  Date: 02/20/2007)
            Input Data File: C:\BMDS\UNSAVED1.(d)
            Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Tue Jun 16 09:01:08 2009
 ================================================================
 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
P[response] = Background  + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the
cumulative normal distribution function

   Dependent variable = COLUMN3
   Independent variable = COLUMN1
   Slope parameter is not restricted

   Total number of observations = 6
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   User has chosen the log transformed model

              Default Initial (and Specified) Parameter Values
                Background   =          0
                 Intercept      t =    -11.8628
                    Slope       =     2.07748

         Asymptotic Correlation Matrix of Parameter Estimates

         ( *** The model parameter(s)  -background  have been estimated at a boundary point, or have been specified
by the user, and do not appear in the correlation matrix )

                     intercept       slope
 intercept             1              -1
   slope              -1               1

                                 Parameter Estimates
                              95.0% Wald Confidence Interval
     Variable        Estimate       Std. Err.     Lower Conf. Limit   Upper Conf. Limit
    background            0             NA
     intercept         -12.51          1.73941         -15.9192          -9.10082
       slope            2.2331        0.321125           1.6037          2.86249

NA - Indicates that this parameter has hit a bound  implied by some inequality constraint and thus
     has no standard error.

                    Analysis of Deviance Table
      Model            Log(likelihood)  # Param's        Deviance  Test d.f.   P-value
    Full model           -50.4451            6
   Fitted model          -54.6333            2              8.37626      4        0.07873
  Reduced model          -113.136            1              125.382      5        <.0001
     AIC:       113.267
```

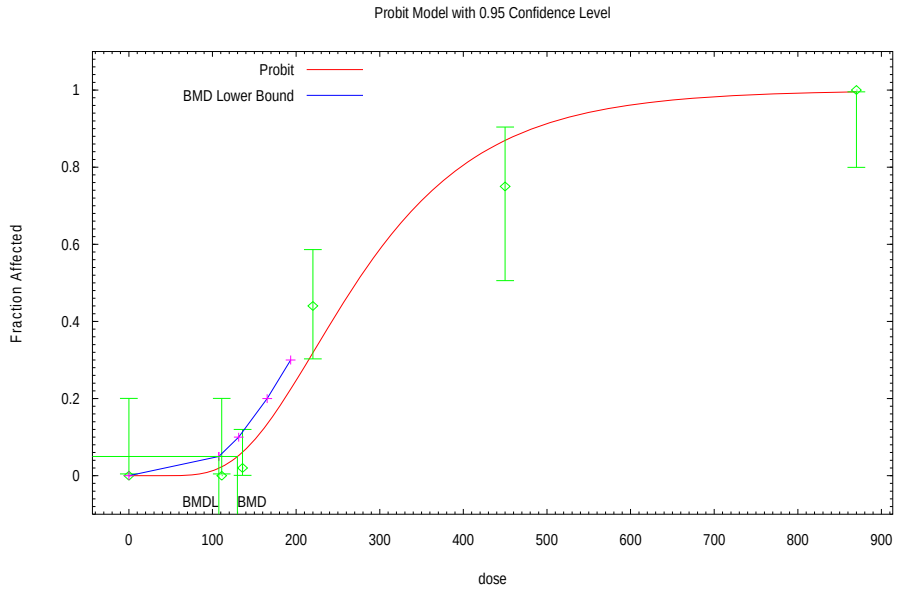
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	20	0.000
111.0000	0.0231	0.462	0	20	-0.688
136.0000	0.0618	3.092	1	50	-1.228
220.0000	0.3208	16.039	22	50	1.806
450.0000	0.8713	17.426	15	20	-1.620
870.0000	0.9954	19.908	20	20	0.304

Chi^2 = 7.96 d.f. = 4 P-value = 0.0931

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 129.736
$BMCL_{05}$ = 107.699



09:01 06/16 2009

Ballantyne (1998); pure red phosphorus; mice: BMC_{01}

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Tue Jun 16 11:23:34 2009
==========================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:
  P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background  =         0
              Intercept   =    -11.8628
                 Slope    =     2.07748

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background  have been estimated at a boundary point, or have been specified
by the user,  and do not appear in the correlation matrix )

                  intercept      slope
 intercept            1            -1
    slope            -1             1

                              Parameter Estimates
                              95.0% Wald Confidence Interval
     Variable      Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
   background            0           NA
    intercept       -12.51       1.73941          -15.9192           -9.10082
        slope        2.2331      0.321125            1.6037            2.86249

NA - Indicates that this parameter has hit a bound  implied by some inequality constraint and thus
    has no standard error.

                  Analysis of Deviance Table
      Model            Log(likelihood)  # Param's          Deviance  Test d.f.   P-value
    Full model          -50.4451            6
   Fitted model         -54.6333            2                8.37626       4       0.07873
  Reduced model          -113.136           1                125.382       5       <.0001
     AIC:       113.267
```

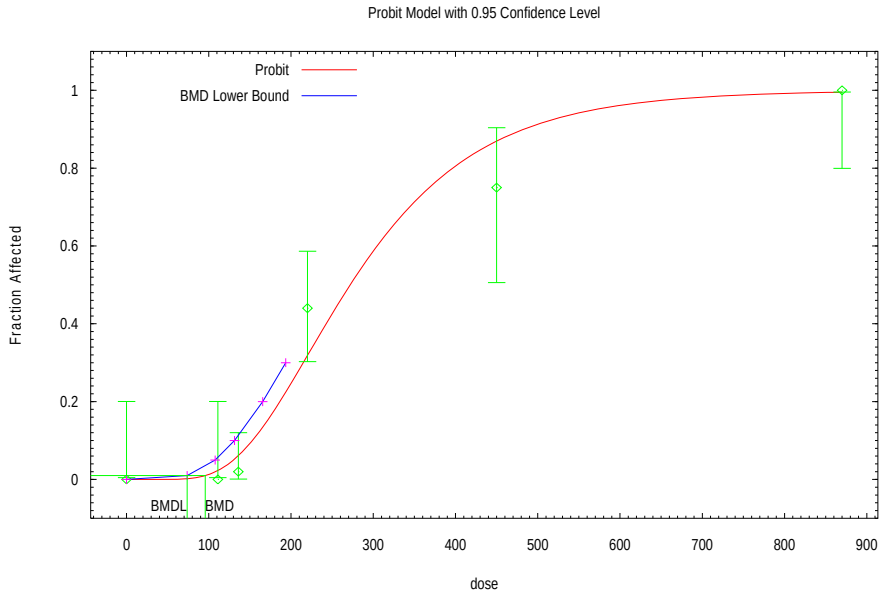
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	20	0.000
111.0000	0.0231	0.462	0	20	-0.688
136.0000	0.0618	3.092	1	50	-1.228
220.0000	0.3208	16.039	22	50	1.806
450.0000	0.8713	17.426	15	20	-1.620
870.0000	0.9954	19.908	20	20	0.304

Chi^2 = 7.96 d.f. = 4 P-value = 0.0931

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC_{01} = 95.6145
BMCL = 73.6406



11:23 06/16 2009

Red phosphorus rats Aranyi (1983) $BMCL_{05}$

```
 ================================================================
            Probit Model. (Version: 2.8;  Date: 02/20/2007)
            Input Data File: C:\BMDS\UNSAVED1.(d)
            Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Wed Jun 10 12:52:38 2009
 ================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:
  P[response] = Background  + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

              Default Initial (and Specified) Parameter Values
                Background   =         0
                 Intercept   =    -24.5057
                     Slope   =     2.94275

        Asymptotic Correlation Matrix of Parameter Estimates
        ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been specified
by the user,  and do not appear in the correlation matrix )

                  intercept      slope
 intercept            1            -1
    slope            -1             1


                        Parameter Estimates
                                        95.0% Wald Confidence Interval
     Variable      Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
   background             0           NA
    intercept      -46.7355      19.6316          -85.2127           -8.25818
        slope       5.72203      2.45465          0.911006            10.5331

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.1128	6			
Fitted model	-20.3531	2	0.480567	4	0.9754
Reduced model	-28.3622	1	16.4988	5	0.005555

AIC: 44.7062

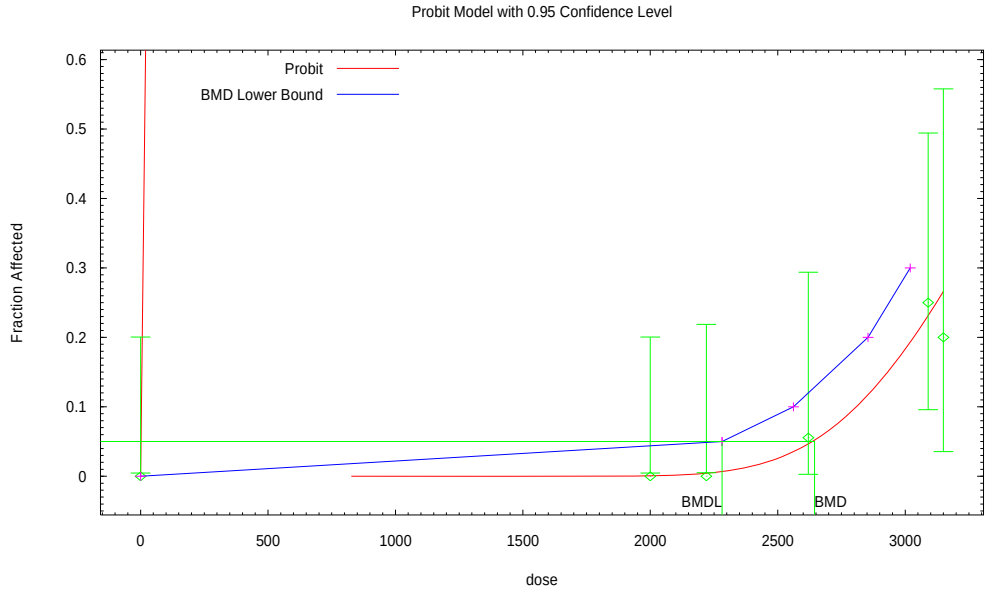
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	20	0.000
2000.0000	0.0006	0.012	0	20	-0.109
2220.0000	0.0041	0.073	0	18	-0.271
2620.0000	0.0448	0.806	1	18	0.221
3090.0000	0.2255	4.511	5	20	0.262
3150.0000	0.2599	2.599	2	10	-0.432

Chi^2 = 0.39 d.f. = 4 P-value = 0.9833

Benchmark Dose Computation

Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 2644.33
$BMCL_{05}$ = 2281.42



12:52 06/10 2009

Red phosphorus Aranyi (1983) rats BMC_{01}

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\ARANYI_RED_PHOS_RATS_BMCL05.(d)
        Gnuplot Plotting File:  C:\BMDS\ARANYI_RED_PHOS_RATS_BMCL05.plt
                                                Wed Jun 10 13:09:08 2009
==========================================================================
BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
  The form of the probability function is:
  P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 6
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background  =         0
              Intercept   =    -24.5057
                 Slope    =     2.94275

       Asymptotic Correlation Matrix of Parameter Estimates
       ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been specified
by the user, and do not appear in the correlation matrix )

                  intercept       slope
intercept             1              -1
slope                -1               1


                      Parameter Estimates

                                        95.0% Wald Confidence Interval
    Variable       Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
  background             0           NA
   intercept       -46.7355      19.6316          -85.2127           -8.25818
       slope        5.72203      2.45465          0.911006            10.5331

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-20.1128	6			
Fitted model	-20.3531	2	0.480567	4	0.9754
Reduced model	-28.3622	1	16.4988	5	0.005555

AIC: 44.7062

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	20	0.000
2000.0000	0.0006	0.012	0	20	-0.109
2220.0000	0.0041	0.073	0	18	-0.271
2620.0000	0.0448	0.806	1	18	0.221
3090.0000	0.2255	4.511	5	20	0.262
3150.0000	0.2599	2.599	2	10	-0.432

Chi^2 = 0.39 d.f. = 4 P-value = 0.9833

Benchmark Dose Computation

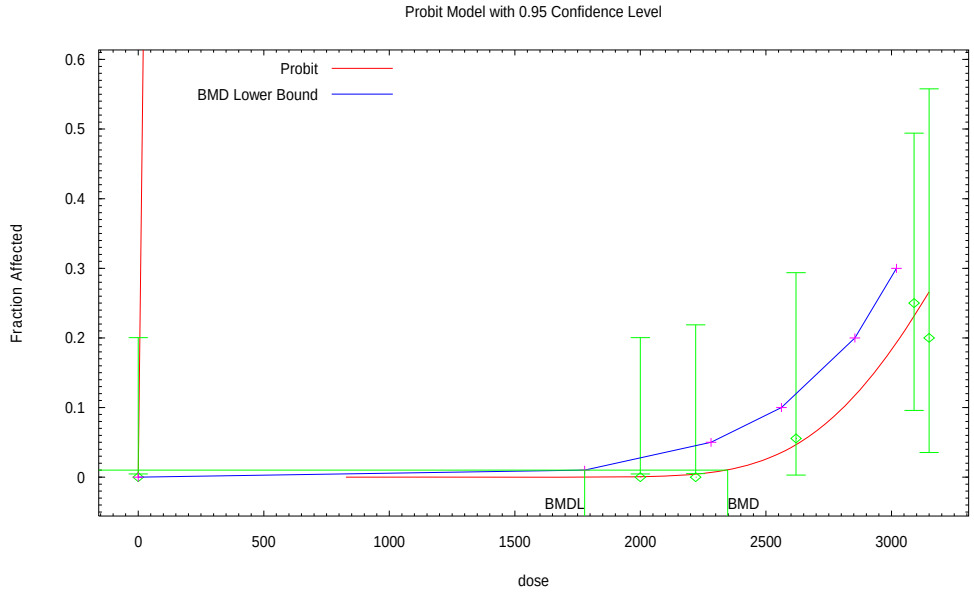
Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMC_{01} = 2347.43

BMCL = 1777.72



13:09 06/10 2009

Burton et al., 1982 rats $BMCL_{05}$

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Thu Jun 11 13:59:37 2009
==========================================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

 The form of the probability function is:
 P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background  =         0
              Intercept   =   -20.6913
                Slope     =    2.50922

       Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s)  -background have been estimated at a boundary point, or have been specified
by the user, and do not appear in the correlation matrix )

                  intercept       slope
intercept               1          -1
   slope               -1           1

                      Parameter Estimates
                           95.0% Wald Confidence Interval
    Variable       Estimate       Std. Err.     Lower Conf. Limit   Upper Conf. Limit
  background             0            NA
   intercept       -20.8672       6.73841          -34.0742           -7.66013
       slope        2.53033      0.810428          0.941915            4.11874

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.
```

Analysis of Deviance Table

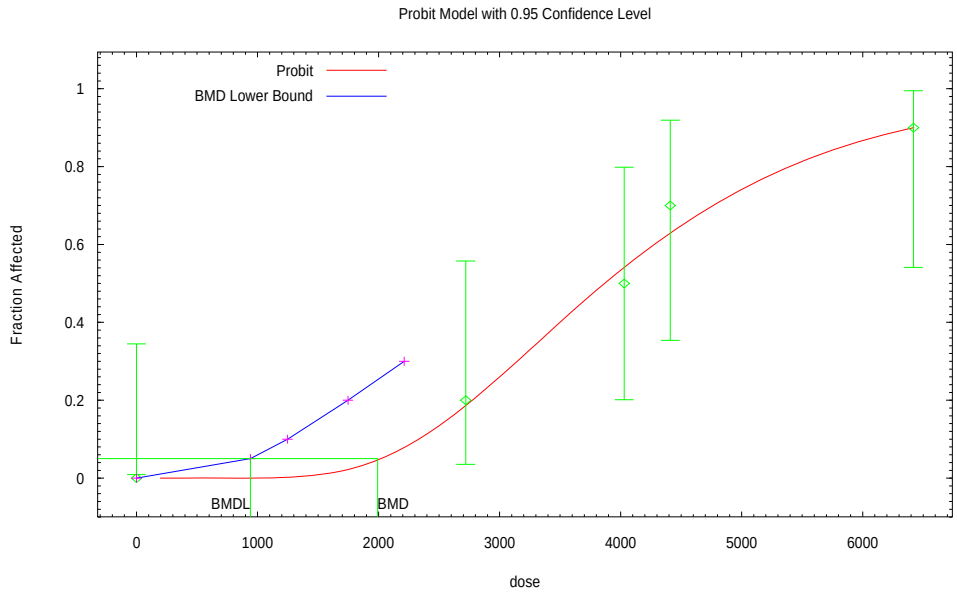
Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-21.295	5			
Fitted model	-21.4313	2	0.272686	3	0.9651
Reduced model	-34.4972	1	26.4044	4	<.0001
AIC:	46.8626				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
2720.0000	0.1959	1.959	2	10	0.033
4030.0000	0.5550	5.550	5	10	-0.350
4410.0000	0.6430	6.430	7	10	0.376
6420.0000	0.9060	9.060	9	10	-0.065

Chi^2 = 0.27 d.f. = 3 P-value = 0.9656

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 1991.77
$BMCL_{05}$ = 940.832



Red phosphorus Burton et al., 1982 rats BMC_{01}

```
 ================================================================
            Probit Model. (Version: 2.8;  Date: 02/20/2007)
            Input Data File: C:\BMDS\UNSAVED1.(d)
            Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Thu Jun 11 14:05:00 2009
 ================================================================
 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
   P[response] = Background + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
   where CumNorm(.) is the cumulative normal distribution function

   Dependent variable = COLUMN3
   Independent variable = COLUMN1
   Slope parameter is not restricted

   Total number of observations = 5
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008

   User has chosen the log transformed model

              Default Initial (and Specified) Parameter Values
                Background  =         0
                 Intercept  =    -20.6913
                     Slope  =     2.50922

        Asymptotic Correlation Matrix of Parameter Estimates
          ( *** The model parameter(s)  -background have been estimated at a boundary point, or have been
          specified by the user, and do not appear in the correlation matrix )

                intercept       slope
intercept           1            -1
   slope           -1             1

                        Parameter Estimates
                                    95.0% Wald Confidence Interval
    Variable       Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
  background             0           NA
   intercept       -20.8672      6.73841          -34.0742           -7.66013
       slope        2.53033     0.810428          0.941915            4.11874

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus
    has no standard error.

                  Analysis of Deviance Table
     Model       Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
   Full mode          -21.295         5
  Fitted model        -21.4313        2        0.272686     3        0.9651
 Reduced model        -34.4972        1        26.4044      4        <.0001

        AIC:        46.8626
```

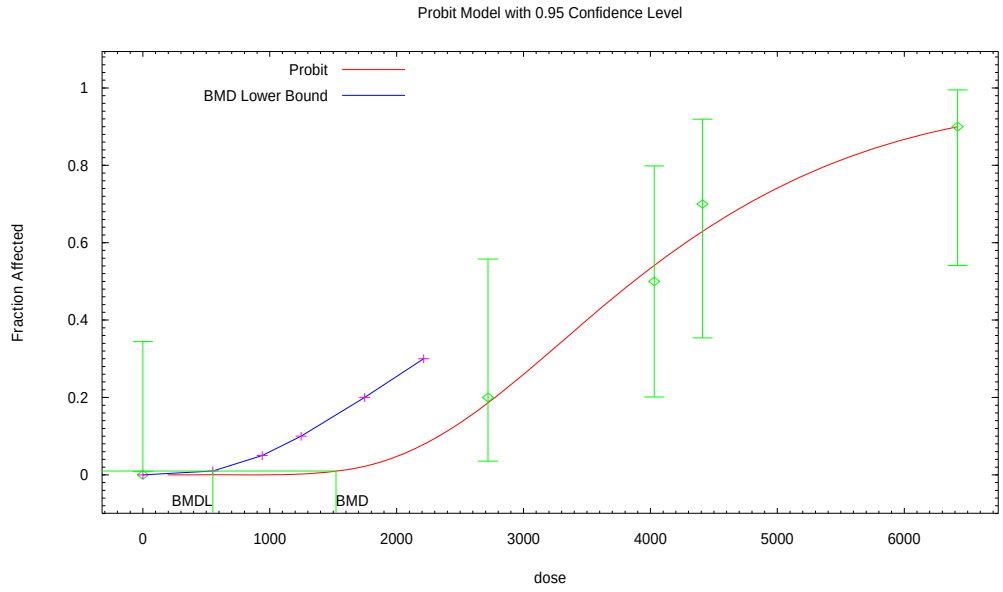
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
2720.0000	0.1959	1.959	2	10	0.033
4030.0000	0.5550	5.550	5	10	-0.350
4410.0000	0.6430	6.430	7	10	0.376
6420.0000	0.9060	9.060	9	10	-0.065

Chi^2 = 0.27 d.f. = 3 P-value = 0.9656

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC_{01} = 1521.49
BMCL = 551.729



14:05 06/11 2009

Burton et al. 1982 rats; red phosphorus/butyl rubber smoke lethality 1-hr inhalation
LC_{50} determination using Litchfield and Wilcoxon (1949)

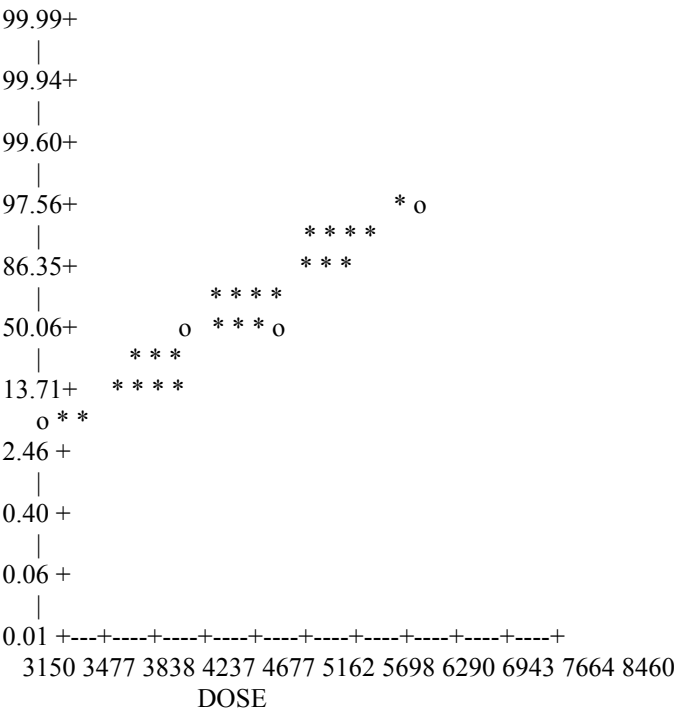
Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
3150.000	2/ 10	6.00	7.13	-1.13	0.0019
4330.000	5/ 10	50.00	39.99	10.01	0.0417
5360.000	7/ 10	70.00	73.96	-3.96	0.0081
8460.000	0/ 1	0(98.40)	98.44	-0.04	0.0000

Values in parentheses are corrected for 0 or 100 percent Total = 0.0518

1-hr LC_{50} = 4596.573(4062.857 - 5200.401)*
Slope = 1.28(1.17 - 1.40)*
* These values are 95 percent confidence limits

Total animals = 31 Total doses = 4 Animals/dose = 7.75
Chi-square = total chi-square X animals/dose = 0.4015
Table value for Chi-square with 2 Degrees of Freedom = 5.9900

LC_{84} = 5867.117 LC_{16} = 3601.170 FED = 1.13 FS = 1.10 A = 1.07



Expected Lethal Dose Values

LC0.1	1662.919
LC1.0	2336.999
LC5.0	2979.820
LC10	3326.297
LC25	3910.188
LC50	4596.573
LC75	5403.445
LC90	6351.954
LC99	9040.861