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TOXICOLOGICAL REVIEW

OF

PHOSGENE

(CAS No. 75-44-5)

**In Support of Summary Information on the
Integrated Risk Information System (IRIS)**

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U.S. Environmental Protection Agency
Washington, DC

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LIST OF ABBREVIATIONS AND ACRONYMS

AEGL	Acute Exposure Guideline Level
ARE	Acute reference exposure
BAL	Bronchio-alveolar lavage
BMD	Benchmark dose
BMDL	Lower-bound confidence limit on the benchmark dose
BMDS	Benchmark Dose Software
BMR	Benchmark response
C	Concentration
CatReg	Categorical regression
CL	Confidence limit
CO ₂	Carbon dioxide
EC	Effective concentration
EPA	U.S. Environmental Protection Agency
ERD	Extra risk dose
FVC	Forced vital capacity
G6PD	Glucose 6-phosphate dehydrogenase
HCl	Hydrochloric acid
HEC	Human equivalent concentration
IRIS	Integrated Risk Information System
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MW	Molecular weight
NCTR	National Center for Toxicological Research
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NPSH	Nonprotein sulfhydryl
NTP	National Toxicology Program
PBPK	Physiologically based pharmacokinetic
PMN	Polymorphonuclear
POD	Point of departure
RfC	Reference concentration
RfD	Reference dose
RGDR	Regional gas-dose ratio
SAR	Structure-activity relationship
SMR	Standard mortality ratio
T	Time
UF	Uncertainty factor

Units of Measure

mg/kg	Milligrams per kilogram body weight
mg/m ³	Milligrams per cubic meter
ng/m ³	Nanograms per cubic meter
ppb	Parts per billion

ppm	Parts per million
ppt	Parts per trillion

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to phosgene. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of phosgene.

In Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response*, EPA has characterized its overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing knowledge gaps, uncertainties, quality of data, and scientific controversies. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at 202-566-1676 (phone), 202-566-1749 (fax), or hotline.iris@epa.gov (email address).

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Summaries of the external peer reviewers' comments and public comments and the disposition of their recommendations are provided in Appendix C.

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of phosgene. IRIS Summaries may include an oral reference dose (RfD), an inhalation reference concentration (RfC), and a carcinogenicity assessment.

The RfD and RfC provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The inhalation RfC (expressed in units of mg/m³) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects).

This document does not attempt to develop concentration values protective of acute toxicity. For reference purposes, Appendix A presents a summary of the phosgene Acute Exposure Guideline Levels (AEGs) that was prepared by the National Academy of Sciences.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is an upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water or per µg/m³ air breathed. Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

Development of these hazard identification and dose-response assessments for phosgene has followed the general guidelines for risk assessment as set forth by the National Research Council (NRC, 1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Guidelines for Reproductive*

Toxicity Risk Assessment (U.S. EPA, 1996a), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposures to Carcinogens* (U.S. EPA, 2005b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Science Policy Council Handbook: Peer Review* (1st and 2nd editions) (U.S. EPA, 1998b, 2000a), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002).

The literature search strategy employed for this compound was based on the CASRN and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through March 2004.

2. CHEMICAL AND PHYSICAL INFORMATION

Phosgene is also known as carbon dichloride oxide, carbonic dichloride, carbon oxychloride, carbonyl chloride, carbonyl dichloride, and chloroformyl chloride. Some relevant physical and chemical properties are listed below (NTP, 2001; WHO, 1997):

CAS number: 75-44-5

Structural formula: COCl_2

Molecular weight: 98.92

Vapor pressure: 1,180 mmHg at 20°C

Water solubility: slight, reacts with water

Boiling point: 8.2°C

Odor threshold: 0.4 to 1.5 ppm

Irritation threshold: 3 ppm

Conversion factor: 1 ppm = 4.05 mg/m³, 1 mg/m³ = 0.247 ppm (25°C, 760 mmHg)

Phosgene is primarily used in the polyurethane industry for the production of polymeric isocyanates (WHO, 1998, 1997; U.S. EPA, 1986c, 1984). Phosgene is also used in the polycarbonate industry and in the manufacture of carbamates and related pesticides, dyes, perfumes, pharmaceuticals, and isocyanates. The majority of phosgene for industrial applications is made on site by the reaction of carbon monoxide and chlorine gas using an activated carbon catalyst. Phosgene may also be produced as a combustion product of carbon tetrachloride, methylene chloride, trichloroethylene, or butyl chloroformate, although these methods are not utilized industrially. Estimated worldwide production exceeds 5 billion pounds (WHO, 1997). Phosgene is a colorless gas at room temperature with an odor ranging from strong and stifling when concentrated to hay-like when diluted. Phosgene is slightly soluble in aqueous media, but, when dissolved, it is very rapidly hydrolyzed to carbon dioxide (CO₂) and hydrochloric acid (HCl), with a half-life at 37°C of approximately 0.026 seconds (Schneider and Diller, 1989; Manogue and Pigford, 1960).

Phosgene levels have been measured in ambient air (U.S. EPA, 1983; Singh et al., 1981, 1977; Singh, 1976). Multiple samples (10–257) were taken from four locations in California within a 24-hour period. The average level for three clean-air (rural and coastal) locations was 87 ng/m³ (21.7 ppt). In the Los Angeles basin, the average was 127.2 ng/m³ (31.8 ppt). These values were also cited by the World Health Organization (WHO, 1997). Kelly et al. (1994) also reported concentrations and transformations of hazardous air pollutants. They reported that the

phosgene ambient concentration median was 80 ng/m³.

Inhalation is the primary exposure route for phosgene. Suspected sources of atmospheric phosgene are fugitive emissions, thermal decomposition of chlorinated hydrocarbons, and photo-oxidation of chloroethylenes. Although the existence of atmospheric sinks for phosgene has been questioned, it is postulated that phosgene's removal from the atmosphere is rather slow (Singh et al., 1977).

The American Conference of Governmental Industrial Hygienists (ACGIH, 2000) recommends a time-weighted average of 0.1 ppm (0.4 mg/m³) to protect against irritation, anoxia, and pulmonary edema. The National Institute for Occupational Safety and Health (NIOSH, 2001) recommended exposure limit is 0.1 ppm, and the Occupational Safety and Health Administration (OSHA, 1993) has promulgated an 8-hour permissible exposure limit of 0.1 ppm.

3. TOXICOKINETICS

Phosgene is rapidly hydrolyzed in aqueous solution to CO₂ and HCl, which are likely to be exhaled (Schneider and Diller, 1989; Diller, 1985; Diller et al., 1979). Consequently, phosgene is not expected to leave the pulmonary circulation following inhalation exposure, nor is exposure by the oral route likely (WHO, 1998, 1997; U.S. EPA, 1986c, 1984). Data on phosgene absorption are not available. Phosgene is electrophilic and undergoes attack by a variety of nucleophiles. The predominant reaction is hydrolysis by water yielding carbon dioxide and hydrochloric acid. It also reacts with a wide variety of nucleophiles, including primary and secondary amines, hydroxy groups, and thiols. In addition, it also reacts with macromolecules, such as enzymes, proteins, or other polar phospholipids, resulting in formation of covalent adducts that can interfere with molecular functions. The loss of enzyme activity may lead to loss of cellular function and cell death (reviewed in WHO, 1998). Studies on the distribution and elimination of phosgene in animals or humans were not located in the published literature.

Phosgene is thought to participate directly in acylation reactions with amino, hydroxyl, or sulfhydryl groups (WHO, 1998, 1997; Schneider and Diller, 1989; U.S. EPA, 1986c; Diller, 1985). Formation of phosgene as a metabolite of other compounds has been hypothesized (reviewed in U.S. EPA, 2001, 1984) but not directly measured, perhaps owing to the rapid reaction of phosgene with tissue molecules or hydrolysis in aqueous solution. Phosgene is believed to be the major intermediate metabolite of chloroform (oxidative metabolism) (U.S. EPA, 2001a). Despite rapid conversion of phosgene to less “toxic” end products, other systemic effects, such as permeability-related edema (Borak and Diller, 2001) and adenosine triphosphate-related changes (Currie et al., 1987), have been noted.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS – EPIDEMIOLOGY, CASE REPORTS

As noted in Section 2, phosgene is a gas at room temperature, and aqueous phosgene rapidly hydrolyzes to CO₂, and HCl; consequently, exposure by the oral route is highly unlikely. Diller and Zante (1982) performed an extensive literature review of human effects from phosgene inhalation exposure and found that a great majority of data were anecdotal or rough estimates and, thus, did not contain reliable exposure concentrations and/or durations. Many case reports describe symptomology and postmortem results from human phosgene poisonings; however, exposure concentrations were not reported.

4.1.1. Acute Inhalation Exposure

The acute toxicity of phosgene inhalation has been well documented in humans (WHO, 1998, 1997; U.S. EPA, 1986c, 1984; Underhill, 1919).

Inhalation of phosgene at high concentrations results in a sequence of events, including an initial bioprotective phase, a symptom-free latent period, and a terminal phase characterized by pulmonary edema (Schneider and Diller, 1989; Diller, 1985). In the initial phase, high concentrations (>3 ppm) may result in a vagal reflex action that causes frequent, shallow respiration and decreased respiratory vital capacity and volume. This, in turn, leads to a decreased arterial CO₂ pressure increase and decreased blood pH. After cessation of exposure, the reflex syndrome shows a tendency to regress.

In the second phase, which may last for several hours postexposure, clinical signs and symptoms are generally lacking (Schneider and Diller, 1989; Diller, 1985). However, histologic examination reveals the beginnings of an edematous swelling, with blood plasma increasingly entering the pulmonary interstitium and alveoli. This may result in damage to the alveolar type I cells and a rise in hematocrit. In exposed humans, the individual is unaware of these processes; thus, this phase is termed the “clinical latent phase.” The length of this phase varies inversely with the inhaled dose.

In the third clinical phase of phosgene toxicity (Schneider and Diller, 1989; Diller, 1985), the accumulating fluid in the lung results in the edema becoming apparent both directly and indirectly. The severity of the edema increases, potentially resulting in decreased gas exchange as the fluid gradually rises from the alveoli to the proximal segments of the respiratory tract. Agitated respiration may cause the protein-rich fluid to take on a frothy consistency. A severe edema may result in an increased concentration of hemoglobin in the blood and congestion of the alveolar capillaries. At sufficiently high exposure levels, the heart also may be affected,

resulting in cardiac failure due to pulmonary congestion. In general, this phase peaks approximately 24 hours after an acute exposure and, assuming lethality does not occur, recedes over the next 3 to 5 days.

A case history of phosgene poisoning was reported in a 45-year-old welder who had symptoms of dyspnea and weakness (Glass et al., 1971). The authors concluded that phosgene poisoning causes reduction of forced vital capacity (FVC), airway obstruction, arterial hypoxia, and impaired co-transfer. Some of the pulmonary events precipitated by phosgene exposure, such as neutrophil and leukocyte infiltration, edema, and bronchial dilation, are also observed in asthmatics in the presence of ozone and nitrous oxide. Although the mechanisms for the phosgene-produced effect (acylation) and the ozone and nitrous oxide effect (oxidation) are presumed to be different, the resulting health endpoint appears to be similar (Jaskot et al., 1991) because phosgene acts as a lung irritant.

Cases of acute phosgene toxicity associated with two large-scale releases of phosgene in Germany and Japan have been reported. In Hamburg, Germany, on May 20, 1928, 11 metric tons (24,640 pounds) of “pure” phosgene escaped from a storage tank, resulting in a large-scale exposure to the airborne gas (Hegler, 1928; Wohlwill, 1928, both cited in U.S. EPA, 1986c). A total of 300 people—some located as far as 6 miles from the site—reported illness within a few days of the release. Of those, 10 died as a result of the exposure. One hospital reported admitting 195 victims on the night of May 20. Of those, 17 were very ill, 15 were moderately ill, and the rest were only slightly affected. Autopsy of six of the fatalities revealed abnormalities primarily in the lungs. Occasional lesions of the kidney, liver, and heart were observed.

In November 1966, phosgene was accidentally released from a factory in Japan (Sakakibara et al., 1967, cited in WHO, 1997). A total of 382 people were reported poisoned, 12 of whom were hospitalized. Signs and symptoms of exposure in the 12 hospitalized patients included headache, nausea, cough, dyspnea, fatigue, pharyngeal pain, chest tightness, chest pain, and fever. Seven patients showed evidence of pulmonary edema, as revealed by chest x-ray 48 hours postexposure. One patient reported lacrimation and redness of the eyes.

4.1.2. Subchronic Inhalation Exposures

Galdston et al. (1947) reported six cases (four women, two men) of phosgene exposure, with exposure ranging from 1 to 24 months. Common symptoms included rapid, shallow breathing; high minute volume; and low oxygen extraction. The measurable changes in pulmonary function that were consistently observed varied in type and severity, but they could not be correlated with the severity of phosgene intoxication or with chronic symptoms.

4.1.3. Occupational Epidemiology Studies

The effect of occupational exposure to phosgene was examined in workers employed from 1943 to 1945 at a uranium processing plant in the United States (Polednak and Hollis, 1985; Polednak, 1980). In the initial report (Polednak, 1980), a comparison was made between a group of 699 male workers exposed daily to phosgene and 9,352 male controls employed during the same time period but not exposed to phosgene. The duration of exposure was generally 2 months to 1 year; the followup period was 30 years. Exposure levels were not reported but were instead described as “low” (undetectable), with the level exceeding 1 ppm four to five times daily. Standard mortality ratios (SMRs) for respiratory diseases were not significantly different between controls (SMR = 113, 95% confidence limit [CL] = 98–130) and exposed workers (SMR = 78, 95% CL = 31–161) relative to cause- and age-specific death rates for white males in the United States. Likewise, no differences in the SMRs for lung cancer were found between controls (SMR = 113, 95% CL = 97–131) and exposed workers (SMR = 127, 95% CL = 66–222). No significant differences were found between controls and exposed workers for any other cause of death.

Interestingly, it should be noted that approximately 30 years after exposure, this cohort showed no statistically significant increases in mortality from overall cancer, from cancers at specific anatomical sites, or from diseases of the respiratory system or in overall mortality. However, the exposure period covered by the study was short, exposed groups were small, and exposure levels were not well documented. Consequently, evidence presented in this study is inadequate to assess the chronic toxicity or carcinogenicity of phosgene.

In the followup study (Polednak and Hollis, 1985), the number of subjects had decreased to 694 male workers who were exposed daily to phosgene and 9,280 male controls who were employed in the same plant but not exposed to phosgene. The SMRs for respiratory diseases were not significantly different between controls (SMR = 119, 95% CL = 106–133) and exposed workers (SMR = 107, 95% CL = 59–180). Likewise, no differences in the SMRs for lung cancer were found between controls (SMR = 118, 95% CL = 105–133) and exposed workers (SMR = 122, 95% CL = 72–193). No significant differences were found between controls and exposed workers for any other cause of death. The authors pointed out, however, that because of the small sample sizes, only large differences in mortality rates would have been detected in these studies.

Polednak and Hollis (Polednak and Hollis, 1985; Polednak, 1980) also examined a subgroup of 106 men who were exposed to high levels of phosgene (thought to be 50 ppm-min or greater) as a result of accidental workplace exposures. The reported overall SMR for all causes for exposed workers was 109 (95% CL = 73–157) in the 1980 study and 121 (95% CL = 86–165) in 1985 follow-up study. In the respiratory disease category, the SMR increased from 219 (3 deaths reported, 1.37 expected, 95% CL not reported) in the 1980 study to 266 (95% CL = 86–622) in the 1985 study; however, several of these cases reported using tobacco, making the

role of phosgene in the deaths uncertain. None of these values reached statistical significance. An attempt was made in the 1985 study to analyze a similar cohort of 91 female workers also exposed to approximately 50 ppm-min, but ascertainment of deaths and followup was less certain for this group and prevented a full analysis. Approximately 35 years after exposure to phosgene, no increase in overall mortality or mortality from cancer or respiratory disease was noted in this cohort.

4.2. ACUTE/SUBCHRONIC AND CHRONIC STUDIES IN ANIMALS

4.2.1. Oral Exposures

No animal studies on the toxicity of phosgene following oral exposure were identified.

4.2.2. Inhalation Exposures

No chronic studies in experimental animals on the effects of inhaled phosgene were located in the published literature. The majority of studies of phosgene are of acute duration, spanning from minutes to several hours. However, several studies (Kodavanti et al., 1997; Franch and Hatch, 1986; Clay and Rossing, 1964; Rossing, 1964) examined the effects of repeated short-term, “acute” exposures over 2 to 12 weeks. These studies are described below.

4.2.2.1. Acute Exposures

A number of studies have examined the effects of acute phosgene exposure in animals. A similar spectrum of effects was seen across the many species examined. Exposures were limited to concentrations between 0.5 and 40 ppm (2 to 160 mg/m³) for intervals ranging from 5 minutes to 8 hours.

Animals exposed to phosgene for a short duration show changes in breathing, including decreased tidal volume and minute volume, increased breathing frequency (Lehnert, 1992), and increased heart rate (Meek and Eyster, 1920). Exposed animals also show decreased body weight relative to air-exposed animals (Lehnert, 1992). An increase in lung weight also has been observed (Sciuto, 1998; Jaskot et al., 1991, 1989). After exposure to phosgene, lungs appear voluminous and heavy, contain considerable amounts of pale yellow fluid, and show signs of edema and emphysema (Ardran, 1950; Durlacher and Bunting, 1947). Exposure also results in changes in bronchio-alveolar lavage (BAL) parameters, including increased protein (Jugg et al., 1999; Sciuto, 1998; Jaskot et al., 1989; Slade et al., 1989; Hatch et al., 1986), phospholipid content (Jugg et al., 1999), and enzyme levels (Lehnert, 1992; Jaskot et al., 1991), as well as increases in the numbers of inflammatory cells (Lehnert, 1992). It has been reported that prior acute exposure to phosgene is protective against the effects of a later acute exposure (Ghio and Hatch, 1996; Box and Cullumbine, 1947).

Histopathologic examination of the lungs of phosgene-exposed animals reveals exposure-dependent edema and a progressive bronchiolar inflammatory response, with an infiltration of polymorphonuclear cells and lymphocytes and the presence of extravasated erythrocytes (Jugg et al., 1999; Lehnert, 1992; Keeler et al., 1990; Gross et al., 1965; Durlacher and Bunting, 1947; Meek and Eyster, 1920). This condition progresses with increasing exposure, causing alveolar hyperplasia, a progressive fibrotic response, and the gorging of capillaries with blood cells. Following phosgene exposure, an initial increase in blood volume occurs, followed by a significant decrease. With the resulting increase in hemoglobin concentration (Meek and Eyster, 1920), it is thought that the volume decrease is the result of fluid entering the lungs during edema formation.

Acute exposure to phosgene also has been shown to result in a decreased immune response in animals, as evidenced by an increased susceptibility to *in vivo* bacterial and injected tumor cells (Selgrade et al., 1989) and viral (Ehrlich and Burleson, 1991) infections as well as a decreased *in vitro* virus-killing and T-cell response (Burleson and Keyes, 1989; Ehrlich et al., 1989). Selgrade et al. (1989) reported that a single 4-hour exposure to phosgene concentrations as low as 0.025 ppm significantly enhanced mortality due to streptococcal infection in mice. Furthermore when the exposure time was increased from 4 to 8 hours, a significant increase in susceptibility to streptococcus was also seen at an exposure concentration of 0.01 ppm. The authors attempted to establish a mechanism for these findings by measuring alveolar macrophage activity. With intratracheal administration of bacteria, which delivers a much larger amount of bacteria than the inhalation route used in the earlier experiments, phosgene concentrations of 0.25 ppm and higher, which is 10-fold higher than the lowest observable effect, had little or no effect on alveolar macrophage phagocytic activity and little or no effect on total cells recovered, viability, or differential cell counts in lavage fluid obtained shortly after exposure. The mechanism(s) responsible for increased sensitivity to bacterial infection are unclear.

4.2.2.2. Subchronic Exposures

Kodavanti et al. (1997) exposed groups of male F344 rats to phosgene levels designed to provide equal products of concentration times time ($C \times T$) for all groups but the lowest exposure concentration. Groups of eight rats were exposed to clean air (control) or phosgene for 6 hours per day as follows: to 0.1 ppm (0.4 mg/m^3) for 5 days per week, to 0.2 ppm (0.8 mg/m^3) for 5 days per week, to 0.5 ppm (2 mg/m^3) for 2 days per week, or to 1 ppm (4 mg/m^3) for 1 day per week for 4 or 12 weeks. Groups of similarly exposed rats were allowed clean air recovery for 4 weeks after 12 weeks of exposure. The measured 12-week average concentrations were as follows (mean \pm SD range): 0.1 ppm group was 0.101 ± 0.002 (0.098–0.113); 0.2 ppm group was 0.201 ± 0.002 (0.196–0.207); 0.5 ppm group was 0.505 ± 0.008 (0.495–0.536); 1 ppm group

was 0.976 ± 0.03 (0.912–1.009). At the end of the exposure or recovery period, animals were sacrificed, and the lungs were weighed and processed for histologic examination. The 0.5 ppm histology samples were inadvertently lost, but other analyses were performed (e.g., BAL, lung volume, and biochemical parameters).

No mortality was reported for any exposure level or time examined. However, small but statistically significant decreases in body weight gain were reported in the 0.5 and 1 ppm rats at both 4 and 12 weeks of exposure. A concentration-dependent increase in relative lung weight was seen following both 4 and 12 weeks of exposure (statistically significant at 0.2 ppm or greater). The phosgene concentration at either time point seemed to drive this response rather than the $C \times T$ product. The effect appeared to be more severe at the end of 4 weeks than after 12 weeks of exposure. Phosgene also increased the lung displacement volume (an index of total lung volume) in all exposed groups at 4 weeks and at 0.2 ppm or greater at 12 weeks of exposure.

Histologic examination of animals exposed for 4 weeks revealed changes in the bronchiolar regions, with a small but apparent thickening and mild inflammation seen at 0.1 ppm that progressed in severity with concentration to a severe inflammation and thickening of the terminal bronchiolar regions and alveolar walls at 1 ppm (Tables 1 and 2). An increase in collagen staining, using Masson's trichrome stain, was seen in the 0.2 and 1 ppm animals, although no elevation of pulmonary hydroxyproline, a measure of collagen deposition, was observed.

**Table 1. Histopathology incidence indicating the number of animals affected following phosgene exposure^a
(from Kodavanti et al., 1997)**

	4 weeks				12 weeks				16 weeks ^c			
Phosgene concentration (ppm)	0.0	0.1 ^d	0.2 ^d	1.0 ^e	0.0	0.1 ^d	0.2 ^d	1.0 ^e	0.0	0.1 ^d	0.2 ^d	1.0 ^e
Number of animals examined	(12)	(8)	(8)	(6)	(12)	(8)	(8)	(8)	(9)	(6)	(7)	(5)
Alveolar effusion	0	0	0	2	0	0	0	1	2	0	0	0
Alveolus, interstitial thickening	0	2	5 ^b	6 ^b	0	2	4 ^b	8 ^b	0	0	0	0
Bronchus, epithelial alteration	0	1	2	3	0	0	0	1	0	0	0	0
Bronchus, inflammation	1	2	2	3	0	0	0	3	0	0	0	0
Terminal bronchiole/alveolus, inflammatory cell influx	2	3	8 ^b	6 ^b	1	3	8 ^b	8 ^b	0	0	1	1
Terminal bronchiole, peribronchiolar alveolus, epithelial alteration	2	4	5 ^b	6 ^b	0	1	7 ^b	8 ^b	0	2	3	2
Terminal bronchiole/peribronchiolar, increased collagen staining	1	1	8 ^b	6 ^b	2	2	8 ^b	8 ^b	2	1	7 ^b	5 ^b

^a Number in each column indicates number of animals affected (of total numbers used in analysis).

^b Statistically significant compared with unexposed (0.0 ppm) group, $p < 0.01$ (pairwise Fisher's exact test).

^c Indicates 12-week exposure, followed by a 4-week recovery period.

^d Phosgene exposure was 6 hours per day, 5 days per week.

^e Phosgene exposure was 6 hours per day, 1 day per week.

Table 2. Pulmonary histopathology severity score in rats following subchronic phosgene^a (from Kodavanti et al., 1997)

	4 weeks				12 weeks				16 weeks ^b			
Phosgene concentration (ppm)	0.0	0.1	0.2	1.0	0.0	0.1	0.2	1.0	0.0	0.1	0.2	1.0
Number of animals examined	(12)	(8)	(8)	(6)	(12)	(8)	(8)	(8)	(9)	(6)	(7)	(5)
Alveolar effusion	0	0	0	0.33	0	0	0	0.13	0.4	0	0	0
Alveolus, interstitial thickening	0	0.25	0.63	1.83	0	0.25	0.5	2.13	0	0	0	0
Bronchus, epithelial alteration	0	0.13	0.50	0.33	0	0	0.13	0.25	0	0	0	0
Bronchus, inflammation	0.08	0.25	0.4	0.83	0	0	0	0.13	0	0	0	0
Terminal bronchiole/alveolus, inflammatory cell influx	0.17	0.38	1.00	3.00	0.08	0.38	1.13	2.13	0	0	0.14	0.16
Terminal bronchiole, peribronchiolar alveolus, epithelial alteration	0.17	0.5	0.63	2.50	0	0.13	0.88	2.38	0	0.33	0.43	0.60
Terminal bronchiole/peribronchiolar, increased collagen staining	0.08	0.13	1.00	1.00	0.17	0.25	1.0	2.0	0.2	0.17	1.0	1.0

^a Severity scores given to individual animals from a complete pathological examination are 0, not remarkable; 1, minimal; 2, slight/mild; 3, moderate; 4, moderately severe; and 5, severe, based on relative evaluation of lesions. Based on severity scoring, a maximum score of 3 was assigned for some of the lesion types at highest phosgene concentrations. Severity scores for each animal within a group were added, and an average score per animal was calculated; this is shown in the table.

^b Indicates 12-week exposure, followed by a 4-week recovery period.

Similar changes were seen following 12 weeks of exposure; the lesions did not appear to have progressed beyond those seen at 4 weeks. Both pulmonary prolyl hydroxylase activity and pulmonary desmosine were elevated at both 4 and 12 weeks of exposure in the 1 ppm animals only. The intensity of collagen staining in the bronchiolar region was elevated (higher than in controls) in the 0.2 and 1 ppm groups. The pulmonary hydroxyproline level was significantly elevated only in the 1 ppm animals after 12 weeks of exposure.

Following 4 weeks of clean air recovery, body weights were significantly reduced only in the 1 ppm rats, with absolute lung weights also significantly increased only in the 1 ppm animals. The displacement volumes returned to control levels regardless of phosgene concentration. Histopathology following 4 weeks of recovery showed considerable, although not complete, recovery of the bronchiolar lesions and inflammation. Both prolyl hydroxylase activity and desmosine levels had returned to normal postrecovery, but hydroxyproline levels in the 0.5 and 1 ppm groups were significantly higher than in controls. Collagen staining remained at the same level of intensity as seen in the 12-week groups dosed at 0.2 and 1 ppm. Phosgene-induced changes in collagen staining were not reversible within the 4-week recovery period, and the severity of lesions in the 12-week exposure group was dependent on concentration, not on the $C \times T$ product.

As a followup to the same study, Hatch et al. (2001) pointed out that hydroxyproline content and collagen staining are standard measures of lung fibrosis and can be considered good markers of chronic injury. Fibrosis is accompanied by decreased lung compliance and diffusion capacity. The critical toxic effect for purposes of defining the point of departure in the RfC derivation is collagen staining, which is indicative of irreversible lung fibrosis. As Table 1 shows, the effect is not statistically significant at 0.1 ppm, but it is significant at 0.2 ppm, not only for the 4- and 12-week exposure groups but also for the 16-week recovery group. Kodavanti et al. (1997) found that, at 0.1 ppm, the lung displacement volume was statistically significantly elevated in the 4-week exposure group but not in the 12-week exposure group or the 16-week recovery group. This effect is not considered an adverse effect of chronic exposure because it diminished with longer exposure (12 vs. 4 weeks), and it disappeared after the 4-week recovery. Taking the pathology incidence findings as indications of chronic toxicity, a lowest-observed-adverse-effect level (LOAEL) of 0.2 ppm (0.8 mg/m³) for collagen staining, indicative of irreversible lung fibrosis, can be identified. The no-observed-adverse-effect level (NOAEL) for this effect was 0.1 ppm in this study.

Rossing (1964) exposed 14 mongrel dogs to phosgene for 30 minutes at concentrations of between 24 and 40 ppm (96 and 160 mg/m³); pretest values for each animal served as its control. The dogs were exposed three times per week until a definite rise was seen in their airway resistance; at that time, the frequency of exposure was reduced to once or twice a week.

Exposures were performed for 10 to 12 weeks. During the fifth and sixth weeks, the experimental schedules were disrupted.

Phosgene exposure resulted in no apparent discomfort to the animals. Seven of the 14 animals died within the first 3 weeks of exposure, and 3 additional animals were sacrificed at the end of 3 weeks. Animals that died during exposure or were sacrificed were autopsied, and their lungs were fixed and examined. The dynamic elasticity rose very quickly, reaching a maximum mean value of four times the control in the first week of exposure. It fell slightly during the next 3 weeks but remained significantly elevated above that of controls. After the disruption of exposure, elastance returned to the week 4 levels (approximately twice those of controls) until the ninth week, when it increased again. Mean lower airway resistance followed a similar pattern, with a rise for the first 4 weeks, a recovery period during the disruption of exposure, and then another rise once exposure had resumed.

During the first 2 to 3 weeks, the animals were often tachypneic and breathed with reduced tidal volume. After the first 3 weeks, the breathing pattern was similar to that seen in patients with obstructive airway disease: the animals had a slow respiratory rate and, frequently, active respiratory effort, as suggested by active contraction of the abdominal muscles. In two animals that were allowed to survive beyond the exposure period, elastance dropped rapidly to normal. Histologic examination revealed bronchiolitis with peribronchiolar edema, hemorrhage, and inflammation at earlier time points (3 weeks or less). In animals surviving to the fourth week and beyond, the inflammatory reaction was still present but less intense, despite continuing exposure. Owing to inadequate reporting of exposure levels, poor experimental design, and inadequate number of animals per treatment group, no NOAEL or LOAEL could be identified from this study.

Clay and Rossing (1964) also described lung histopathology for a separate group of dogs as described in Rossing (1964). They exposed groups of mongrel dogs (sex not specified) to phosgene at levels of between 24 and 40 ppm (96 and 160 mg/m³) for 30 minutes for one to three exposures per week. Group 1 animals (n = 2) consisted of unexposed controls; group 2 dogs (n = 7) were exposed one or two times and sacrificed 1–2 days postexposure; group 3 animals (n = 7) were exposed 4–10 times and sacrificed up to 7 days postexposure; group 4 animals (n = 5) were exposed 15–25 times and sacrificed immediately or up to 2 weeks postexposure; and group 5 animals (n = 4) were exposed 30–40 times and sacrificed immediately or up to 12 weeks after the final exposure. The lungs of the sacrificed animals were inflated with fixative and dried. Both histologic sections and 1-mm-thick macrosections of the dried lungs were examined for all groups.

Both micro- and macroscopic examination revealed progressive pulmonary changes with increasing number of exposures. Microscopic changes revealed acute bronchiolitis and

peribronchiolitis that affected only scattered sections of the lung at the lowest number of exposures. With increasing number of exposures, a progression to a chronic obliterative bronchiolitis was seen, with fibrotic changes that affected the majority, but not all, of the lung tissue. Macrosections similarly revealed little or no changes in animals exposed one or two times, with a progressing fibrosis and emphysema seen with increasing number of exposures, resulting in severe dilation of the respiratory bronchioles and increased alveolar pore size in animals exposed 30–40 times. Owing to the poor design of the study and the inadequate number of experimental animals and dose level tested, no NOAEL or LOAEL values could be identified.

Franch and Hatch (1986) performed a series of experiments examining the effects of inhaled phosgene in male Sprague-Dawley rats. In the first exposure regimen, groups of rats (4–10 per group) were exposed to 0 or 1 ppm (4.05 mg/m³) of phosgene for 4 hours and then sacrificed immediately after exposure or at 1, 2, 7, 14, or 38 days postexposure. Body weights were decreased to 13% below those of controls ($p < 0.01$) on the first day postexposure and then rose toward control values, reaching 3% below control values on day 14 of recovery. Food intake was also significantly decreased in exposed animals on days 1–3 postexposure before returning to nearly normal values. Lung wet weights were significantly elevated in exposed rats immediately after exposure and remained elevated through day 7 postexposure. No change in nonprotein sulfhydryl (NPSH) content was seen immediately postexposure, but it showed an upwardly increasing trend thereafter. G6PD activity was elevated over that of controls from days 1–14 postexposure.

The second regimen consisted of a single 7-hour exposure during which one rat per group (control, exposed) was sacrificed each hour; the experiment was replicated three times. Lung weights were significantly increased 4 hours into the exposure and beyond, whereas NPSH content was decreased. No significant change in G6PD activity was seen.

In their third exposure regimen, Franch and Hatch (1986) exposed groups of male Sprague-Dawley rats to 0.125 (0.5 mg/m³) or 0.25 ppm (1 mg/m³) of phosgene for 4 hours per day, 5 days per week, for 17 total exposures over 4 weeks. Lung weight was significantly increased at exposure day 7 and later in the 0.25 ppm group and at day 17 in the 0.125 ppm group. Pooled over all time points, the 0.25 ppm group had higher NPSH content than did the 0.125 ppm group, and it was significantly greater than in controls. In animals allowed to recover postexposure, lung weights and NPSH levels returned to near control levels. Histology of the lungs after 17 days of exposure to 0.25 ppm of phosgene revealed moderate multifocal mononuclear-cell accumulations in the walls of the terminal bronchioles and a minimal type-II cell hyperplasia; lesions in the 0.125 ppm groups were minimal.

Selgrade et al. (1995) administered *Streptococcus zooepidemicus* bacteria via an aerosol spray to the lungs of male Fischer 344 rats immediately after phosgene exposure and measured

the subsequent clearance of bacteria. They also evaluated the immune response of uninfected rats similarly exposed to phosgene, as measured by an increase in the percentage of polymorphonuclear leukocytes (PMN) in lung lavage fluid. The exposure regimen was similar to that of Kodavanti et al. (1997); animals inhaled phosgene at concentrations of 0, 0.1, or 0.2 ppm, 6 hours per day, 5 days per week, and 0.5 ppm, 6 hours per day, 2 days per week, for 4 and 12 weeks. For each of the 12-week exposure regimen, additional groups of animals were assessed for all endpoints at 4 weeks postexposure.

Within 24 hours after bacterial infection, the lungs of unexposed animals cleared the bacteria, but in animals exposed to phosgene for both 4 and 12 weeks at all three concentrations the clearance was impaired. After 4 weeks of recovery following 12 weeks of phosgene exposure, the bacteria clearance was comparable to that of unexposed animals. In uninfected rats, the % PMN cells was statistically significantly higher than in the unexposed group in all 4-week phosgene exposure groups, and it was also higher at the highest concentration (0.5 ppm) in the 12-week exposure group. In the 4-week recovery animals, no difference in % PMN cells was observed between the exposed and control groups. This experiment shows that all phosgene concentrations from 0.1 to 0.5 ppm impaired resistance to bacterial infection and that the immune response is stimulated by phosgene exposure. After 4 weeks following exposure, bacterial resistance is back to normal and there is no immune response in excess of unexposed controls.

In an earlier experiment measuring the same effects with a single 6-hour exposure to phosgene concentrations of 0.1 and 0.2 ppm, Yang et al. (1995) also reported a decrease in bacterial clearance in the lungs at 24 hours post infection, but over a period of 72 hours post-infection it returned to normal in the 0.1 ppm group. In comparison with single exposures, the multiple daily exposures extending to 4 and 12 weeks in the Selgrade et al. (1995) report showed a slight enhancement of effect in the 0.1 ppm group at 24 hours post-infection, but no “adaptation,” or lessening of the effect. Yang et al. (1995) found that if the bacteria are administered 18 hours after single phosgene exposures rather than immediately, the clearance is normal, indicating that recovery from the toxic effect of phosgene is rapid. Selgrade et al. (1995) suggested that in a repeated cycle of intermittent exposures there is an increased chance for infection to occur during and immediately after each exposure period.

4.3. REPRODUCTIVE/DEVELOPMENTAL TOXICITY STUDIES

No epidemiological studies examining the effects of phosgene on reproduction or development for any exposure duration or route in humans were located in the published literature. A case report by Gerritsen and Buschmann (1960) describes a 7-months-pregnant woman who survived severe phosgene-induced pulmonary edema and subsequently delivered a

normal, full-term infant. No experimental animal studies have been reported on the effects of phosgene on reproductive and developmental organ systems. Therefore, the data from which to draw any conclusions about potential reproductive/developmental effects of phosgene in humans or animals are inadequate.

4.4. OTHER EFFECTS

4.4.1. Dermal Toxicity

Skin contact with phosgene has been known to cause severe skin burns in humans. Vapor contact with moist or wet skin can lead to irritation and erythema (WHO, 1997). No dermal toxicity studies in experimental animals have been conducted.

4.4.2. Ocular Toxicity

In humans, low vapor concentration exposure to phosgene gas can cause conjunctival inflammation, and high vapor concentration exposure can lead to corneal opacifications and perforation (Grant and Schuman, 1993).

4.4.3. Neurotoxicity

Phosgene-induced hypoxia and hypotension may cause anoxic injury to the brain (Borak and Diller, 2001).

4.4.4. Genotoxicity

The *in vivo* cytogenetic effects of phosgene inhalation were investigated in mice at 5, 10, or 15 ppm for 6 hours. No evidence was found that phosgene is clastogenic, aneuploidogenic, or capable of inducing sister chromatid exchanges and micronuclei (Klingerman et al., 1994). Furthermore, Reichert et al. (1983) reported that phosgene was negative under the conditions of the Ames bacterial mutagenicity assay with and without metabolic activation. The authors concluded that the negative result was likely due to phosgene reacting rapidly in the test medium. Additional *in vitro* testing would be subject to similar technical limitations imposed by the water reactivity of phosgene. As discussed, the physical and chemical properties of phosgene preclude a valid *in vivo* test of genetic toxicity.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS

4.5.1. Oral

No published studies on the toxicity of phosgene following oral exposure in animals were found. The lack of oral studies reflects the fact that phosgene is a gas at room temperature, and that aqueous phosgene rapidly hydrolyzes to CO₂ and HCl.

4.5.2. Inhalation

No relevant published studies are available with which to evaluate the nonpulmonary effects of inhaled phosgene. Therefore, the discussion in this section focuses on pulmonary effects. The acute toxicity of phosgene inhalation in humans and animals has been well documented (Underhill, 1919, as reviewed in WHO, 1998, 1997; U.S. EPA, 1986c, 1984). Acute inhalation of phosgene results in a sequence of events, including an initial bioprotective phase, a symptom-free latent period, and a terminal phase characterized by pulmonary edema (Schneider and Diller, 1989; Diller, 1985).

Phosgene is not expected to leave the pulmonary circulation following inhalation exposure. The effects of inhaled phosgene reported in human and animal studies have been attributed to a direct effect on the respiratory tissues or to secondary consequences resulting from damage to the respiratory system. The toxicity of phosgene is thought to result from its ability to directly participate in acylation reactions with amino, hydroxyl, or sulfhydryl groups (WHO, 1998, 1997; Schneider and Diller, 1989, as discussed in U.S. EPA, 1986c; Diller, 1985).

4.5.3. Mode of Action Information

Fibrosis is a common consequence of various exogenous insults to a variety of parenchymal tissues in the lung. The underlying mechanism of the induction and progression of fibrosis—at both the molecular and cellular levels—is not well understood. Fibrosis is characterized by a dense, hard mass in the lung; it may be diffuse and interstitial in character rather than nodular. Phosgene-induced pulmonary inflammation and fibrosis in the experimental animals provides a good model for chronic pulmonary inflammation and fibrosis in humans. Connective tissue may develop both interstitial and intra-alveolar fibrosis following short-term exposure. Hydroxyproline content and the activities of prolyl hydroxylase and galactosyl-hydroxy-lysyl glucotransferase were increased in the lungs of rats exposed to phosgene. These observations were reported by Kodavanti et al. (1997) and later by Hatch et al. (2001), who also indicated that lung fibrosis can be considered a good marker for chronic injury from exposure to phosgene. Borak and Diller (2001) reviewed the biochemical mechanisms that lead to adult respiratory distress syndrome due to phosgene exposure; they are summarized below. In addition, several other postulated biochemical mechanism studies are also reviewed that relate to phosgene mode of action.

Phosgene is a highly reactive gas capable of damaging a variety of biological macromolecules in an oxidant-like fashion. This activity potentially results from at least two separate chemical reactions: acylation and hydrolysis.

Acylation, the more important and rapid mechanism, results from the reaction of phosgene with nucleophilic moieties, such as the amino, hydroxyl, and sulfhydryl groups of

tissue macromolecules. Acylation causes destruction of proteins and lipids, irreversible alterations of membrane structures, and disruption of enzyme and other cell functions. Exposure to phosgene depletes lung nucleophiles, particularly glutathione, and restoration of glutathione seems to protect against phosgene-induced injury (Sciuto and Moran, 1999; Sciuto et al., 1998, 1995; Schroeder and Gurtner, 1992; Jaskot et al., 1991; Sciuto and Gurtner, 1989). For several days after acute phosgene exposure, tissue levels of antioxidant enzymes, such as glutathione reductase and superoxide dismutase, increase as part of the lungs' response to injury (Jaskot et al., 1991).

In addition to acylation, phosgene is hydrolyzed to HCl as shown below:



The formation of HCl occurs on moist membranes and may cause irritation and tissue damage (Diller, 1985). Because of the limited water solubility of phosgene, it is unlikely that large quantities of HCl could result from the exposure of biological tissues. However, small amounts do form and may contact moist membranes of the eye, nasopharynx, and respiratory tract. Hydrolysis to HCl is the probable cause of immediate inflammation and discomfort after phosgene exposure at concentrations greater than 3 ppm ($>12 \text{ mg/m}^3$).

Pulmonary cellular glycolysis and oxygen uptake following phosgene exposure are depressed and, thus, leads to a corresponding decrease in the levels of intracellular adenosine triphosphate and cyclic adenosine monophosphate (Sciuto et al., 1996; Kennedy et al., 1989; Currie et al., 1985). This is associated with increased water uptake by epithelial, interstitial, and endothelial cells (Helm, 1980). The semipermeability of the blood-air barrier becomes gradually compromised as a result of fluid entering the interstitial and alveolar spaces. Later, the blood-air barrier disrupts, opening channels for the flooding of alveoli (Diller et al., 1969; Schulz, 1959). Compression of pulmonary microvasculature leads to the opening of arteriovenous shunts (Schocimerich et al., 1975). The onset of pulmonary edema correlates temporally with the decrease in adenosine triphosphate levels (Currie et al., 1985). Interventions that increase intracellular cyclic adenosine monophosphate, such as treatment with phosphodiesterase inhibitors (e.g., aminophylline), beta-adrenergic agonists (e.g., isoproterenol), or cyclic adenosine monophosphate analogs, markedly reduce pulmonary edema formation in animals exposed to phosgene (Sciuto et al., 1998, 1997, 1996; Kennedy et al., 1989).

Phosgene exposure also has been shown to cause lipid peroxidation in lungs. In mice and guinea pigs, phosgene exposure of 22 ppm via inhalation for 20 minutes increased levels of lipid peroxidation products, such as thiobarbituric acid-reactive substances in tissue and bronchio-alveolar lavage fluid (Sciuto et al., 1998).

The effects of phosgene on pulmonary arachidonic-acid metabolism were studied both in vivo and in vitro (Madden et al., 1991). Male Wistar rats were exposed to 0.05, 0.10, 0.25, 0.50, or 1 ppm phosgene for 4 hours. Lung lavage fluid total and differential cellularity and viability were determined at 0, 4, 20, or 44 hours after exposure. Furthermore, the lavage fluid was analyzed for prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and leukotriene C4, leukotriene D4 plus leukotriene E4 (LTCDE4). Phosgene at 1 ppm significantly decreased lavage fluid cell viability at all time points but resulted in transient decrease at 0.1 ppm only at 4 and 20 hours. The decreases in PGE2, LTB4, and LTCDE4 induced by the 0.1 and 0.25 ppm exposures returned to, or exceeded, the control values at 44 hours postexposure. Phosgene did not affect the PGE2 and LTCDE4 formation in rat macrophages. The authors concluded that phosgene-induced alterations in arachidonic-acid metabolism may be involved in its toxicity. Guo et al. (1990) investigated the role of arachidonate mediators in phosgene-induced lung toxicity in male New Zealand rabbits. The authors concluded that phosgene stimulated the synthesis of lipoxygenase products of arachidonic-acid metabolism, which appear to contribute to pulmonary edema.

Increased thromboxane production occurred in human pulmonary microvascular endothelial cells after phosgene exposure in vitro (Cheli et al., 1995). Neutrophils migrated to the lung surface in large numbers following phosgene exposure in several animal species (Robinson, 1994; Schroeder and Gurtner, 1992). Pre-exposure injections of cyclophosphamide, which significantly reduced circulating neutrophil counts, also decreased neutrophil migration to the lungs and limited phosgene-induced edema and mortality (Ghio et al., 1991).

Acyltransferase activity in alveolar type II cell microsomes (which is necessary for the synthesis of pulmonary surfactant) was shown to be inhibited in rabbits after edematogenic doses of phosgene (Frosolono and Passarelli, 1978).

The above studies shed some light on the postulated mechanisms of phosgene toxicity; however, they are inadequate to define modes of action at the cellular level.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

Based on the criteria in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the available toxicity and mode(s) of action data provide inadequate information to assess the carcinogenic potential of phosgene. A single epidemiology study of phosgene-exposed workers (Polednak and Hollis, 1985; Polednak, 1980) was not considered adequate for evaluating carcinogenic potential in humans. Furthermore, no animal cancer bioassays of phosgene have been conducted to evaluate carcinogenic potential in experimental animals.

Phosgene has been identified as a reactive intermediate in the metabolism of a number of chemical carcinogens, including chloroform (Pohl et al., 1981, 1977); however, its role in the

carcinogenesis of these compounds is not clearly understood. The reactive metabolites of chloroform covalently bind to proteins and lipids but only minimally to DNA and nucleic acids. The failure of the reactive species (e.g., phosgene, trichloromethyl free radical, and other metabolites) to significantly bind to DNA has been ascribed to their short half-lives and to their lack of nuclear penetration (as cited in U.S. EPA, 2001a).

There is some concern for the carcinogenic potential of phosgene on the basis of SAR analysis because the two chlorines (linked to the carbonyl group) are highly reactive; however, phosgene rapidly hydrolyzes into CO₂ and HCl, such that exposure to phosgene might not result in a reaction with nuclear DNA. However, no data exist regarding DNA alkylation as a result of exposure to phosgene. Covalent binding of phosgene with cellular macromolecules has been proposed as a mechanism of chloroform-induced hepatic and renal toxicity (Pohl et al., 1980a, b), and it is generally accepted that the carcinogenic activity of chloroform resides in its highly reactive intermediate metabolites, such as phosgene. Irreversible binding of reactive chloroform metabolites to cellular macromolecules supports several theoretical concepts as a mechanism for possible phosgene's carcinogenicity (as discussed in the *Toxicological Review of Chloroform*; U.S. EPA, 2001a).

4.7. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

4.7.1. Possible Childhood Susceptibility

No published studies are available to evaluate the effects of phosgene exposure on children or young experimental animals.

4.7.2. Possible Gender Differences

No published studies have directly compared the effects of phosgene inhalation exposure in males and females.

4.7.3. Other

No published experimental animal or human epidemiological studies are available to evaluate the effects of phosgene in the geriatric population or in individuals with compromised disease conditions, such as asthmatics or those with respiratory impairments.

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

No published studies on the toxicity of phosgene following oral exposure in humans or experimental animals were located. Phosgene is a gas at room temperature, and aqueous phosgene rapidly hydrolyzes to CO₂ and HCl. Therefore, exposure by the oral route is unlikely and the lack of data precludes derivation of an RfD.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

For effects other than cancer, the risk from exposure via the inhalation route is assessed by deriving an inhalation RfC. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime. Like the RfD, the RfC is based on the assumption that a threshold exists for certain toxic effects. Exposure to phosgene for a short period of time can have serious acute effects (NAS, 2002). Therefore, the RfC cannot be directly compared to average air concentrations without also examining available benchmarks regarding acute effects from the inhalation of phosgene (see Appendix A).

In this assessment, the RfC was estimated using three different approaches: the standard NOAEL/LOAEL approach, which has been used extensively in the past (U.S. EPA, 1994b); the benchmark dose (BMD) approach, which is currently being used by the Agency and has several advantages over the NOAEL/LOAEL approach (U.S. EPA, 2000c); and a categorical regression (CatReg) approach, which is suited to the analysis of severity-graded data and makes use of recently developed EPA CatReg software (U.S. EPA, 2000e). Use of these approaches has the potential to add multiple dimensions of information that include the slope of the dose-response curve and the severity of effect.

5.2.1. Choice of Principal Study and Critical Effect(s)

In the selection of principal studies for identifying critical endpoints of phosgene toxicity, two studies are relevant for deriving the RfC: Selgrade et al. (1995) and Kodavanti et al. (1997). These are subchronic inhalation studies with periods of recovery following exposure. Both studies have limitations, not being of chronic duration; however, they have similar exposure protocols and used the same experimental animal strain (F344 rats) to measure two different endpoints (immune response and pulmonary damage).

The subchronic study in rats reported by Kodavanti et al. (1997) and the followup study by Hatch et al. (2001) are considered to be suitable for development of an RfC. Results of the

study are summarized in Tables 1 and 2. The most sensitive target organ following chronic inhalation exposure to phosgene appeared to be the lungs. The investigators observed statistically nonsignificant terminal bronchiolar changes and interstitial thickening of the alveolar walls, inflammatory cell influx, and epithelial alterations of the terminal bronchioles at 0.1 ppm after 4 and 12 weeks of exposure and a statistically significant increase in lung displacement volume in all exposed groups after 4 weeks of exposure. The incidence and severity of these effects increased in the 0.2 ppm and 1 ppm exposed groups. These effects were not statistically significantly increased after a 4-week recovery period; they may be adverse, but they are not persistent. Other effects noted at the 0.2 and 1 ppm exposure levels were as follows: a statistically significant increase in collagen staining within thickened terminal bronchioles that was more intense at 1 ppm and persisted after a 4-week recovery period; and a statistically significantly increase in lung displacement volume and lung/body weight changes, which returned to control levels after the 4-week recovery period.

Collagen staining was considered by Kodavanti et al. (1997) as a marker of chronic lung damage, and an increase in lung displacement volume was considered as a sensitive indicator of structural changes in the lung. These changes and the other histopathological changes noted in Table 1 are considered adverse effects and, consequently, BMD and Cat Reg modeling were done, as described in the next section.

Selgrade et al. (1995) concluded that phosgene exposure at 0.1, 0.2, and 0.5 ppm impaired resistance to bacterial infection in rats. However, at the 0.5 ppm concentration, an immune response was observed in noninfected animals. Phosgene is toxic to the immune cells that are in the lungs, but after phosgene exposure stops, the cells repopulate the lung from elsewhere in the body and no permanent damage to immune system cells is evident. It appears that concentration rather than exposure duration is the more critical factor for the extent of toxic response to phosgene, even at these low concentrations. A concentration of 0.1 ppm is considered as a LOAEL for this effect in this study.

5.2.2. Methods of Analysis for Point of Departure, Including Application of Models (BMD, NOAEL/LOAEL, and CatReg)

This assessment makes use of two dose-response modeling software suites developed by EPA, the Benchmark Dose Software (BMDS) (U.S. EPA, 2001b) and CatReg (U.S. EPA, 2000e). BMD assessment methods (U.S. EPA, 2000c, 1995) and supporting software were developed to improve upon the NOAEL/LOAEL approach by taking into account the quality of the study and the complete dose-response, and the CatReg software was developed to allow for the evaluation of categorically graded responses over time. The following sections describe how three assessment methods (BMD, NOAEL/LOAEL, and CatReg) were used to analyze the

critical effects identified from the Kodavanti et al. (1997) rat subchronic inhalation study to obtain a point of departure (POD) for use in derivation of an RfC for phosgene. These sections also describe attempts to use the BMD approach for the Selgrade et al. (1995) study and the decision to use the NOAEL/LOAEL approach instead for that study.

5.2.3. BMD Approach

Kodavanti et al., 1997

Following subchronic inhalation exposure of phosgene, Kodavanti et al. (1997) found that the most sensitive target organ in rats is the lung, as discussed in Section 5.2.1. Lung hydroxyproline content and trichrome staining for collagen are standard methods for measuring lung fibrosis and can be considered reliable chronic injury markers. Support for this is found in the present study, which showed lack of reversibility of the collagen accumulation and possibly even a progression during the 4-week recovery period, terminal bronchiolar thickening and inflammatory cell influx, and an increase in the lung displacement volume. Measurements of hydroxyproline in the whole lung, which is considered to be a chemical manifestation of fibrosis, were statistically increased in the high-dose group (1 ppm) only and were persistent after the recovery period. Concentration seems to be more important than duration in determining this pathology response. Collagen staining increased slightly at 4 weeks and increased markedly at 12 weeks in both the 0.2 and 1 ppm groups, the effect at 1 ppm being more intense. For the BMD approach taken in this assessment, it is assumed that the administered concentration is an appropriate dose-metric. Although this assumption is uncertain (see discussion in paragraph 2 below), there is no reasonable alternative assumption. The Kodavanti et al. (1997) data at 1.0 ppm is not used for the BMD modeling because the exposure duration (once per week) differs markedly from the 0.1 and 0.2 ppm groups (5 times per week) and from continuous exposure. The BMD approach attempts to fit curves to the dose-response data for a given endpoint. It has the advantage of taking most of the dose-response data into account when determining the POD as well as estimating the lowest dose for which an adverse effect may have a specific probability of occurring. This approach is used when a biologically based dose-response model cannot be formulated.

A benchmark analysis was performed for lung effects considered to be adverse, as discussed in Sections 4.2.2 and 5.2.1. An overall summary of this analysis is provided in Appendix B, Table B-1. A summary of the results most relevant to the development of a POD for quantification of phosgene noncancer risk is provided in Table 3 for 4- and 12-week exposures. The lower-bound confidence limit values reported in Table 3 represent the 95% BMDL (lower-bound confidence limit on the benchmark dose) on the estimated ppm exposure associated with a 10% extra risk (dichotomous endpoints) or a one-standard-deviation change

from the estimated control mean (continuous endpoints, lung volume change).¹ The 10% response level was chosen as the point of departure (POD) for several reasons: (1) The small size of the treated and control animals (only eight were exposed) does not allow the detection of statistically significant effects below 10%. (2) A POD of larger than 10% cannot be justified because the collagen staining is considered to be a toxicological significant finding of fibrosis. (3) A POD of 10% is the default assumption used in the RfC methodology. Although 4-week data are not used to derive the POD for an RfC, they are provided in Table 3 for comparison purposes.

Table 3. Benchmark dose results from a subchronic study in rats (Kodavanti et al., 1997)

Effects ^a	BMD/BMDL ^b (ppm)	
	12-week exposure	4-week exposure
Interstitial thickening of the alveolus	0.044/0.025	0.026/0.015
Inflammatory cell influx to terminal bronchiole/alveolus	0.083/0.031	0.087/0.031
Epithelial alteration of terminal bronchiole/peribronchiolar alveolus	0.078/0.026	0.031/0.017
Increased collagen staining of terminal bronchiole/peribronchiolar	0.10/0.018	0.11/0.053
Displacement volume, left lung (mL/kg body weight × 100)	0.081/0.059 ^c	0.083/0.060 ^c

^a Only endpoints for which a dose-response could be modeled are listed.

^b EPA's Benchmark Dose Software (BMDS), versions 1.3 and 1.4 were used to estimate the BMDLs. For dichotomous endpoints, BMDLs are the 95% BMDL on the ppm exposure for a 10% extra risk. More details on the BMD analysis, including data analyzed, models used, and options employed, are presented in Appendix B.

^c For this continuous endpoint, the BMDL represents a one-standard-deviation change from the estimated control mean. The means and standard deviations for this endpoint were obtained in an e-mail dated October 22, 2001, from Dr. Urmila Kodavanti, U.S. EPA/NHEERL, to Dr. Jeff Gift, U.S. EPA/NCEA.

An element of the BMD approach is the use of several models to determine which one best fits the data.² The model that best fits the experimental data is used when the mode of

¹BMD analyses at 15, 5, and 1% were also performed and are reported in Appendix B for the 4- and 12-week exposure durations. However, the exposure group size of eight rats per exposure group is not conducive to obtaining response estimates below 10%. One indication of this is the fact that as the BMR% goes down (i.e., x = 15%, 10% to 5% to 1%) the BMDx/BMDLx ratio goes up (i.e., 3.9, 5.6 to 10.5 to 44.1) for the collagen staining, multistage model. This ratio indicates that although the BMDLx's are all 95% confidence intervals, in a certain sense the "variability and/or reliability" of the models is considerably worse at BMRs below 10%.

²EPA's BMD Software (BMDS), versions 1.3 and 1.4, were used for this effort. BMDS can be downloaded from the Internet at www.epa.gov/ncea/bmbs.htm. BMDS facilitates the application of BMD methods by providing simple data-management tools and an easy-to-use interface to run multiple models on the same dose-response data set. At this time, BMDS offers nine different models appropriate for the analysis of dichotomous (quantal) data (Gamma, Logistic, Log-Logistic, Multistage, Probit, Log-Probit, Quantal-Linear, Quantal-Quadratic,

action is not known and, consequently, there is no theoretical basis for choosing a particular model. As described in EPA's BMD technical guidance (U.S. EPA, 2000c), this is done by measures of fit. In this case, the multistage model provided the best fit of all the dichotomous models (see Appendix B) to the endpoint characterized as increased collagen staining of terminal bronchioles. The dose-response data for the incidence of collagen staining and the multistage model fitting these data are shown in Figure 1, which graphically shows the BMD_{10} and the $BMDL_{10}$. The $BMDL_{10}$ for this effect is 0.018 ppm.

Weibull), continuous data (Linear, Polynomial, Power, Hill), and four nested models appropriate for developmental toxicology data (NLogistic, NCTR, Rai, and Van Ryzin). Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the benchmark concentration, and the BMDL.

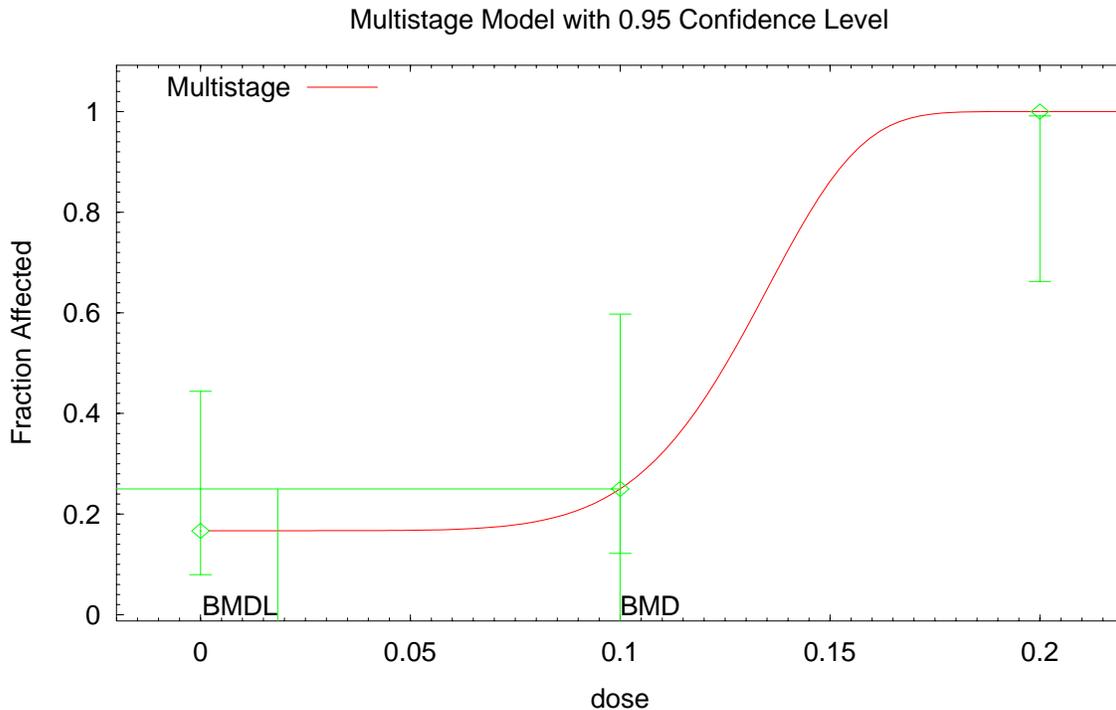


Figure 1. Increased collagen staining of terminal bronchiole/peribronchiolar region (multistage model)

In the absence of a relevant physiologically based pharmacokinetic (PBPK) model, RfC default methods for lung toxicity caused by gaseous exposures (U.S. EPA, 1994a, b) were used to derive human equivalent concentrations (HECs) from the 12-week BMDLs reported in Appendix B-1. This was done in three steps by (1) converting the exposure from ppm to mg/m^3 , (2) adjusting from intermittent to continuous exposure, and (3) extrapolating from rats to humans using the rat-to-human regional gas-dose ratio (RGDR):

1. *Converting from ppm to mg/m^3 .* The molecular weight (MW) of phosgene is 98.92. Assuming 25°C and 760 mmHg, the NOAEL (mg/m^3) = $0.018 \text{ ppm} \times 98.92/24.45 = 0.0728 \text{ mg}/\text{m}^3$.

2. *Adjusting from intermittent to continuous exposure.* The default method (U.S. EPA, 1994b) is based on an assumption that the total dose is the proper dose-metric for the effect. Total dose is equal to the concentration (C), which is proportional to the rate at which the agent is delivered to the cells, multiplied by duration of exposure (T) (i.e., Haber's Law). However, Kodavanti et al. (1997) found that the severity of the collagen-staining lesions and the concentration of hydroxyproline, both irreversible after a 4-week recovery period following

dosing with phosgene, were dependent on concentration and not on the product of $C \times T$. The hydroxyproline data for this experiment are given in Hatch et al. (2001); Kodavanti et al. (1997) show the same data in graphical form. A more detailed examination of these data reveals that hydroxyproline concentration in the 12-week study increased with both C (at fixed T) and T (at fixed C), and it also increased with the product of $C \times T$. Therefore, the proper dose-metric is a combination of these factors; perhaps it is $C \times T^a$, where “a” is a fractional power of duration. The experimental data are not definitive enough to derive a numerical description of the dose-response surface. There are no data for collagen staining or for hydroxyproline resulting from daily exposures in the range from 1 hour per day to 24 hours per day. However, two studies employing continuous exposure show that toxic effects are proportional to the $C \times T$ product. In the range of 0.5 minutes to 2 hours (5 to 500 mg/m³ [0.74 to 74 ppm], $C \times T = 37.5$ to 563 ppm-min), the lethality to cats of phosgene poisoning is proportional to $C \times T$ (Flury, 1921, as cited in U.S. EPA, 1986c). In the range of 5 minutes to 8 hours (2 to 16 mg/m³ [0.5 to 4 ppm], $C \times T = 12$ to 360 ppm-min), a measure of pulmonary gas exchange in rats was proportional to $C \times T$ (Rinehart and Hatch, 1964, as cited in U.S. EPA, 1986c). Therefore, it is likely that collagen staining would also follow the $C \times T$ product for exposures of fractions of a day. The study of Kodavanti et al. (1997) directly implies that intermittent exposures to a certain concentration for 7 days per week would have the same effect as intermittent exposure for 5 days per week. As pointed out by Hatch et al. (2001), the repair events following a continuous exposure are not well understood, so the transition from daily (intermittent) exposure to continuous exposure cannot be made with any certainty. However, the assumption is made here that continuous exposures for 7 days per week would have the same effect as intermittent exposures for 7 days per week. Therefore, in the standard default method for adjusting for continuous exposures, the traditional 5/7 factor is not needed.

The Selgrade et al. (1995) data supply independent evidence that, in the intermittent exposure range of 2 to 5 days per week, concentration rather than the $C \times T$ product determines toxicity. In that study, 0.5 ppm for 2 days per week had a much greater effect on impairment of bacterial resistance than 0.2 ppm for 5 days per week, even though the $C \times T$ product was identical.

In view of these considerations, the BMDL from the Kodavanti et al. (1997) study, adjusted for continuous exposure, is as follows:

$$\text{BMDL}_{\text{ADJ}} = 0.0728 \text{ mg/m}^3 \times 6/24 = 0.0182 \text{ mg/m}^3$$

3. *Extrapolating from rats to humans.* The HEC corresponding to the BMDL_{ADJ} (BMDL_{HEC}) was calculated for a gas:respiratory tract effect in the thoracic region, taking into

account volume breathed per day and the surface area of the thoracic region of the rat lung versus the human lung. This is the standard procedure for dose conversions from animals to humans for Category 1 gases, which are completely and irreversibly absorbed by the lung (U.S. EPA, 1994b). The thoracic region, which consists of both the pulmonary and tracheobronchial regions of the lungs, was chosen for three reasons. First, some of these lesions have been classified as pulmonary lesions. Second, some of the assays measured would not make a distinction between the two lung regions (e.g., whole-lung prolyl hydroxylase and hydroxyproline as an index of collagen synthesis, volume displacement measurements). Third, some lesions appear to occur in both regions (bronchus inflammation, alveolar interstitial thickening).

The RGDR for the thoracic region of the respiratory tract (RGDR_{TH}) is used to adjust for differences between rat and human ventilation rates and thoracic surface areas and is calculated as follows (values used in this derivation were taken from U.S. EPA, 1988):

$$\text{RGDR}_{\text{TH}} = (\text{MV}_a/\text{S}_a)/(\text{MV}_h/\text{S}_h) = 1.51$$

where:

MV_a (minute ventilation for F344 rats) = 0.19 m³/day,

S_a (thoracic surface area for F344 rats) = 3,423 cm²,

MV_h (minute ventilation for humans) = 20 m³/day, and

S_h (thoracic surface area for humans) = 543,200 cm².

The BMDL_{HEC} was calculated by multiplying the BMDL_{ADJ} by the RGDR_{TH}:

$$\text{BMDL}_{\text{HEC}} = 0.0182 \text{ mg/m}^3 \times 1.51 = 0.0275 \text{ mg/m}^3$$

Selgrade et al. (1995)

Application of the benchmark dose approach to the Selgrade et al. (1995) data is problematic because of the difficulties establishing what level of bacterial resistance adversely affects the overall health and survival of the animals. The extent, duration, and health consequences of impaired bacterial resistance from phosgene exposure is highly dependent on secondary factors such as the exposure scenario involved, the health status of the exposed individual, and the type of infection. Since the quantitative relevance of the rat model of bacterial resistance to humans is unknown, it would be inappropriate to use these results in a benchmark dose determination of the RfC.

5.2.4. NOAEL/LOAEL Approach

The impairment of bacterial resistance observed by Selgrade et al. (1995) occurred at a lower concentration (0.1 ppm) than the morphological lung damage observed by Kodavanti et al. (1997). Therefore, the POD for the NOAEL/LOAEL approach for deriving an RfC is 0.1 ppm. As was done for the BMD approach described above, RfC default methods for lung toxicity caused by gaseous exposures (U.S. EPA, 1994a, b), in the absence of a relevant PBPK model, were used to derive the HEC corresponding to the LOAEL of 0.1 ppm. Using the same default procedures described in Section 5.2.3, a $LOAEL_{HEC}$ of 0.15 mg/m^3 is estimated ($0.1 \text{ ppm} \times 4.05 = 0.405 \text{ mg/m}^3$; $0.405 \times 6/24 = 0.101 \text{ mg/m}^3$; $0.101 \times 1.51 = 0.153 \text{ mg/m}^3$).

5.2.5. CatReg Approach

As described in Appendix B-2, a CatReg analysis was performed using the individual animal scores³ that resulted in the severity grade averages reported in Table 2. For purposes of the CatReg analysis, and to ensure that the scores assigned by Kodavanti were appropriately weighted according to the severity of the various endpoints, the scores assigned to endpoints that did not significantly regress or disappear during the 4-week recovery period (epithelial alteration and collagen staining of the terminal bronchioles) were increased by 1 severity grade, and the scores of endpoints deemed to have recognized and serious long-term consequences (collagen staining) were increased by an additional severity grade (see Table B-2a). Thus, reversible lesions scored as “minimal” received a severity grade of 1, reversible lesions scored as “slight/mild” and potentially irreversible lesions scored as “minimal” received a severity grade of 2, and potentially irreversible lesions scored as “slight/mild” or any occurrence of a lesion considered to have long-term consequences (collagen staining) received a severity grade of 3. The data at 1.0 ppm is not used in the CatReg analysis because the exposure duration (once per week) differs markedly from the 0.1 and 0.2 ppm groups (5 times per week) and from continuous exposure. CatReg analysis was used to approximate ppm exposure levels that would result in a 10, 20, and 30% extra risk⁴ of attaining a severity grade 1, 2, or 3 level of lung effect. As discussed in Appendix B-2, the analysis did not indicate that time was an explanatory variable, so the results presented in Table 4 are for the 4- and 12-week data combined. The combined analysis is preferred because time does not appear to be a significant factor for most of the endpoints reported and because of the small number of animals involved in this study.

The CatReg analysis cannot be compared directly to the NOAEL and BMDL analyses at this time and is not appropriate for use in the derivation of an RfC because EPA has not

³Personal communication between Dr. Jeff Gift and Dr. U.P. Kodavanti.

⁴As described in Appendix B-2, extra risk is what is generally used in a BMD analysis and is defined as the estimated increased risk over background ($P_d - P_0$) divided by the maximum risk with background excluded ($1 - P_0$).

published guidance for the application of CatReg to Agency risk assessments and because the CatReg software does not provide an estimate of the lower bound confidence limit on the extra risk dose (ERD) that would be comparable to the BMDL.⁵ However, CatReg does provide a maximum likelihood estimate, the ERD, that is comparable to the BMD and, because all of the observations from the critical study can be severity graded and used in CatReg, it provides an estimate of the ERD that is informed by more of the response data. Therefore, the ERD₁₀ estimate of 0.05 ppm for a severity grade 3 effect (Table 4), which would include collagen staining, can be compared to the BMD₁₀ estimates for collagen staining in Table B-1d of Appendix B-1. This comparison reveals that the CatReg ERD₁₀ estimate for severity grade 3 is similar to the BMD₁₀ estimate of 0.1 ppm for collagen staining alone and falls between the BMD₁₀ and the BMDL₁₀ estimate of 0.018 ppm.

Table 4. Results of CatReg analysis of severity-graded lung lesions reported by Kodavanti et al. (1997) [estimates of the exposures that would cause a 10, 20, and 30% probability of an effect equal to or greater than severity grade 1, 2, and 3 (ERD₁₀, ERD₂₀, and ERD₃₀)]

Severity grade	ERD ₁₀ (ppm)	ERD ₂₀ (ppm)	ERD ₃₀ (ppm)	Model	Link function
1	0.021	0.038	0.051	Cumulative Odds model	CLogLog
2	0.031	0.052	0.068		
3	0.050	0.077	0.096		

5.2.6. Comparison of Approaches

Each approach considered for determining the POD has strengths and limitations; however, combining the three approaches yields a consistent and more robust determination of the POD for the phosgene RfC. The NOAEL/LOAEL approach allows for a crude comparison of results between multiple species and the target species. This approach is less dependent on having the same experimental paradigms and results for comparison (e.g., a NOAEL/LOAEL can be determined experimentally with less dependence on characterization of other points on the dose-response curve). Using the NOAEL/LOAEL approach, the LOAEL for impairment of host defenses against bacterial infection of the lung is 0.1 ppm for male rats (Selgrade et al., 1995). This value was converted to a LOAEL_{HEC} of 0.15 mg/m³, about fivefold higher than the

⁵In particular, CatReg does not provide an estimate of the standard error associated with its estimate of background risk, which is used in derivation of the ERD (see Appendix B-2 for details).

BMDL_{HEC} estimate of 0.03 mg/m³.

A major disadvantage of the NOAEL approach is that NOAELs and LOAELs are restricted to the set of doses used. BMD estimates are the results of interpolation using sound statistical principles and so can take on any value in a range of doses. This results in the BMD approach having the following advantages over NOAELs for dose-response assessment:

- BMDs can be more consistent among different studies.
- BMDs, because they are based on interpolation, do not depend on sample size, whereas NOAELs, because they are essentially based on statistical testing, depend on sample size, such that, for the same dose-response, smaller sample sizes yield larger potential NOAELs.
- The statistical uncertainty of a BMD estimate can be calculated and weighed in a risk assessment, whereas the uncertainty of a NOAEL calculation cannot.

CatReg requires the user to classify each effect within a study, or combination of effects, into severity levels. Duration of exposure, as well as concentration, is included in CatReg because it affects the probability of achieving the various severity levels. “Duration” can be omitted, however, which is convenient when all subjects are exposed for the same duration or, as is the case for this assessment, when duration is not an important explanatory variable.

CatReg fits a cumulative probability distribution to the combined data from all treatment groups using the method of maximum likelihood estimation. From the probability distribution, with parameters replaced by their estimates (i.e., the fitted model), the estimated probability of any specified severity level or worse (e.g., mild adverse or worse) can be determined at any specified concentration and duration. Viewed as an “exposure-response curve” (or “exposure-response relationship”), an “exposure” is a combination of concentration and duration and “response” is the probability of an adverse effect (of specified severity or worse) occurring at that exposure.

Although the BMD approach has several advantages over the NOAEL approach, neither it nor the NOAEL approach is capable of incorporating severity grades into a quantitative assessment. In this case, for certain endpoints, such as inflammatory cell influx to terminal bronchiole/alveolus and increased collagen staining of terminal bronchiole/peribronchiolar, incidence data did not indicate a response at the low dose that was significantly different from that of controls (Kodavanti et al., 1997) (Table 1), yet severity score data (see Table 2) indicate that there may be some level of response at the low dose. This illustrates how BMD and NOAEL analyses are sometimes not reflective of a changing profile of severity of response and emphasizes the usefulness of a CatReg analysis that does account for differences in severity of

response. Hence, a CatReg analysis that can explicitly account for severity-graded lung effects was performed to supplement the BMD analysis (Appendix B-2).

As mentioned above, when the dose-response data for all severity grade effects are considered together in a CatReg analysis, the ERD₁₀ estimate for a severity grade 3 effect of 0.05 ppm is similar to, but about half that of, the BMD₁₀ estimates obtained from the application of several models to the collagen staining data of Kodavanti et al. (1997) (Table B-1d of Appendix B-1). The multistage model used in the derivation of the 0.018 ppm BMDL₁₀ point of departure discussed above was the only model whose 95% lower bound confidence interval encompassed (is lower than) the 0.05 ppm ERD₁₀ estimate. This provides additional justification for the choice of a relatively flexible multistage model for derivation of the BMDL point of departure.

5.2.7. RfC Derivation: Application of Uncertainty Factors

Uncertainty factors⁶ (UFs) are applied to account for recognized uncertainties in extrapolation from experimental conditions to the assumed human scenario (i.e., chronic exposure over a lifetime). Historically, UFs are applied as values of 10 in a multiplicative fashion (Dourson and Stara, 1983). Recent EPA practice, however, also includes use of a partial UF of 10^{1/2} (3.162) (U.S. EPA, 2002) on the assumption that the actual values for the UFs are

⁶RfDs apply to lifetime human environmental exposure and include sensitive subgroups. Differences between study conditions and conditions of human environmental exposure may make a dose that appears to be safe in an experiment not safe in the environment. UFs account for differences between study conditions and conditions of human environmental exposure. These differences include the following:

- a. Variation from average humans to sensitive humans: RfDs apply to the human population, including sensitive subgroups, but studies rarely target sensitive humans. Sensitive humans could be adversely affected at doses lower than those in a general study population; consequently, general-population NOAELs are reduced to cover sensitive humans.
- b. Uncertainty in extrapolating from animals to humans: If an RfD is developed from animal studies, the animal NOAEL is reduced to reflect pharmacokinetic and pharmacodynamic factors that may make humans more sensitive than animals.
- c. Uncertainty in extrapolating from subchronic NOAELs to chronic NOAELs: RfDs apply to lifetime exposure, but sometimes the best data come from shorter studies. Lifetime exposure can have effects that do not appear in a shorter study; consequently, a safe dose for lifetime exposure can be less than the safe dose for a shorter period. If an RfD is developed from less-than-lifetime studies, the less-than-lifetime NOAEL is adjusted to estimate a lifetime NOAEL.
- d. Uncertainty in extrapolating from LOAELs to NOAELs: RfDs estimate a dose that is without appreciable risks, but sometimes adverse effects are observed at all study doses. If an RfD is developed from a dose where there are adverse effects, that dose is adjusted to estimate a NOAEL.
- e. Other factors reflecting professional assessment of scientific uncertainties not explicitly treated above, including completeness of the overall database, minimal sample size, or poor exposure characterization.

log-normally distributed. In the assessments, when a single partial UF is applied, the factor is rounded to 3, such that the total factor for a UF of 3 and 10, for example, would be 30 (3×10). When two partial UFs are evoked, however, they are not rounded, such that a UF of 3, 3, and 10 would result in total uncertainty of 100 (actually $10^{1/2} \times 10^{1/2} \times 10$). UFs applied for this RfC assessment and the justification for their use are as follows:

1. **Human variation: $UF_H = 10$.** This factor is used to account for the variation in susceptibility within the human population and for the possibility that the data available are not representative of sensitive subgroups and lifestyles, including children (U.S. EPA, 2002). For phosgene, two studies are suitable for derivation of the RfC, and, because they are in animals, they cannot be regarded as representative of sensitive humans. Therefore the default value of 10 is appropriate.
2. **Animal-to-human uncertainty: $UF_A = 3$.** Use of an RGDR to estimate an HEC is deemed to largely account for the pharmacokinetic portion of this uncertainty. A threefold UF is retained to account for uncertainties regarding pharmacodynamic differences between animals and humans.
3. **Subchronic-to-chronic uncertainty: $UF_S = 3$.** The PODs are based on adverse effects in two subchronic inhalation studies. The full factor of 10 is not appropriate because the lung damage observed by Kodavanti et al. (1997) and the impairment in bacterial resistance observed by Selgrade et al. (1995) are not likely to progress significantly with further exposure. However, a partial factor of 3 is still necessary because of the remaining uncertainty in predicting full lifetime effects from both 12-week studies.
4. **LOAEL-to-NOAEL uncertainty: $UF_L = 3$ in the NOAEL/LOAEL approach; $UF_L = 1$ in the BMD approach.** A partial uncertainty factor of 3 rather than the full factor of 10 is used in the NOAEL/LOAEL approach because the impairment of lung immunological function in the Selgrade et al. (1995) study at the LOAEL of 0.1 ppm is considered to be a minimal effect. The effect is local to the lung, resulting in the impairment of the bacterial clearance process; the impairment occurs only during the exposure and it does not persist after phosgene exposure stops. No uncertainty factor is applied to the 0.018 ppm BMDL derived from collagen staining in the Kodavanti et

al. (1997) study because this POD is consistent with the NOAEL⁷ of 0.1 ppm given the small group sizes in this study and because it represents minimal severity of lung damage.

5. **Database: UF_D = 1.** In general, a database UF is needed to account for the potential for deriving an underprotective RfC as a result of an incomplete characterization of the toxicity (U.S. EPA, 2002). This includes areas where there is a complete lack of information as well as areas where existing data indicate that further information on a particular subject has the potential for demonstrating effects at lower exposures. Because phosgene is a chemically reactive agent with an extremely short half-life in water and in lung tissue, its effects when inhaled are not likely to be observed outside the lung, and no such effects have been observed to date. While it is recognized that the investigation of systemic effects following phosgene exposure has not been the focus of existing studies, there is no reason to expect that reproductive, developmental, or other systemic effects would occur, and no UF is needed for the absence of data on these effects. In view of the Selgrade et al. (1989) finding of increased sensitivity to bacterial infection in mice due to short-term (4 and 8 hour) phosgene exposures (section 4.2.2.1) at lower concentrations than in the sub-chronic rat experiments (Selgrade et al., 1995), there is a possibility that a longer-term study in mice might show effects at a lower concentration than in rats. That possibility would be a rationale for a data base uncertainty factor of greater than one. However, the species difference between the response in mice and rats is small and adequately accounted for in the subchronic-to-chronic factor of 3 and the animal-to-human factor of 3, and a separate data base uncertainty factor is not necessary.

The PODs derived using the NOAEL/LOAEL and BMD approaches are compared in Table 5. A POD of 0.03 mg/m³, derived from the BMD analysis of collagen-staining lesions in terminal bronchioles, is chosen for derivation of the RfC. The BMD approach is preferred because it is based on the entire dose-response data. Using the BMD approach, the RfC is calculated as follows:

$$\text{RfC} = 0.03 \text{ mg/m}^3 \div 100 = 3\text{E-}4 \text{ mg/m}^3$$

⁷This does not mean that the 0.1 ppm level is deemed to be a true no-effect level. It is recognized that responses at putative NOAELs can be as high as 20% (U.S. EPA, 2000c).

Table 5. Application of uncertainty factors (UFs) for two different approaches for deriving the RfC

Factor	NOAEL/LOAEL^a Approach	BMDL^b Approach
POD (mg/m³)	0.15	0.03
UF _H	10	10
UF _A	3	3
UF _S	3	3
UF _L	3	1
UF _D	1	1
UF _(Total)	300	100
RfC (mg/m³)	5E-4	3E-4

^aThe LOAEL_{HEC}, based on impairment of resistance to bacterial infection in the Selgrade et al. (1995) study, was the point of departure (POD). It is shown for comparison purposes only.

^bThe BMDL_{HEC}, based on collagen staining in the Kodavanti et al. (1997) study, was the POD used to derive the RfC.

5.2.8. Previous RfC Assessment

The health effects data for phosgene were evaluated in the IRIS database in 1990 and were determined to be inadequate for derivation of an inhalation RfC.

5.3. CANCER ASSESSMENT

5.3.1. Oral Slope Factor

No studies on the carcinogenicity of phosgene following oral exposure in humans or animals were located. Therefore, the lack of data precludes the derivation of an oral slope factor for phosgene.

5.3.2. Inhalation Unit Risk

No studies on the carcinogenicity of phosgene in animals and no carcinogenicity studies which adequately characterized inhalation exposure in humans were located. The Polednak (1980) study of mortality among men occupationally exposed to phosgene was considered inadequate to derive cancer unit risk. Thus, the lack of relevant data precludes the derivation of an inhalation unit risk for phosgene.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Phosgene (CAS No. 75-44-5) has a chemical formula of COCl_2 and a molecular weight of 98.92. At room temperature, it is a colorless gas with an aroma of moldy hay that may be stifling at high concentrations. Phosgene is poorly soluble in water and is rapidly hydrolyzed to CO_2 and HCl in aqueous solution. Industrially, phosgene is used as a chemical intermediate, primarily in the polyurethane industry. The majority of phosgene used industrially is produced by the reaction of carbon monoxide and chlorine gas using an activated charcoal catalyst, and it is used at the production site.

Data on the effects of phosgene following exposure by the oral route are lacking. Because phosgene is a gas at room temperature and because it is highly reactive and hydrolyzes rapidly in water to CO_2 and HCl , exposure to phosgene by the oral route is unlikely to occur.

The acute effects of phosgene inhalation have been well studied. Short-term exposure results in the development of pulmonary edema and an increased concentration of hemoglobin in the blood resulting from a decreased blood volume. At relatively high concentrations (>3 ppm, or 12 mg/m^3), irritation of the eyes and alterations in respiratory parameters may occur. Symptoms of acute exposure (>0.5 ppm, or 2 mg/m^3) increase in severity with both concentration (C) and time (T), as described by Haber's Law. At sufficiently high $C \times T$ levels, death may occur as a result of hypoxia or cardiac failure, both believed to be secondary responses resulting from the severe pulmonary edema associated with high levels of inhaled phosgene.

Inhalation of phosgene for subchronic or chronic durations is less well studied; there are limited human data and very few animal studies. Available studies point to the respiratory tract as the target for subchronic phosgene toxicity. The lungs are identified as the primary target organ in all species. In addition, immunotoxicity has been observed in a few animal studies; the importance of these findings to human hazard cannot be addressed at this time. U.S. and international health and safety institutions have determined that 0.1 ppm (0.4 mg/m^3) phosgene is an exposure limit that offers some protection in occupational settings. According to the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is inadequate information to assess the carcinogenic potential of phosgene.

6.2. DOSE RESPONSE

6.2.1. Noncancer/Oral

Phosgene is a gas at room temperature and rapidly hydrolyzes to CO₂ and HCl in aqueous solution; exposure by the oral route is unlikely. Available data for humans and animals are inadequate to assess the potential chronic toxicity of phosgene following oral exposure. Data on the effects of phosgene on reproductive function or on the developing organism are not available.

6.2.2. Noncancer/Inhalation

The RfC was derived using the BMD approach to estimate a lower confidence limit on the toxic lung effects observed in the 12-week study by Kodavanti et al. (1997). Five measures of toxicity were modeled at doses of 0.1 and 0.2 ppm (0.4 and 0.8 mg/m³): (1) epithelial alteration of terminal bronchioles and peribronchiolar alveoli, (2) increased collagen staining of terminal bronchioles, (3) interstitial thickening of alveoli, (4) influx of inflammatory cells into the terminal bronchioles and alveoli, and (5) lung volume. The BMD and BMDL values for various benchmark response levels (15, 10, 5, and 1%) were calculated for each of the five responses using seven different dose-response models. The 10% response level was chosen as the lowest level of response that can be reliably modeled. The results giving the lowest value of the BMD₁₀ for each response were selected, and the lowest collagen-staining data were chosen to characterize the BMD₁₀ and BMDL₁₀ for the entire study. Using this procedure, a BMDL₁₀ of 0.018 ppm was derived. This value from the rat data was adjusted for continuous human exposure by using the RGDR and exposure duration data. The resulting POD is 0.03 mg/m³. The RfC was derived by dividing by a composite UF of 100 (10 for human variability and 3 each for animal-to-human uncertainty in pharmacodynamics and subchronic-to-chronic animal data). UFs of 3 are actually 10^{1/2}, so when two factors of 3 are present, the combined UF is 10. Therefore, the RfC is 0.03/100 = 3E-4 mg/m³.

Two additional alternative approaches were considered (the LOAEL/NOAEL approach and the CatReg approach). The NOAEL/LOAEL approach uses the LOAEL of 0.1 ppm in the Selgrade et al. (1995) study as the POD. This was adjusted for continuous human exposure by using the exposure duration and RGDR to give a POD of 0.15 mg/m³. The total UF was 300 (10 for human variation and 3 each for animal-to-human, subchronic-to-chronic and LOAEL-to-NOAEL). The resulting RfC using this approach is 0.15/300 = 5E-4 mg/m³.

The CatReg approach uses the EPA CatReg model applied to graded severity of lung responses. The model estimated from the Kodavanti et al. (1997) study that the exposure concentration associated with a 10% extra risk of attaining a severity grade 3 effect in rats (e.g., “minimal” or more severe collagen staining) would be 0.05 ppm. This result cannot be

compared directly to the BMDL₁₀ or NOAEL but provides justification for the choice of the Multistage model for derivation of the BMDL point of departure. The BMDL₁₀ POD of 0.018 ppm obtained from the Multistage model is well below the CatReg ERD₁₀ estimate and the 0.05 to 0.07 ppm range of BMDL₁₀ estimates provided by the other BMDS models.

6.2.3. Cancer/Oral and Inhalation

Available data in humans are inadequate to assess the potential carcinogenicity of phosgene. In addition, chronic animal bioassays are not available.

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APPENDIX A: ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR PHOSGENE

The development and application of AEGLs was first described in NAS (2002). They represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3, and AEGL-1 levels as appropriate, are developed for each of five exposure periods (10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population, including infants and children and other individuals who may be susceptible. The three AEGLs are defined as follows.

AEGL-1 is the airborne concentration (expressed as ppm or mg/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory 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/m³) 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/m³) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentration below AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, nonsensory 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.

Appropriate data were not available for deriving AEGL-1 values for phosgene. Odor cannot be used as a warning for potential exposure. The odor threshold is reported to be between 0.5 and 1.5 ppm, a value above or approaching AEGL-2 and AEGL-3 values, and tolerance to the pleasant odor of phosgene occurs rapidly. Furthermore, following odor detection and minor irritation, serious effects may occur after a clinical latency period of 24 hours.

AEGL-2 values were based on chemical pneumonia in rats (2 ppm for 90 min) (Gross et al., 1965). An uncertainty factor (UF) of 3 was applied for interspecies extrapolation because little species variability is observed with both lethal and nonlethal endpoints after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations because of the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals. Therefore, the total UF is 10. The 1.5-hour value was then scaled to the 30-minute value and the 1-, 4-, and 8-hour AEGL exposure periods using $C^n \times T = k$, where $n = 1$ (Haber's Law), because Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber, 1924). The 30-minute value is also adopted as the 10-minute value because extrapolation would yield a 10-minute AEGL-2 value approaching concentrations producing alveolar edema in rats; Diller et al. (1985) observed alveolar pulmonary edema in rats exposed to 5 ppm phosgene for 10 minutes. Applying a total of UF of 10 to this data point yields a supporting 10-minute value of 0.5 ppm.

The 30-minute and 1-, 4-, and 8-hour AEGL-3 values were based on the highest concentration causing no mortality in the rat after a 30-minute exposure (15 ppm) (Zwart et al., 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed with both lethal and nonlethal endpoints after exposure to phosgene. A UF of 3 was applied to account for sensitivity of phosgene toxicity (binding to macromolecules and irritation), which is not expected to vary greatly between individuals. Therefore, the total UF is 10. The value was then scaled to the 1-, 4-, and 8-hour AEGL periods using $C^n \times T = k$, where $n = 1$ (Haber's Law), because Haber's Law has been shown to be valid for phosgene within certain limits. Haber's Law was originally derived from phosgene data (Haber, 1924). The 10-minute AEGL-3 value was based on the highest concentration causing no mortality in the rat or mouse (36 ppm) after a 10-minute exposure (Zwart et al., 1990). A UF of 3 was applied for interspecies extrapolation because little species variability is observed with both lethal and nonlethal endpoints after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations because of the steep concentration-response curve and because the mechanism of phosgene toxicity (binding to macromolecules and irritation) is not expected to vary greatly between individuals (total UF = 10). The calculated values are listed in Table A-1.

Table A-1. Summary of AEGL values for phosgene [ppm (mg/m³)]

Classification	10-minute value	30-minute value	1-hour value	4-hour value	8-hour value	Endpoint (reference)
AEGL-1 Nondisabling	NA	NA	NA	NA	NA	NA
AEGL-2 Disabling	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)	Chemical pneumonia rats (Gross et al., 1965)
AEGL-3 Lethal	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)	Highest concentration causing no mortality in the rat after a 30-minute or 10-minute exposure (Zwart et al., 1990)

Source: NAS (2002).

Available from: <http://www.epa.gov/oppt/aegl/results7.htm>

APPENDIX B: BMD AND CATREG ANALYSES

APPENDIX B-1: SUMMARY OF BENCHMARK DOSE (BMD) ANALYSIS

EPA's Benchmark Dose Software (BMDS), versions 1.3 and 1.4, were used to perform a benchmark analysis of lung effects reported in the subchronic study by Kodavanti et al. (1997). The BMD approach involves the use of several models to determine which one best fits the data. As described in EPA's BMD technical guidance (U.S. EPA, 2000c), this is done by comparing both the graphical fit and the statistical measures of fit. Tables B-1a through B-1e summarize the textual output of the model runs, including AIC and *p* value measures of statistical fit. Following the tables, complete output files, including graphical plots, are included for model runs used in the derivation of each endpoint BMDL₁₀ value.

Table B-1a. Kodavanti et al. (1997): Interstitial thickening of the alveolus in male rats

ppm	n	4-week exposure					12-week exposure				
0	12	0					0				
0.1	8	2					2				
0.2	8	5					4				
NOAEL (ppm)		0.1					0.1				
NOAEL(HEC) (mg/m ³) ^a		0.15					0.15				
BMDs and BMDLs ^b Model		BMD/					BMD/				
		AIC	P	BMD	BMDL	BMDL	AIC	P	BMD	BMDL	BMDL
Multistage^c	10%	22.00	0.82	0.026	0.015	1.73333	22.13	0.98	0.033	0.018	1.8333
	15%							0.050	0.027	1.8519	
	5%							0.016	0.0086	1.8605	
	1%							0.0031	0.00168	1.8452	
Weibull^d	10%	23.58	1.0	0.056	0.015	3.73333	24.09	1.0	0.045	0.018	2.5
	15%							0.064	0.027	2.3704	
	5%							0.026	0.0086	3.0233	
	1%							0.0071	0.0017	4.1765	
Gamma^e	10%	23.58	1.0	0.06	0.015	4	24.09	1.0	0.05	0.018	2.7778
	15%							0.065	0.027	2.4074	
	5%							0.027	0.0086	3.1395	
	1%							0.0085	0.0017	5	
Logistic	10%	24.46	0.43	0.079	0.046	1.71739	25.29	0.34	0.085	0.05	1.7
	15%							0.11	0.068	1.6176	
	5%							0.056	0.028	2	
	1%							0.016	0.0063	2.5397	
Log-Logistic^f	10%	23.58	1.0	0.062	0.010	6.2	24.09	1.0	0.05	0.012	4.1667
	15%							0.067	0.019	3.5263	
	5%							0.031	0.0055	5.6364	
	1%							0.011	0.0011	10	
Probit	10%	24.16	0.51	0.075	0.043	1.74419	25.00	0.40	0.08	0.047	1.7021
	15%							0.10	0.065	1.5385	
	5%							0.052	0.026	2	
	1%							0.016	0.0059	2.7119	
Log-Probit^f	1%	23.58	1.0	0.065	0.028	2.32143	22.09	1.0	0.055	0.032	1.7188
	15%							0.070	0.041	1.7073	
	5%							0.038	0.022	1.7273	
	1%							0.019	0.011	1.7273	
Selected BMD/BMDL₁₀ value (ppm)^g			0.026	0.015				0.044	0.025		
BMDL₁₀(HEC) (mg/m³)^a				0.016					0.038		

^a Human equivalent concentration (HEC) calculated via EPA methods (U.S. EPA, 1994b). The regional gas-dose ratio for the thoracic region of the respiratory tract (RGDR_{TH}) was used (see details in Section 5.2.3 of the main text).

^b BMDL estimates are 95% lower confidence limits on the dose that would elicit 10, 15, 5, or 1% extra risk.

^c Betas restricted to ≥0 in multistage/polynomial models; parsimony used to select polynomial order.

^d Power always restricted to ≥1 in Weibull and Power models.

^e Power always restricted to ≥1 in Gamma and Hill models.

^f Slope always restricted to ≥1 in Log-Logistic and Log-Probit models.

^g Selected models (results in bold) were chosen based on statistical (AIC, *p*, scaled residual values) and visual assessment per BMD guidance (U.S. EPA, 2000c). May represent an average of more than one BMDL if model fits are similar.

NOAEL = no-observed-adverse-effect level determined via statistical comparison with control response; NA = not applicable or not applied; ZD = zero degrees of freedom; *p* value could not be calculated.

Table B-1b. Kodavanti et al. (1997): Inflammatory cell influx to terminal bronchiole/alveolus in male rats

ppm	n	4-week exposure					12-week exposure				
		AIC	P	BMD	BMDL	BMDL	AIC	P	BMD	BMDL	BMDL
0	12	2					1				
0.1	8	3					3				
0.2	8	8					8				
NOAEL (ppm)		0.1					0.1				
NOAEL(HEC) (mg/m ³) ^a		0.15					0.15				
BMDs and BMDLs ^b		BMD/					BMD/				
Model		AIC	P	BMD	BMDL	BMDL	AIC	P	BMD	BMDL	BMDL
Multistage ^c	10%	25.40	0.98	0.082	0.013	6.30769	21.47	1.0	0.077	0.012	6.4167
	15%								0.084	0.018	4.6667
	5%								0.067	0.0057	11.754
	1%								0.048	0.0011	43.636
Weibull ^d	10%	27.40	ZD	0.084	0.033	2.54545	23.47	ZD	0.079	0.029	2.7241
	15%								0.085	0.037	2.2973
	5%								0.069	0.019	3.6316
	1%								0.051	0.0069	7.3913
Gamma ^e	10%	25.49	0.83	0.084	0.040	2.1	21.52	0.87	0.081	0.035	2.3143
	15%								0.086	0.043	2
	5%								0.073	0.025	2.92
	1%								0.061	0.012	5.0833
Logistic	10%	28.00	0.16	0.031	0.018	1.72222	23.02	0.28	0.041	0.022	1.8636
	15%								0.053	0.031	1.7097
	5%								0.025	0.012	2.0833
	1%								0.0066	0.0026	2.5385
Log-Logistic ^f	10%	25.40	0.99	0.094	0.050	1.88	21.47	0.99	0.092	0.046	2
	15%								0.095	0.054	1.7593
	5%								0.089	0.036	2.4722
	1%								0.081	0.021	3.8571
Probit	10%	27.88	0.16	0.028	0.017	1.64706	23.03	0.27	0.035	0.020	1.75
	15%								0.047	0.029	1.6207
	5%								0.021	0.011	1.9091
	1%								0.0051	0.0023	2.2174
Log-Probit ^f	10%	27.40	ZD	0.093	0.050	1.86	23.47	ZD	0.091	0.046	1.9783
	15%								0.094	0.053	1.7736
	5%								0.087	0.037	2.3514
	1%								0.081	0.025	3.24
Selected BMD/BMDL ₁₀ value (ppm) ^g		0.087					0.027				
BMDL ₁₀ (HEC) (mg/m ³) ^a		0.041					0.037				

^a Human equivalent concentration (HEC) calculated via EPA methods (U.S. EPA, 1994b). The regional gas-dose ratio for the thoracic region of the respiratory tract (RGDR_{TH}) was used (see details in Section 5.2.3 of the main text).
^b BMDL estimates are 95% lower confidence limits on the dose that would elicit 10, 15, 5, or 1% extra risk.
^c Betas restricted to ≥0 in multistage/polynomial models; parsimony used to select polynomial order.
^d Power always restricted to ≥1 in Weibull and Power models.
^e Power always restricted to ≥1 in Gamma and Hill models.
^f Slope always restricted to ≥1 in Log-Logistic and Log-Probit models. The Log-logistic model was deemed to be inappropriate for this endpoint because of the large impact that a maximum high-dose response has on its shape in the low-dose region.
^g Selected models (results in bold) were chosen based on statistical (AIC, *p*, scaled residual values) and visual assessment per BMD guidance (U.S. EPA, 2000c). May represent an average of BMDLs from selected models.

NOAEL = no-observed-adverse-effect level determined via statistical comparison with control response; NA = not applicable or not applied; ZD = zero degrees of freedom; *p* value could not be calculated.

Table B-1c. Kodavanti et al. (1997): Epithelial alteration of terminal bronchiole/peribronchiolar alveolus, male rat

ppm	n	4-week exposure					12-week exposure				
0	12	2					0				
0.1	8	4					1				
0.2	8	5					7				
NOAEL (ppm)		0.1					0.1				
NOAEL(HEC) (mg/m³)^a		0.15					0.15				
BMDs and BMDLs^b		BMD/					BMD/				
Model		AIC	P	BMD	BMDL	BMDL	AIC	P	BMD	BMDL	BMDL
Multistage^c	10%	36.56	0.79	0.024	0.012	2	14.48	0.82	0.078	0.026	3
	15%							0.090	0.039	2.3077	
	5%							0.061	0.013	4.6923	
	1%							0.035	0.0025	14	
Weibull^d	10%	36.56	0.79	0.024	0.012	2	16.06	1.0	0.094	0.044	2.1364
	15%							0.11	0.056	1.9643	
	5%							0.079	0.030	2.6333	
	1%							0.052	0.012	4.3333	
Gamma^e	10%	36.56	0.79	0.024	0.012	2	16.06	1.0	0.096	0.050	1.92
	15%							0.10	0.061	1.6393	
	5%							0.084	0.036	2.3333	
	1%							0.065	0.018	3.6111	
Logistic	10%	36.87	0.53	0.042	0.026	1.61538	16.12	0.85	0.096	0.054	1.7778
	15%							0.11	0.068	1.6176	
	5%							0.078	0.034	2.2941	
	1%							0.041	0.0091	4.5055	
Log-Logistic^f	10%	36.49	0.94	0.017	0.0064	2.65625	16.06	1.0	0.096	0.055	1.7455
	15%							0.10	0.065	1.5385	
	5%							0.084	0.041	2.0488	
	1%							0.062	0.021	2.9524	
Probit	10%	36.85	0.55	0.041	0.026	1.57692	16.06	0.95	0.095	0.050	1.9
	15%							0.11	0.64	0.1719	
	5%							0.079	0.032	2.4688	
	1%							0.050	0.0084	5.9524	
Log-Probit^f	10%	36.66	0.69	0.043	0.023	1.86957	16.06	1.0	0.096	0.057	1.6842
	15%							0.10	0.066	1.5152	
	5%							0.086	0.046	1.8696	
	1%							0.070	0.030	2.3333	
Selected BMD/BMDL₁₀ value (ppm)^g		0.031 0.017					0.078 0.026				
BMDL₁₀(HEC) (mg/m³)^a		0.026					0.040				

^a Human equivalent concentration (HEC) calculated via EPA methods (U.S. EPA, 1994b). The regional gas-dose ratio for the thoracic region of the respiratory tract (RGDR_{TH}) was used (see details in Section 5.2.3 of the main text).

^b BMDL estimates are 95% lower confidence limits on the dose that would elicit 10, 15, 5, or 1% extra risk.

^c Betas restricted to ≥0 in multistage/polynomial models; parsimony used to select polynomial order.

^d Power always restricted to ≥1 in Weibull and Power models.

^e Power always restricted to ≥1 in Gamma and Hill models.

^f Slope always restricted to ≥1 in Log-Logistic and Log-Probit models.

^g Selected models (results in bold) were chosen based on statistical (AIC, *p*, scaled residual values) and visual assessment per BMD guidance (U.S. EPA, 2000c). May represent an average of BMDLs from selected models.

NOAEL = no-observed-adverse-effect level determined via statistical comparison with control response; NA = not applicable or not applied; ZD = zero degrees of freedom; *p* value could not be calculated.

Table B-1d. Kodavanti et al. (1997): Increased collagen staining of terminal bronchiole/peribronchiolar, male rats

ppm	n	4-week exposure					12-week exposure				
		AIC	P	BMD	BMDL	BMD/BMDL	AIC	P	BMD	BMDL	BMD/BMDL
0	12			1					2		
0.1	8			1					2		
0.2	8			8					8		
NOAEL (ppm)				0.1					0.1		
NOAEL(HEC) (mg/m³)^a				0.15					0.15		
BMDs and BMDLs^b						BMD/					BMD/
Model						BMDL					BMDL
Multistage^c	10%	16.91	0.99	0.11	0.027	4.07407	23.81	1.0	0.10	0.018	5.5556
	15%								0.11	0.028	3.9286
	5%								0.091	0.0087	10.46
	1%								0.075	0.0017	44.118
Weibull^d	10%	18.91	ZD	0.11	0.068	1.61765	25.81	ZD	0.10	0.053	1.8868
	15%								0.11	0.062	1.7742
	5%								0.091	0.040	2.275
	1%								0.073	0.021	3.4762
Gamma^e	10%	17.66	0.48	0.096	0.071	1.35211	24.17	0.63	0.092	0.059	1.5593
	15%								0.098	0.067	1.4627
	5%								0.083	0.048	1.7292
	1%								0.069	0.031	2.2258
Logistic	10%					indeterminate ^g					indeterminate ^g
	5%										
	1%										
Log-Logistic^f	10%	16.91	0.98	0.1	0.079	1.26582	23.81	0.99	0.10	0.068	1.4706
	15%								0.10	0.075	1.3333
	5%								0.096	0.057	1.6842
	1%								0.088	0.038	2.3158
Probit	10%					indeterminate ^g					indeterminate ^g
	5%										
	1%										
Log-Probit^f	10%	18.91	ZD	0.10	0.079	1.26582	25.81	ZD	0.10	0.068	1.4706
	15%								0.10	0.074	0.1351
	5%								0.096	0.059	1.6271
	1%								0.090	0.045	2
Selected BMD/BMDL₁₀ value (ppm)^h				0.11	0.027				0.10	0.018	
BMDL₁₀(HEC) (mg/m³)^a				0.041					0.028		

^a Human equivalent concentration (HEC) calculated via EPA methods (U.S. EPA, 1994b). The regional gas-dose ratio for the thoracic region of the respiratory tract (RGDR_{TH}) was used (see details in Section 5.2.3 of the main text).
^b BMDL estimates are 95% lower confidence limits on the dose that would elicit 10, 15, 5, or 1% extra risk.
^c Betas restricted to ≥0 in multistage/polynomial models; parsimony used to select polynomial order.
^d Power always restricted to ≥1 in Weibull and Power models.
^e Power always restricted to ≥1 in Gamma and Hill models.
^f Slope always restricted to ≥1 in Log-Logistic and Log-Probit models. The Log-logistic model was deemed to be inappropriate for this endpoint because of the large impact that a maximum high-dose response has on its shape in the low-dose region.
^g Inadequate model fit, *p*<0.1.
^h Selected models (results in bold) were chosen based on statistical (AIC, *p*, scaled residual values) and visual assessment per BMD guidance (U.S. EPA, 2000c). May represent an average of BMDLs from selected models.

NOAEL = no-observed-adverse-effect level determined via statistical comparison with control response; NA = not applicable or not applied; ZD = zero degrees of freedom; *p* value could not be calculated.

Table B-1e. Kodavanti et al. (1997): Volume displaced, left lung (mL/kg body weight × 100)

ppm		4-week exposure			12-week exposure							
		n	S.D.	n	S.D.							
0		12	0.12	11	0.0937							
0.1		8	0.1614	7	0.0725							
0.2		8	0.0767	8	0.1428							
NOAELs												
NOAEL (ppm)		0.1			0.1							
NOAEL(HEC) (mg/m³)^a		0.15			0.15							
BMDs and BMDL_s^b												
Model	STD	4-week exposure					12-week exposure					
		AIC	P	BMD	BMDL	BMDL	AIC	P	BMD	BMDL	BMDL	
Polynomial^c	1	-86.24	0.93	0.083	0.060	1.38333	-87.16	0.55	0.081	0.059	1.3729	
	1.5								0.12	0.88	0.1364	
	0.5								0.041	0.029	1.4138	
	0.1								0.0081	0.0059	1.3729	
Power^d	1	-84.24	ZD	0.083	0.060	1.38333	-85.52	ZD	0.10	0.060	1.6667	
	1.5								0.14	0.090	1.5556	
	0.5								0.060	0.030	2	
	0.1								0.018	0.0060	3	
Hill^e	1	indeterminate ^f					indeterminate ^f					
	1.5											
	0.5											
	0.1											
Selected BMD/BMDL₁₀ value (ppm)^g		0.083			0.060			0.081			0.059	
BMDL₁₀(HEC) (mg/m³)^a					0.092						0.090	

^a Human equivalent concentration (HEC) calculated via EPA methods (U.S. EPA, 1994b). The regional gas-dose ratio for the thoracic region of the respiratory tract (RGDR_{TH}) was used (see details in Section 5.2.3 of the main text).

^b BMDL estimates are 95% lower confidence limits on the dose that would result in a response equal to 1, 1.5, 0.5, or 0.1 standard deviations from the control mean.

^c Betas restricted to ≥0 in multistage/polynomial models; parsimony used to select polynomial order.

^d Power always restricted to ≥1 in Weibull and Power models.

^e Power always restricted to ≥1 in Gamma and Hill models.

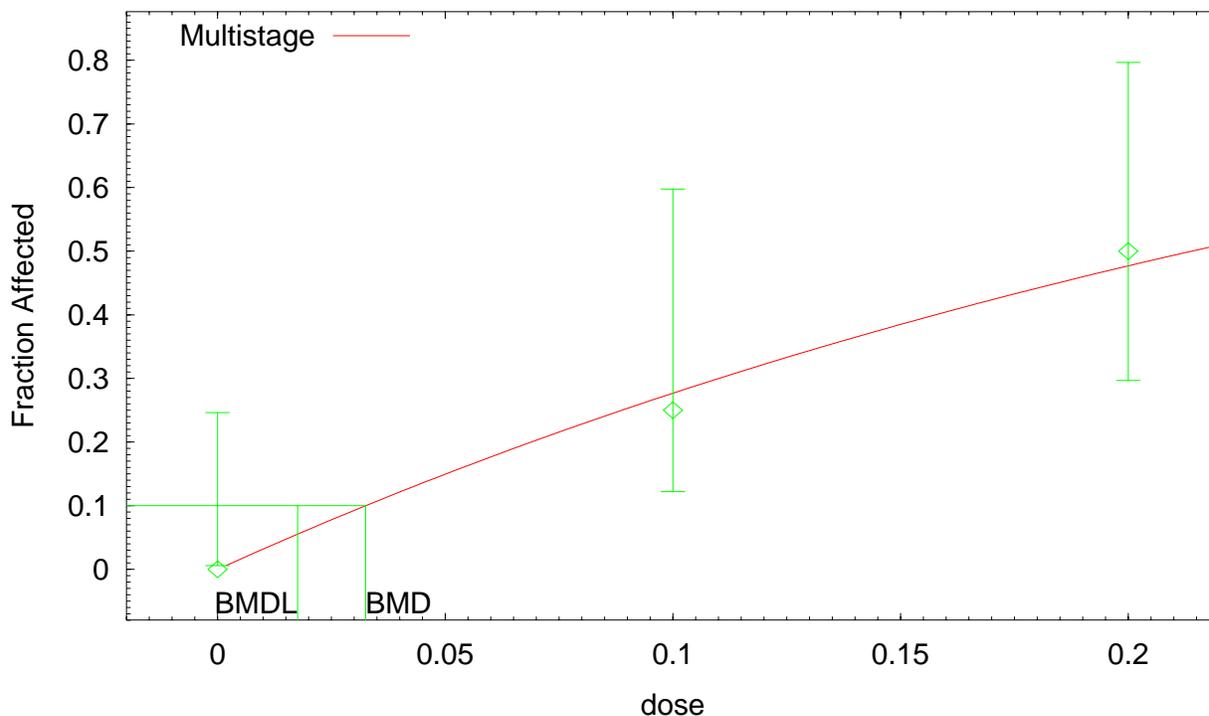
^f Inadequate model fit, *p*<0.1.

^g Selected models (results in bold) were chosen based on statistical (AIC, *p*, scaled residual values) and visual assessment per BMD guidance (U.S. EPA, 2000c). May represent an average of BMDLs from selected models.

NOAEL = no-observed-adverse-effect level determined via statistical comparison with control response; NA = not applicable or not applied; ZD = zero degrees of freedom; *p* value could not be calculated.

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Interstitial Thickening of the Alveolus in Male Rats (12 Weeks) – Multistage Model

Multistage Model with 0.95 Confidence Level



15:41 08/03 2004

```
=====
Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
Input Data File: F:\BMDS\DATA\PHOSGENE\AIT-12WK-MUL.(d)
Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\AIT-12WK-MUL.plt
Thu Oct 25 15:31:04 2001
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = AIT-12wk
Independent variable = Dose

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 2
Total number of specified parameters = 0
Degree of polynomial = 1

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Interstitial Thickening of the Alveolus in Male Rats (12 Weeks) – Multistage Model

Background = 0
Beta(1) = 3.46574

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)

Beta(1)

Beta(1) 1

Parameter Estimates		
Variable	Estimate	Std. Err.
Background	0	NA
Beta(1)	3.24026	2.09548

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)	Deviance	Test DF	P-value
Full model	-10.0439			
Fitted model	-10.067	0.0462843	2	0.9771
Reduced model	-14.5482	9.00875	2	0.01106

AIC: 22.134

Goodness of Fit					
Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.
i: 1	0.0000	0.0000	0	12	0.000
i: 2	0.1000	0.2768	2	8	-0.134
i: 3	0.2000	0.4769	4	8	0.092

Chi-square = 0.05 DF = 2 P-value = 0.9774

Benchmark Dose Computation

Specified effect = 0.1

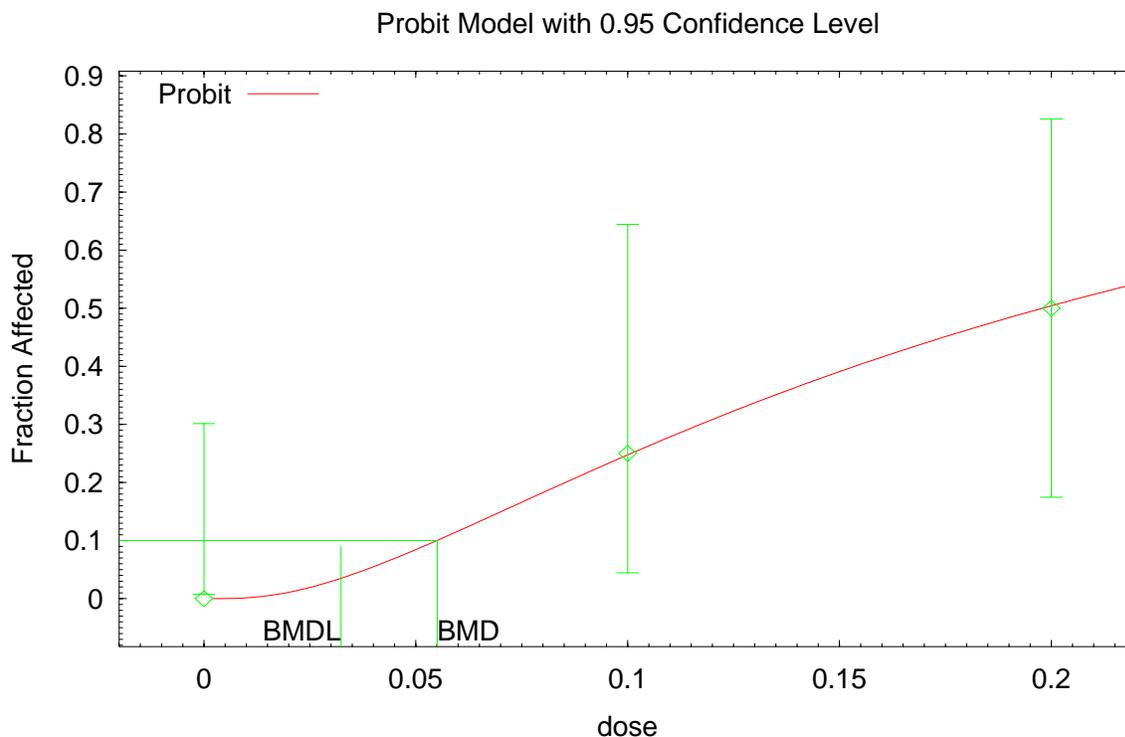
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0325161

BMDL = 0.0175799

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Interstitial Thickening of the Alveolus in Male Rats (12 Weeks) – Log Probit Model



15:48 08/03 2004

```
=====
Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
Input Data File: F:\BMDS\DATA\PHOSGENE\AIT-12WK-LOG-PRO.(d)
Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\AIT-12WK-LOG-PRO.plt
Thu Oct 25 15:31:28 2001
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{Background} + (1 - \text{Background}) * \text{CumNorm}(\text{Intercept} + \text{Slope} * \text{Log}(\text{Dose})),$$

where CumNorm(.) is the cumulative normal distribution function

Dependent variable = AIT-12wk
Independent variable = Dose
Slope parameter is restricted as slope >= 1

Total number of observations = 3
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

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Interstitial Thickening of the Alveolus in Male Rats (12 Weeks) – Log Probit Model

Background = 0
Intercept = 1.6281
Slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

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

intercept

intercept 1

Parameter Estimates		
Variable	Estimate	Std. Err.
Background	0	NA
Intercept	1.61798	0.326388
Slope	1	NA

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)	Deviance	Test DF	P-value
Full model	-10.0439			
Fitted model	-10.0443	0.000811983	2	0.9996
Reduced model	-14.5482	9.00875	2	0.01106

AIC: 22.0885

Goodness of Fit					
Dose	Est_Prob.	Expected	Scaled		
			Observed	Size	Residual
0.0000	0.0000	0.000	0	12	0
0.1000	0.2468	1.974	2	8	0.02101
0.2000	0.5034	4.027	4	8	-0.01928

Chi-square = 0.00 DF = 2 P-value = 0.9996

Benchmark Dose Computation

Specified effect = 0.1

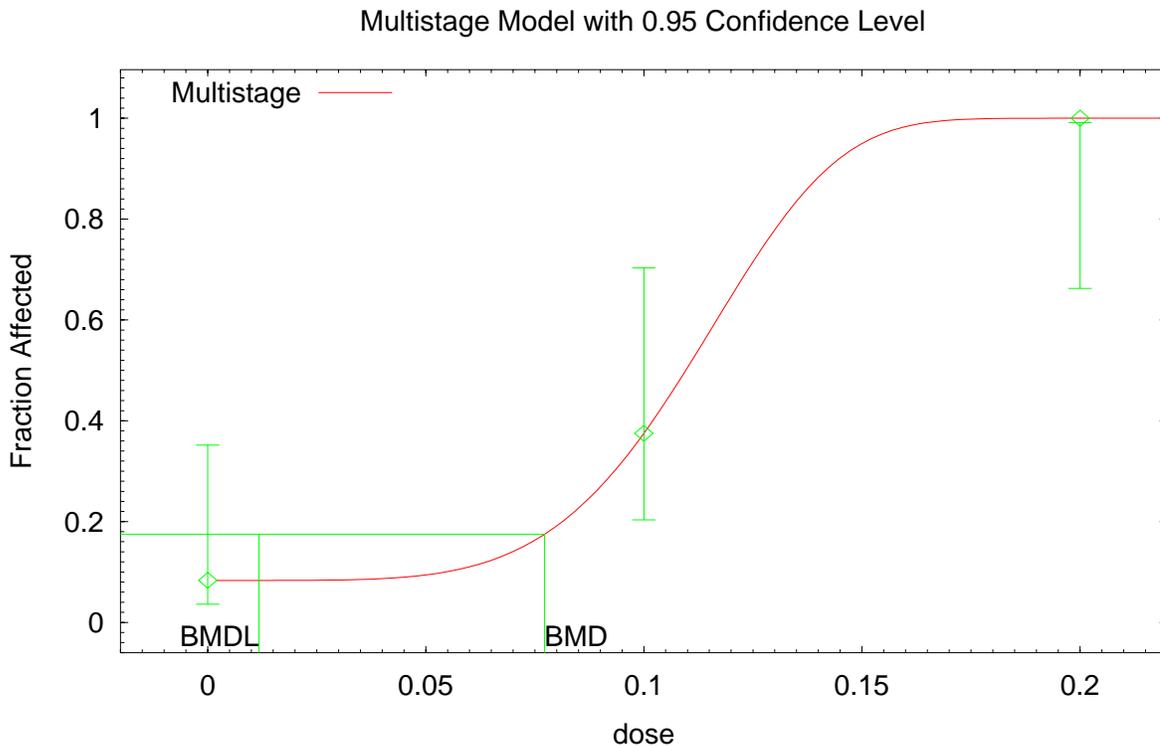
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.055049

BMDL = 0.0323742

**Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values
Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) –
Multistage Model**



```
=====
Multistage Model. $Revision: 2.1 $ $Date: 2000/08/21 03:38:21 $
Input Data File: F:\BMDS\DATA\PHOSGENE\INF-12WK-MUL.(d)
Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\INF-12WK-MUL.plt
Thu Oct 25 16:17:32 2001
=====
```

BMDS MODEL RUN

Observation # < parameter # for Multistage model.

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^1 - \text{beta}2 * \text{dose}^2 - \text{beta}3 * \text{dose}^3 - \text{beta}4 * \text{dose}^4 - \text{beta}5 * \text{dose}^5)]$$

The parameter betas are restricted to be positive

Dependent variable = INF-12wk

Independent variable = Dose

Total number of observations = 3
Total number of records with missing values = 0
Total number of parameters in model = 6
Total number of specified parameters = 0
Degree of polynomial = 5

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) – Multistage Model

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 1
Beta(1) = 5e+020
Beta(2) = 2.5e+021
Beta(3) = 1.25e+022
Beta(4) = 6.25e+022
Beta(5) = 3.125e+023

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1) -Beta(2) -Beta(3) -Beta(4)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(5)
Background	1	-0.56
Beta(5)	-0.56	1

Parameter Estimates

Variable	Estimate	Std. Err.
Background	0.0833264	0.275955
Beta(1)	0	NA
Beta(2)	0	NA
Beta(3)	0	NA
Beta(4)	0	NA
Beta(5)	38308.2	53667

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)	Deviance	Test DF	P-value
Full model	-8.73454			
Fitted model	-8.73457	6.96773e-005	1	0.9933
Reduced model	-19.1214	20.7738	2	<.0001

AIC: 21.4691

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Chi^2 Res.	
i: 1	0.0000	0.0833	1.000	1	12	0.000
i: 2	0.1000	0.3751	3.000	3	8	-0.000
i: 3	0.2000	1.0000	8.000	8	8	1.000

Chi-square = 0.00 DF = 1 P-value = 0.9953

**Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values
Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) –
Multistage Model**

Benchmark Dose Computation

Specified effect = 0.1

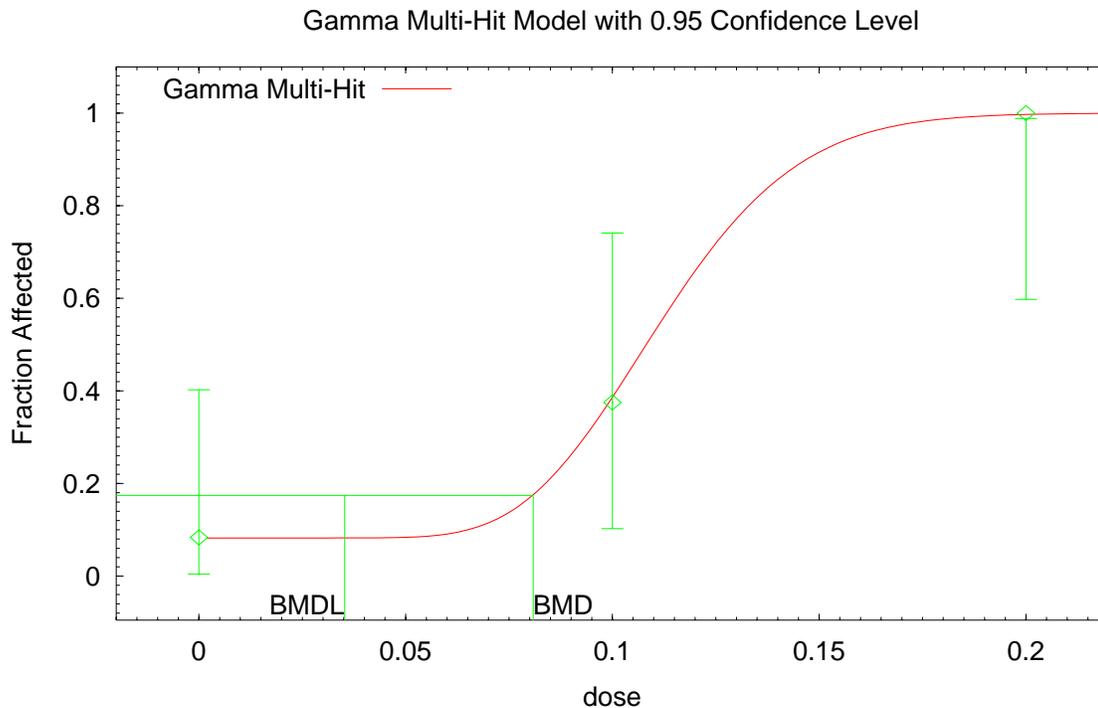
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0772462

BMDL = 0.0117632

**Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values
Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) –
Gamma Model**



15:53 08/03 2004

=====
\$Revision: 2.2 \$Date: 2001/03/14 01:17:00 \$
Input Data File: F:\BMDS\DATA\PHOSGENE\INF-12WK-GAM.(d)
Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\INF-12WK-GAM.plt

Thu Oct 25 16:33:03 2001

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

The form of the probability function is:

$P[\text{response}] = \text{background} + (1 - \text{background}) * \text{CumGamma}[\text{slope} * \text{dose}, \text{power}]$ ,  
where CumGamma(.) is the cumulative Gamma distribution function

Dependent variable = INF-12wk  
Independent variable = Dose  
Power parameter is restricted as power >=1

Total number of observations = 3  
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

Default Initial (and Specified) Parameter Values

Background = 0.115385  
Slope = 7.44381  
Power = 1.3

## Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) – Gamma Model

Asymptotic Correlation Matrix of Parameter Estimates

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

|            | Background | Slope |
|------------|------------|-------|
| Background | 1          | -0.28 |
| Slope      | -0.28      | 1     |

| Parameter Estimates |           |           |
|---------------------|-----------|-----------|
| Variable            | Estimate  | Std. Err. |
| Background          | 0.0823419 | 0.0785952 |
| Slope               | 158.604   | 20.2326   |
| Power               | 18        | NA        |

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) | Deviance | Test DF | P-value |
| Full model                 | -8.73454        |          |         |         |
| Fitted model               | -8.75909        | 0.049106 | 1       | 0.8246  |
| Reduced model              | -19.1214        | 20.7738  | 2       | <.0001  |

AIC: 21.5182

| Goodness of Fit |            |          |          |                 |
|-----------------|------------|----------|----------|-----------------|
| Dose            | Est._Prob. | Expected | Observed | Scaled Residual |
| 0.0000          | 0.0823     | 0.988    | 1        | 12 0.01249      |
| 0.1000          | 0.3830     | 3.064    | 3        | 8 -0.04677      |
| 0.2000          | 0.9971     | 7.977    | 8        | 8 0.153         |

Chi-square = 0.03 DF = 1 P-value = 0.8725

Benchmark Dose Computation

Specified effect = 0.1

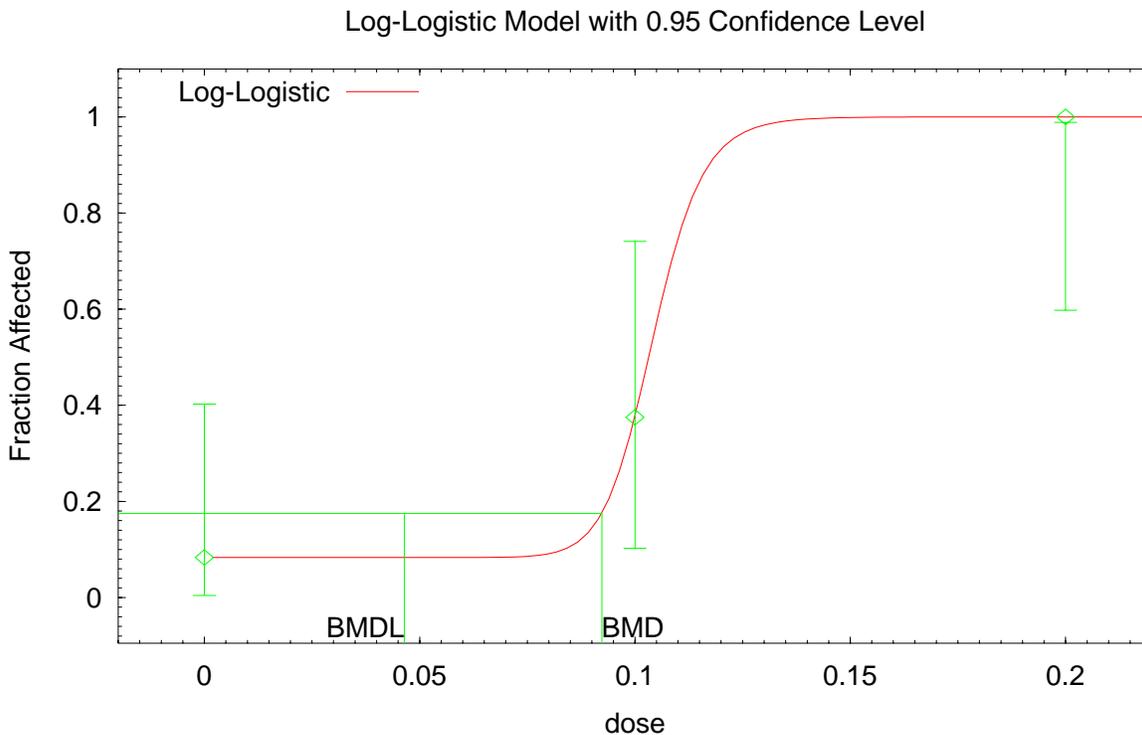
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0808407

BMDL = 0.0352477

**Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values  
Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) –  
LogLogistic Model**



```
=====
Logistic Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:20 $
Input Data File: F:\BMDS\DATA\PHOSGENE\INF-12WK-LOG-LOG.(d)
Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\INF-12WK-LOG-LOG.plt
Thu Oct 25 16:29:08 2001
=====
```

BMDS MODEL RUN

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

Dependent variable = INF-12wk  
Independent variable = Dose  
Slope parameter is restricted as slope >= 1

Total number of observations = 3  
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 Parameter Values  
Background = 0.0833333  
Intercept = 11.1814

# Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Inflammatory Cell Influx to Terminal Bronchiole/Alveolus, Male Rats (12 Weeks) – LogLogistic Model

Slope = 5.187

Asymptotic Correlation Matrix of Parameter Estimates

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

|            | Background | Intercept |
|------------|------------|-----------|
| Background | 1          | -0.3      |
| Intercept  | -0.3       | 1         |

| Parameter Estimates |           |           |
|---------------------|-----------|-----------|
| Variable            | Estimate  | Std. Err. |
| Background          | 0.0833321 | 0.0797846 |
| Intercept           | 40.6845   | 0.903084  |
| Slope               | 18        | NA        |

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) | Deviance    | Test DF | P-value |
| Full model                 | -8.73454        |             |         |         |
| Fitted model               | -8.7346         | 0.000119887 | 1       | 0.9913  |
| Reduced model              | -19.1214        | 20.7738     | 2       | <.0001  |

AIC: 21.4692

| Goodness of Fit |            |          |          |      |                 |
|-----------------|------------|----------|----------|------|-----------------|
| Dose            | Est._Prob. | Expected | Observed | Size | Scaled Residual |
| 0.0000          | 0.0833     | 1.000    | 1        | 12   | 1.567e-005      |
| 0.1000          | 0.3750     | 3.000    | 3        | 8    | -6.786e-005     |
| 0.2000          | 1.0000     | 8.000    | 8        | 8    | 0.007742        |

Chi-square = 0.00 DF = 1 P-value = 0.9938

Benchmark Dose Computation

Specified effect = 0.1

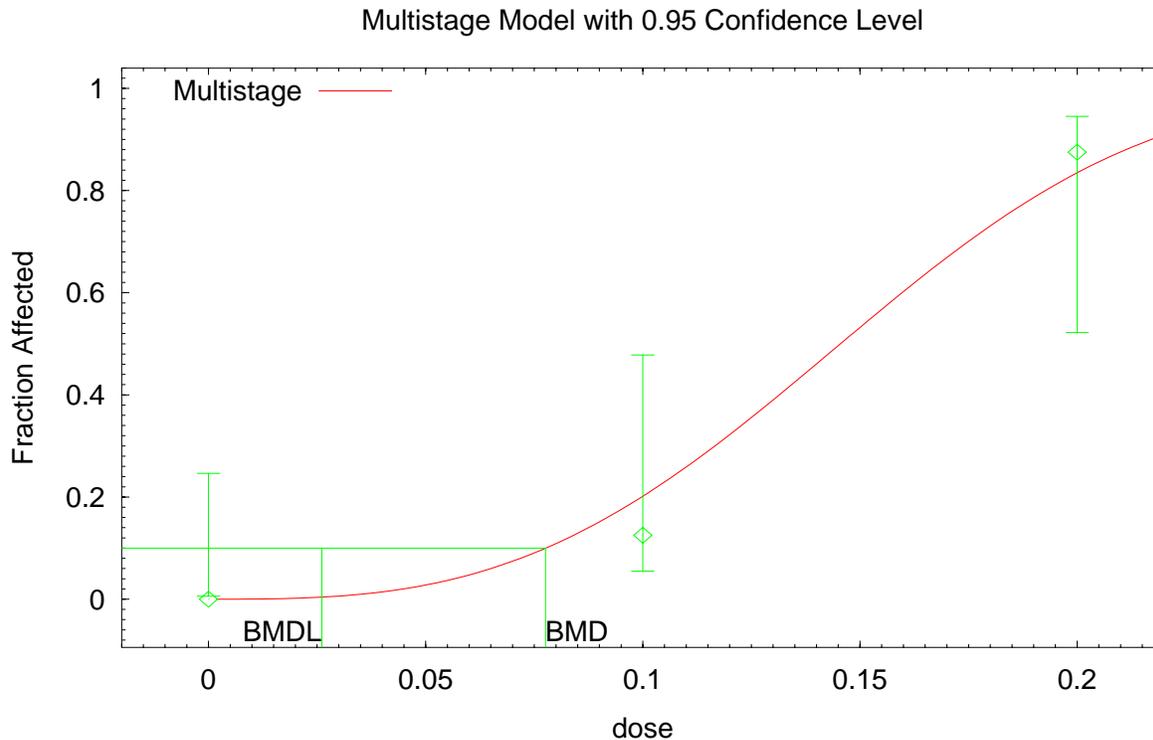
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0923365

BMDL = 0.0464352

**Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values  
Epithelial Alteration of Terminal Bronchiole/Peribronchial Alveolus (12 Weeks) –  
Multistage Model**



16:00 08/03 2004

=====  
 Multistage Model. \$Revision: 2.1 \$ \$Date: 2000/08/21 03:38:21 \$  
 Input Data File: F:\BMDS\DATA\PHOSGENE\EPI-12WK-MUL.(d)  
 Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\EPI-12WK-MUL.plt

Fri Oct 26 10:22:13 2001

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

Observation # < parameter # for Multistage model.  
 The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^{\text{beta}2} * \text{dose}^{\text{beta}3} * \text{dose}^{\text{beta}3})]$$

The parameter betas are restricted to be positive

Dependent variable = EPI-12wk  
 Independent variable = Dose

Total number of observations = 3  
 Total number of records with missing values = 0  
 Total number of parameters in model = 4  
 Total number of specified parameters = 0  
 Degree of polynomial = 3

Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

# Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Epithelial Alteration of Terminal Bronchiole/Peribronchial Alveolus (12 Weeks) – Multistage Model

## Default Initial Parameter Values

Background = 0  
Beta(1) = 0  
Beta(2) = 100  
Beta(3) = 250

## Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Background -Beta(1) -Beta(2)  
have been estimated at a boundary point, or have been specified by the user,  
and do not appear in the correlation matrix )

Beta(3)

Beta(3)      1

## Parameter Estimates

| Variable   | Estimate | Std. Err. |
|------------|----------|-----------|
| Background | 0        | NA        |
| Beta(1)    | 0        | NA        |
| Beta(2)    | 0        | NA        |
| Beta(3)    | 225.422  | 104.079   |

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) | Deviance | Test DF | P-value |
|---------------|-----------------|----------|---------|---------|
| Full model    | -6.02832        |          |         |         |
| Fitted model  | -6.24181        | 0.426967 | 2       | 0.8078  |
| Reduced model | -16.7515        | 21.4465  | 2       | <.0001  |

AIC:      14.4836

## Goodness of Fit

| Dose | Est_Prob. | Expected | Observed | Size | Chi^2 Res. |
|------|-----------|----------|----------|------|------------|
| i: 1 | 0.0000    | 0.0000   | 0        | 12   | 0.000      |
| i: 2 | 0.1000    | 0.2018   | 1        | 8    | -0.477     |
| i: 3 | 0.2000    | 0.8353   | 7        | 8    | 0.289      |

Chi-square = 0.38    DF = 2    P-value = 0.8249

## Benchmark Dose Computation

Specified effect = 0.1

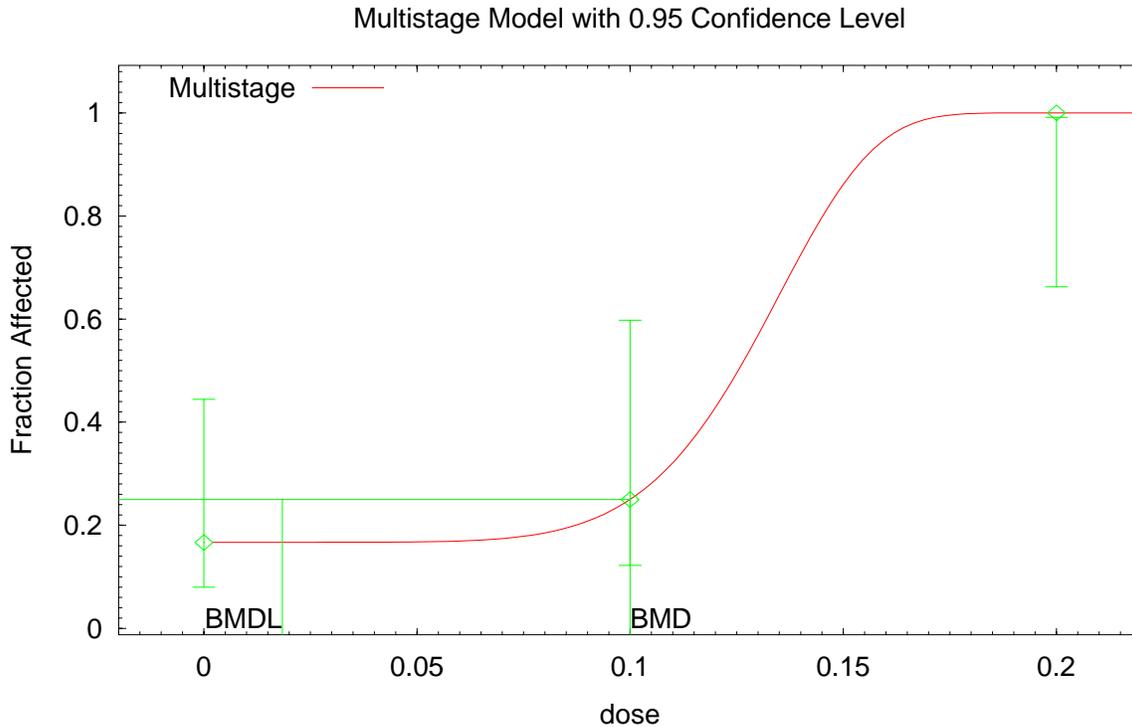
Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.0776057

BMDL = 0.0261034

**Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Increased Collagen Staining of Terminal Bronchiole/Peribronchiolar (12 Weeks) – Multistage Model**



=====  
 Multistage Model. \$Revision: 2.1 \$ \$Date: 2000/08/21 03:38:21 \$  
 Input Data File: F:\BMDS\DATA\PHOSGENE\STA-12WK-MUL.(d)  
 Gnuplot Plotting File: F:\BMDS\DATA\PHOSGENE\STA-12WK-MUL.plt  
 =====

Tue Oct 30 17:17:48 2001

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

Observation # < parameter # for Multistage model.  
 The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta}1 * \text{dose}^1 - \text{beta}2 * \text{dose}^2 - \text{beta}3 * \text{dose}^3 - \text{beta}4 * \text{dose}^4 - \text{beta}5 * \text{dose}^5 - \text{beta}6 * \text{dose}^6 - \text{beta}7 * \text{dose}^7)]$$

The parameter betas are restricted to be positive

Dependent variable = STA-12wk  
 Independent variable = Dose

Total number of observations = 3  
 Total number of records with missing values = 0  
 Total number of parameters in model = 8  
 Total number of specified parameters = 0  
 Degree of polynomial = 7

Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

## Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Increased Collagen Staining of Terminal Bronchiole/Peribronchiolar (12 Weeks) – Multistage Model

### Default Initial Parameter Values

Background = 1  
 Beta(1) = 5e+020  
 Beta(2) = 2.5e+021  
 Beta(3) = 1.25e+022  
 Beta(4) = 6.25e+022  
 Beta(5) = 3.125e+023  
 Beta(6) = 1.5625e+024  
 Beta(7) = 7.8125e+024

### Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Beta(1) -Beta(2) -Beta(3) -Beta(4) -Beta(5) -Beta(6) have been estimated at a boundary point, or have been specified by the user, and do not appear in the correlation matrix )

|            | Background | Beta(7) |
|------------|------------|---------|
| Background | 1          | -0.6    |
| Beta(7)    | -0.6       | 1       |

| Parameter Estimates |              |              |
|---------------------|--------------|--------------|
| Variable            | Estimate     | Std. Err.    |
| Background          | 0.166651     | 0.261628     |
| Beta(1)             | 0            | NA           |
| Beta(2)             | 0            | NA           |
| Beta(3)             | 0            | NA           |
| Beta(4)             | 0            | NA           |
| Beta(5)             | 0            | NA           |
| Beta(6)             | 0            | NA           |
| Beta(7)             | 1.05428e+006 | 5.06411e+006 |

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) | Deviance     | Test DF | P-value |
| Full model                 | -9.90542        |              |         |         |
| Fitted model               | -9.90542        | 1.84535e-005 | 1       | 0.9966  |
| Reduced model              | -19.1214        | 18.432       | 2       | <.0001  |

AIC: 23.8108

### Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Chi^2 Res. |        |
|------|------------|----------|----------|------|------------|--------|
| i: 1 | 0.0000     | 0.1667   | 2.000    | 2    | 12         | 0.000  |
| i: 2 | 0.1000     | 0.2500   | 2.000    | 2    | 8          | -0.000 |
| i: 3 | 0.2000     | 1.0000   | 8.000    | 8    | 8          | 1.000  |

Chi-square = 0.00    DF = 1    P-value = 0.9976

## **Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values Increased Collagen Staining of Terminal Bronchiole/Peribronchiolar (12 Weeks) – Multistage Model**

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

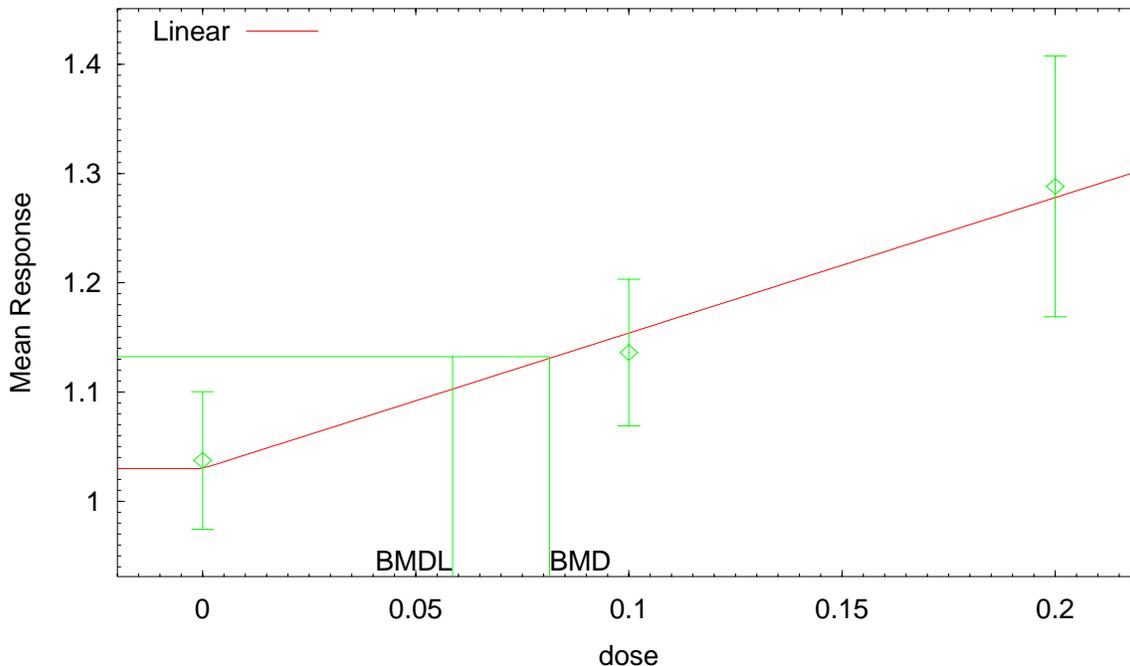
Confidence level = 0.95

BMD = 0.0999908

BMDL = 0.018414

**Model Runs Used in the Derivation of Table B-1 Selected BMDL<sub>10</sub> Values  
Volume Displaced, Left Lung (mL/kg body weight × 100) (12 Weeks) – Polynomial Model**

Linear Model with 0.95 Confidence Level



08:16 08/04 2004

=====  
 Polynomial Model. Revision: 2.3 Date: 09/08/2003  
 Input Data File: U:\BMDS\DATA\PHOSGENE\10%OUTFILES\LVD-12WK-POLY.(d)  
 Gnuplot Plotting File: U:\BMDS\DATA\PHOSGENE\10%OUTFILES\LVD-12WK-POLY.plt  
 Mon Aug 02 09:28:17 2004  
 =====

BMDS MODEL RUN  
 ~~~~~

The form of the response function is:

$$Y[\text{dose}] = \text{beta}_0 + \text{beta}_1 * \text{dose} + \text{beta}_2 * \text{dose}^2 + \dots$$

Dependent variable = MEAN

Independent variable = Dose

rho is set to 0

The polynomial coefficients are restricted to be positive

A constant variance model is fit

Total number of dose groups = 3

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

Default Initial Parameter Values

alpha = 0.0113983

rho = 0 Specified

beta_0 = 1.02848

beta_1 = 1.2542

Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values Volume Displaced, Left Lung (mL/kg body weight × 100) (12 Weeks) – Polynomial Model

Parameter Estimates

Variable	Estimate	95.0% Wald Confidence Interval		
		Std. Err.	Lower Conf. Limit	Upper Conf. Limit
alpha	0.0102218	0.002835	0.00466525	0.0157783
beta_0	1.03121	0.0286698	0.975016	1.0874
beta_1	1.24267	0.234088	0.783862	1.70147

Asymptotic Correlation Matrix of Parameter Estimates

	alpha	beta_0	beta_1
alpha	1	5.1e-008	-9.7e-008
beta_0	5.1e-008	1	-0.72
beta_1	-9.7e-008	-0.72	1

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Obs Std Dev	Est Mean	Est Std Dev	Chi^2 Res.
0	11	1.04	0.0937	1.03	0.101	0.202
0.1	7	1.14	0.0725	1.16	0.101	-0.506
0.2	8	1.29	0.143	1.28	0.101	0.237

Model Descriptions for Likelihoods Calculated

Model A1: $Y_{ij} = \mu(I) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2: $Y_{ij} = \mu(I) + e(ij)$
 $\text{Var}\{e(ij)\} = \sigma(I)^2$

Model R: $Y_i = \mu + e(I)$
 $\text{Var}\{e(I)\} = \sigma^2$

Likelihoods of Interest

Model	Log(likelihood)	d.f.	AIC
A1	46.759659	4	-85.519318
A2	48.576042	6	-85.152085
fitted	46.582087	3	-87.164174
R	36.527257	2	-69.054514

Test 1: Does response and/or variances differ among dose levels (A2 vs. R)

Test 2: Are Variances Homogeneous (A1 vs A2)

Test 3: Does the Model for the Mean Fit (A1 vs. fitted)

Tests of Interest

Test	$-2 \cdot \log(\text{Likelihood Ratio})$	Test df	p-value
Test 1	24.0976	4	<.0001
Test 2	3.63277	2	0.1626
Test 3	0.355144	1	0.5512

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels. It seems appropriate to model the data

The p-value for Test 2 is greater than .05. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .05. The model chosen appears to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

Risk Type = Estimated standard deviations from the control mean

**Model Runs Used in the Derivation of Table B-1 Selected BMDL₁₀ Values
Volume Displaced, Left Lung (mL/kg body weight × 100) (12 Weeks) – Polynomial Model**

Confidence level = 0.95

BMD = 0.0813596

BMDL = 0.058627

APPENDIX B-2: EXPLANATION OF CATREG ANALYSIS

CatReg is a computer program developed to support toxicologists and health scientists in the conduct of exposure-response analyses. Prior to performing categorical regression using CatReg, effects observed in toxicological studies must be assigned to ordinal severity categories (e.g., no effect, adverse effect, severe effect) and associated with the exposure conditions (e.g., concentration and duration) under which the effects occurred. CatReg executes a regression analysis of the severity scores and exposure parameters. The categorization of observed responses allows expression of dichotomous, continuous, and descriptive data in terms of effect severity and supports the analysis of the data from single studies or a combination of similar studies. CatReg is designed to work with S-PLUS® Professional version 3 or higher, and the user must have access to this software to execute the CatReg program.¹ Although familiarity with S-PLUS® may assist the user, an understanding of the S-PLUS® programming language is not required.

In the case of dichotomous data for phosgene, the lung is assessed in terms of presence or absence of an effect, such as the collagen-staining effect observed following phosgene exposure (Table B-1d, Appendix B-1). The mathematical form of the models that were used to compute the benchmark dose-probability relationship is a function that is nondecreasing as x increases and takes only values between 0 and 1 (properties required of a cumulative probability function).

As is the case in the Kodavanti et al. (1997) report, experimental effects may be reported in more detail than simply “absence” or “presence,” which allows for more detailed data analysis using CatReg. For example, the number of animals in each treatment group and the number with varying degrees of inflammation may be classified into severity levels, such as “no adverse effect,” “mild adverse effect,” or “moderate/severe effect.” After classifying the observations into the severity levels (which are now the “data” to be input to CatReg), the data are *ordinal* (ranked in terms of severity) and *categorical* (each animal in each treatment group is in a severity category or a range of severity categories). Duration of exposure, as well as concentration, is included in CatReg because it affects the probability of achieving the various severity levels. “Duration” can be omitted, however, which is convenient when all subjects were exposed for the same duration, or if duration is not considered to be an explanatory variable (as has been determined to be the case for this analysis).

In the CatReg analysis of data from Kodavanti et al. (1997), the scores assigned by the

¹A version of CatReg that will run in the freely distributable R statistical platform is under development, but has not been released to date.

study authors were weighted according to the severity of the various endpoints as follows for endpoints that did not significantly regress or disappear during the 4-week recovery period (epithelial alteration and collagen staining of the terminal bronchioles) were increased by 1 severity grade, and the scores of endpoints deemed to have recognized and serious long-term consequences (collagen staining) were increased by an additional severity grade (see Tables B-2a-1 and B-2a-2). Thus, the absence of a lesion was scored as a severity grade of 0, reversible lesions scored as “minimal” by the study authors received a severity grade of 1, reversible lesions scored as “slight/mild” and potentially irreversible lesions scored as “minimal” by the study authors received a severity grade of 2, and potentially irreversible lesions scored by study authors as “slight/mild” or any occurrence of a lesion considered to have long-term consequences (collagen staining) received a severity grade of 3. Table B-2b is the input file for CatReg that was generated from the data for the 4-week, 12-week, and combined exposure periods.

Table B-2a-1. Adjusted severity grades for CatReg analysis of lung lesions in rats exposed to phosgene for 4 weeks (Kodavanti et al., 1997)

4-Week Controls	1	2	3	4	5	6	7	8	9	10	11	12
Alveolar effusion												
Alveolus, interstitial thickening												
Bronchus, epithelial alteration												
Bronchus, inflammation							1					
Terminal bronchiole/alveolus, inflammatory cell influx	1											1
Alveolus, epithelial alteration						2						2
Increased collagen staining												3
Assigned Severity Grade	1	0	0	0	0	2	1	0	0	0	0	3
0.1 ppm Exposure Group	1	2	3	4	5	6	7	8				
Alveolar effusion												
Alveolus, interstitial thickening					1		1					
Bronchus, epithelial alteration							1					
Bronchus, inflammation	1						1					
Terminal bronchiole/alveolus, inflammatory cell influx		1	1		1							
Alveolus, epithelial alteration	2	2			2			2				
Increased collagen staining							3					
Assigned Severity Grade	2	2	1	0	2	0	3	2				
0.2 ppm Exposure Group	1	2	3	4	5	6	7	8				
Alveolar effusion												
Alveolus, interstitial thickening		1	1	1	1			1				
Bronchus, epithelial alteration			2		2							
Bronchus, inflammation			1		1							
Terminal bronchiole/alveolus, inflammatory cell influx	1	1	1	1	1	1	1	1				
Alveolus, epithelial alteration		2	2	2	2			2				
Increased collagen staining	3	3	3	3	3	3	3	3				
Assigned Severity Grade	3											

Table B-2a-2. Adjusted severity grades for CatReg analysis of lung lesions in rats exposed to phosgene for 12 weeks (Kodavanti et al., 1997)

12-Week Controls	1	2	3	4	5	6	7	8	9	10	11	12
Alveolar effusion												
Alveolus, interstitial thickening												
Bronchus, epithelial alteration												
Bronchus, inflammation												
Terminal bronchiole/alveolus, inflammatory cell influx				1								
Alveolus, epithelial alteration												
Increased collagen staining		3		3								
Assigned Severity Grade	0	3	0	3	0	0	0	0	0	0	0	0
0.1 ppm Exposure Group	1	2	3	4	5	6	7	8				
Alveolar effusion												
Alveolus, interstitial thickening				1	1							
Bronchus, epithelial alteration												
Bronchus, inflammation												
Terminal bronchiole/alveolus, inflammatory cell influx			1	1		1						
Alveolus, epithelial alteration		2										
Increased collagen staining			3			3						
Assigned Severity Grade	0	2	3	1	1	3	0	0				
0.2 ppm Exposure Group	1	2	3	4	5	6	7	8				
Alveolar effusion												
Alveolus, interstitial thickening	1	1		1	1							
Bronchus, epithelial alteration						1						
Bronchus, inflammation												
Terminal bronchiole/alveolus, inflammatory cell influx	1	1	1	2	1	1	1	1				
Alveolus, epithelial alteration	2	2	2	2	2		2	2				
Increased collagen staining	3	3	3	3	3	3	3	3				
Assigned Severity Grade	3											

Table B-2b. CatReg input data file for 4-week, 12-week, and combined analysis

ppm	Weeks	Target	Nsub	GpSize	Incid	SevLo	SevHi
0	4	Lung	12	1	8	0	0
0	4	Lung	12	1	2	1	1
0	4	Lung	12	1	1	2	2
0	4	Lung	12	1	1	3	3
0.1	4	Lung	8	1	2	0	0
0.1	4	Lung	8	1	1	1	1
0.1	4	Lung	8	1	4	2	2
0.1	4	Lung	8	1	1	3	3
0.2	4	Lung	8	1	8	3	3
0	12	Lung	12	1	10	0	0
0	12	Lung	12	1	2	3	3
0.1	12	Lung	8	1	3	0	0
0.1	12	Lung	8	1	2	1	1
0.1	12	Lung	8	1	1	2	2
0.1	12	Lung	8	1	2	3	3
0.2	12	Lung	8	1	8	3	3
0	Combined	Lung	24	1	18	0	0
0	Combined	Lung	24	1	2	1	1
0	Combined	Lung	24	1	1	2	2
0	Combined	Lung	24	1	3	3	3
0.1	Combined	Lung	16	1	5	0	0
0.1	Combined	Lung	16	1	3	1	1
0.1	Combined	Lung	16	1	5	2	2
0.1	Combined	Lung	16	1	3	3	3
0.2	Combined	Lung	16	1	16	3	3

CatReg was used to fit a cumulative probability distribution to the 4-week and 12-week data and the 4-week and 12-week data combined. Given a concentration C and duration T , CatReg models the distribution of Y as

$$\Pr(Y \geq s / C, T) = H[(a_s + b_1 * f_1(C) + b_2 * f_2(T))]$$

for ordinal scores $s = 1, \dots, S$. This is the probability of attaining a severity score of 1 or higher

at some specified concentration and duration of exposure. The parameter a_1 is the intercept for severity equals 1, and a_s is an increment in the intercept for severity equals s versus severity equals 1, for $s = 2, \dots, S$. b_1 and b_2 determine the relationship between the response and concentration and duration, respectively; unrestricted odds models can be chosen such that b 's may depend on the severity level of interest. CatReg can restrict the slopes so that they are the same across all severity levels; thus, the slopes are simply b_1 and b_2 .

H is a probability function that takes values between 0 and 1. The inverse of H is called the link function, which is used to obtain the parameter estimates. There are several possible choices for the inverse of H : logit, probit, and log-log functions (see U.S. EPA, 2000e, p. 4). Transformation functions, f_1 and f_2 , transform D and T to another scale, usually a base-10 logarithm.

The intercept term at a specified severity level determines the probability of occurrence when concentration and duration are both zero (i.e., the probability of a “background” response at that severity level). The coefficients of concentration and duration (along with the model used) determine how rapidly the probability of response (at a specified severity level) increases as concentration and duration increase. The larger the coefficient of concentration, the more rapidly the probability increases as concentration increases, and similarly for duration; the smaller the coefficient of a variable, the less sensitive the probability is to a change in the variable. The coefficient of duration for all model runs of the 4-week and 12-week data was a very small number, approximately -0.04 ($SE = 0.05$). In addition, a Z-test of the null hypothesis that there is no time effect yielded a p value of 0.425, well above the p value of 0.05 that would cause us to reject the hypothesis. For these reasons, the results of the CatReg analyses of the combined 4-week and 12-week data are used.

The primary goal of this analysis is to determine the CatReg estimate that is most comparable to the BMD_{10} estimates for collagen staining that are presented in Appendix B-1 (Table B-1d). This was determined to be the 10% extra risk dose (ERD_{10}) for a severity score equal to 3, using the combined 4-week and 12-week data.² The ERD_{10} for a severity score of 3 is defined as the dose d^* that satisfies

$$\frac{\Pr(Y \geq 3 \mid D = d^*) - \Pr(Y \geq 3 \mid D = 0)}{1 - \Pr(Y \geq 3 \mid D = 0)} = 0.1$$

Thus, the ERD_{10} is the dose that is associated with a 10% relative change from the background response at severity level 3 or greater. If the probability of a severity level 3

²Other extra risk values and severity grades were evaluated and are presented for comparison purposes.

response or greater were 0 at 0 concentration, the ERD_{10} would be equal to the 10% effective concentration (EC_{10}), a value that the currently released version of CatReg can estimate directly. Because this probability is not 0 at 0 in this case, additional calculations are necessary.³

To determine the best model for finding the extra risk doses, the appropriate link function and model had to be identified.⁴ Next, the data needed to be evaluated to determine whether the slopes of the response curves associated with each severity level could be assumed to be parallel, allowing for the use of a simplified model. The more complex, unrestricted model, in which the severity levels are assumed to have individual slopes, was run first. The CatReg parallel test (partest) was then used to determine whether slope parameters estimated in a model run for each severity level are equivalent. When the slopes were found to not significantly differ from each other, the simpler model that assumes a common slope (parallel curves) was employed. The test was insignificant (simpler model was justified) for most endpoints.

Table B-2c shows the results of the model test. The cumulative odds model (cloglog link function) was chosen because it resulted in the lowest deviance values. The unrestricted form of this model was not deemed necessary because the parallel test of CatReg did not find that the loss of 2 degrees of freedom that this would require was justified. The results for the application of this model to the combined 4-week and 12-week severity graded data are shown in Table B-2d. The ERD_{10} for a severity score equal to 3, using the combined 4-week and 12-week data, is estimated to be approximately 0.05 ppm.

³The current Splus version of CatReg does not give extra risk doses directly at this time; however, it does provide the information needed to derive them. To calculate the background risk ($\Pr(Y \geq 3 | D = 0)$ in the above equation) one must use the severity 3 intercept parameter estimate (α_3) provided by CatReg to solve the function of interest (e.g., the logit function, $\Pr(Y \geq 3 | D) = \exp[\alpha_3 + \beta_1 * D] / (1 + \exp[\alpha_3 + \beta_1 * D])$), where $D = 0$. Then solve:

$$\Pr(Y \geq 3 | D = d^*) = 0.1 * (1 - \Pr(Y \geq 3 | D = 0)) + \Pr(Y \geq 3 | D = 0)$$

CatReg can then be used to calculate the dose (EC) associated with $\Pr(Y \geq 3 | D = d^*)$. This is the desired d^* , the 10% extra risk dose for a severity 3 effect.

⁴See Section 2.2 of the CatReg documentation (U.S. EPA, 2000e) for the method for determining the best link function.

Table B-2c. Selection of model for use in derivation of ERD values

Scale	Link	Model	Deviance	df	Chi-square	df	p-value	Parallel test result
None	Probit	Cumulative Odds model	92.5099	5	0.5952022	2	0.74260	This is generally considered not significant, indicating that it would be more appropriate to use the simpler restricted cumulative model.
None	Probit	Unrestricted Cumulative model	91.98678	3				
None	CLogLog	Cumulative Odds model	87.81308	5	0.3337553	2	0.84630	This is generally considered not significant, indicating that it would be more appropriate to use the simpler restricted cumulative model .
None	CLogLog	Unrestricted Cumulative model	87.42469	3				
Log	Logit	Cumulative Odds model	109.2512	5	0.588963	2	0.74492	This is generally considered not significant, indicating that it would be more appropriate to use the simpler restricted cumulative model .
Log	Logit	Unrestricted Cumulative model	108.7628	3				
Log	Probit	Cumulative Odds model	109.6004	5	0.9155587	2	0.63269	This is generally considered not significant, indicating that it would be more appropriate to use the simpler restricted cumulative model .
Log	Probit	Unrestricted Cumulative model	108.8286	3				
Log	CLogLog	Cumulative Odds model	108.7272	5	0.3245027	2	0.85023	This is generally considered not significant, indicating that it would be more appropriate to use the simpler restricted cumulative model .
Log	CLogLog	Unrestricted Cumulative model	108.348	3				

ERD = Extra risk dose.

Table B-2d. Results of CatReg analysis of severity-graded lung lesions reported by Kodavanti et al. (1997) [estimates of the exposures that would cause a 10, 20, and 30% extra risk of an effect equal to or greater than severity grade 1, 2, and 3 (ERD₁₀, ERD₂₀, and ERD₃₀)]

Severity grade	Model	Link function	ERD ₁₀ (ppm)	ERD ₂₀ (ppm)	ERD ₃₀ (ppm)
1	Cumulative Odds model	CLogLog	0.02122672	0.03756418	0.05128771
2			0.03084543	0.05159007	0.0678657
3			0.04991843	0.07659892	0.09580849

ERD = Extra risk dose.

APPENDIX C: SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

The Toxicological Review and IRIS summary for phosgene have undergone both internal peer review performed by scientists within EPA and a more formal external peer review performed by scientists in accordance with EPA guidance on peer review (U.S. EPA, 1998b, 2000a). Comments made by the internal reviewers were addressed prior to submitting the documents for external peer review and are not part of this appendix. Three external peer reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific questions in areas of scientific controversy or uncertainty. A summary of significant comments made by the external reviewers and EPA's response to these comments follows. EPA also received scientific comments from the public. These comments and EPA's response are included in a separate section of this appendix.

The reviewers considered the overall quality of the Toxicological Review and IRIS summary to be good. A number of editorial suggestions were offered. These included identification of typographical errors, insufficiently clear text, incomplete descriptions of complex calculations, and use of inconsistent concentration units. Revisions and corrections were incorporated in the document as appropriate.

Comments from External Peer Review

A. RfC Derivation

1. Principal Study

Comment: All three reviewers agreed with the Agency's selection of Kodavanti et al. (1997) as the principal study for the derivation of the RfC. One reviewer suggested that the Franch and Hatch (1986) study be used to support the findings of the Kodavanti et al. study.

Response: The Agency disagrees that the findings of Franch and Hatch (1986) should be used as support for the derivation of the RfC based on Kodavanti et al. (1997). Although the doses were similar in the two studies, different lung effects were observed.

2. Methods of Analysis

Comment 1: The reviewers generally supported the Agency's use of three methods for derivation of the RfC (LOAEL/NOAEL, BMD and categorical regression). Two reviewers expressed the least preference for the LOAEL/NOAEL approach, considering it to be the least statistically robust method. One of these reviewers expressed more confidence in the BMD method than the other two methods. The second reviewer considered the decision to use the benchmark dose analysis with the categorical regression analysis in a supporting role to be appropriate.

Response 1: The Toxicological Review provides a comparison of the three approaches, including a discussion of the strengths and limitations of each. The Agency believes that the use of three approaches yields a more robust determination of the point of departure for the phosgene RfC.

Comment 2: Two reviewers offered comments on the BMD approach. One reviewer recommended a 5% response level as the point of departure for quantal endpoints in the BMD approach rather than a 10% level because the former was considered a closer approximation of the NOAEL. A second reviewer observed that for continuous data, the Agency used one standard deviation to define the benchmark response, but recommended that EPA consider two or more standard deviations from the mean based on Kodell and West (Risk Analysis, 1993). One reviewer recommended that the appendix with documentation of the BMD approach include a complete description of the actual source data and the methods and assumptions used, and that this appendix be appended to the IRIS summary as well as the Toxicological Review.

Response 2: A 5% level of response was rejected because a group size of only eight rats did not provide sufficient statistical power to derive a 5% response level. The second reviewer referred to the continuous lung displacement volume data; the BMR selected for this continuous endpoint was one standard deviation. The Agency notes that the use of one standard deviation for continuous data is standard Agency practice as described in the *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c). The Toxicological Review and IRIS summary were revised to provide a better description and interpretation of the principal study (Kodavanti et al., 1997); citations for the published references, which provide the source data, are included in the appendix. It is not current practice to include detailed data in the IRIS summary; the Toxicological Review for phosgene now contains a complete description of the actual source data and detailed assumptions for the BMD modeling.

Comment 3: One reviewer recommended modifying the calculation in the categorical regression analysis to include the lower 95% confidence bound on the CatReg point of departure.

Response 3: EPA has not published guidance for the use of CatReg for the determination of a point of departure for use in Agency risk assessments. The primary purpose of the CatReg analysis in this assessment is to show how a categorical regression analysis that takes into account the different severity grades of responses reported by Kodavanti et al. (1997) compares with the BMD analysis. The maximum likelihood estimate, ERD, reported by CatReg is comparable to the BMD estimate reported by BMDS. The lower bound confidence limit on the ERD is not reported because the existing version of the Agency's CatReg software does not provide an estimate of the lower bound confidence limit on the ERD that is comparable to the BMDL reported by BMDS.

3. NOAEL/LOAEL Approach

Comment: Three reviewers commented on the $C \times T$ assumption (Haber's Law) used to adjust from the intermittent exposure received by animals in the Kodavanti et al. (1997) study (6 hours/day, 5 days/week) to continuous exposure. All three acknowledged the complexity of the issues associated with application of the $C \times T$ assumption to the Kodavanti et al. data for phosgene. One reviewer agreed with the Agency's use of the default $C \times T$ procedure given insufficient evidence to justify departure from the default. A second reviewer recommended not leaving the concentration unadjusted, and offered no suggestions for a better approach. The third reviewer indicated he was not opposed to the $C \times T$ approach as presented, but recommended that a more thorough discussion of the default assumption be provided.

Response: A discussion of the applicability of Haber's Law in making the exposure adjustment from intermittent dosing in the animal experiments to continuous exposures has been added. It says essentially that although Haber's Law applies to acute exposures lasting on the order of minutes to several hours, it does not apply to intermittent exposures where there is a daily recovery period. In the latter situation, the data indicate that concentration is the appropriate dose metric. In the absence of data on continuous exposure for longer than several hours, the document assumes that continuous dosing for periods ranging from 6 to 24 hours would cause a progressive increase in lung damage; therefore, the $C \times T$ dose metric is appropriate for that period of time.

4. Uncertainty Factors

Comment 1: One reviewer noted that the appropriate uncertainty factors were applied and adequately explained. Two other reviewers agreed with the uncertainty factors applied by the EPA for variation in human susceptibility (UF_H), animal to human extrapolation, and subchronic to chronic extrapolation. One reviewer commented that the uncertainty factor for subchronic to

chronic extrapolation appeared reasonable, but that the evidence advanced to support the choice of uncertainty factors was not adequate.

Response 1: The justifications for the uncertainty factors were expanded.

Comment 2: One reviewer questioned whether a LOAEL to NOAEL uncertainty factor (UF_L) as large as 10 was supported by the dose-response data. A second reviewer considered the UF_L , which was applied to the LOAEL/NOAEL and categorical regression approaches to be reasonable, but further noted that this uncertainty factor was not applied in the benchmark dose approach. This reviewer recommended that an UF_L of 10 be applied in the benchmark dose approach because he did not consider a $BMDL_{10}$ as similar to an unqualified NOAEL. This reviewer offered as an alternative but less desirable option to use the $BMDL_{10}$ with a UF_L of 3.

Response 2: The subchronic study by Selgrade et al. (1995) was used for the NOAEL/LOAEL analysis in place of the Kodavanti et al. (1997) study because it identified a lower LOAEL. A partial uncertainty factor of 3 rather than the full factor of 10 was used in the NOAEL/LOAEL approach because the impairment of lung immunological function in the Selgrade et al. (1995) study at the LOAEL of 0.1 ppm was considered to be a minimal effect. The effect was local to the lung, resulting in the impairment of the bacterial clearance process; the impairment occurred only during the exposure and it was not persistent after phosgene exposure stopped. EPA disagrees with the recommendation to include a UF_L for the BMD method. Because the data on collagen staining were considered to represent minimal severity of lung damage, the $BMDL_{10}$ associated with a 10% response was considered an appropriate point of departure. Further, it is current Agency practice not to apply an additional uncertainty factor for LOAEL to NOAEL extrapolation when using the BMD approach. Accordingly, no additional uncertainty factor for LOAEL to NOAEL extrapolation was included in the BMD approach.

Comment 3: Two reviewers questioned the inclusion of a database uncertainty factor of 3 for lack of chronic reproductive and developmental studies, noting the lack of consistency with statements elsewhere in the assessment that, due to the reactivity of phosgene, the primary toxic impacts are expected to occur at the point of first contact. One of the two reviewers supported removing the uncertainty factor based on lack of reproductive/developmental studies. The second reviewer observed that any effects on reproduction or development secondary to respiratory impairment of mothers or newborn offspring would be avoided where the health-protective level was low enough to avoid such damage to the respiratory system. This reviewer raised the possible concern that impacts on the respiratory system might exacerbate or even

cause asthma in some individuals, including children, although no evidence was presented to imply that such differential impacts would exceed the default UF_H of 10. The reviewer recommended that further consideration be given to whether additional uncertainty factors are needed specifically to protect children from this or other health impacts.

Response 3: The database uncertainty factor was changed from 3 to 1. As noted by the external reviewers, effects outside the respiratory system are not expected because of the short half-life of phosgene in the respiratory system, and it would not be expected that phosgene will migrate to the systemic circulation in concentrations large enough to cause reproductive or developmental effects. Justification for a database uncertainty factor of 1 was provided.

B. Cancer Weight of Evidence

Comment: Two reviewers agreed with the Agency conclusion that the available evidence for phosgene are inadequate to draw conclusions about the carcinogenicity of the chemical. The third reviewer offered no comments on cancer weight of evidence.

Response: No response is required.

C. Other Comments

Comment 1: One reviewer observed that the characterization of the exposure duration in the Kodavanti et al. (1997) study on page 9 of the Toxicological Review as a “repeated acute exposure” was inaccurate, and that it was more correctly characterized as a subchronic study.

Response 1: EPA recognizes that a 12-week exposure is not an acute study. The Toxicological Review (Section 4.2.2.1) referred to “acute” exposures (in quotes) as the characterization that the authors used in the description of their study.

Comment 2: One reviewer recommended that consistent concentration units be used throughout the document.

Response 2: The assessment was revised to provide equivalent concentration units to facilitate the conversion between units (e.g., from ppm to mg/m^3).

Comment 3: One reviewer observed that the CatReg point estimate of 0.088 ppm is sometimes

expressed as 0.09 and sometimes as 0.1, but this value should be consistent throughout the document.

Response 3: For the calculation of the HEC at the bottom of page 26 of the external review draft of the Toxicological Review, the CatReg value of 0.088 ppm, which reflects the unadjusted exposure concentration from the animal study, was rounded to 0.09 ppm. The human equivalent concentration (HEC) was calculated as 0.098 mg/m^3 , which was rounded to 0.1 mg/m^3 . Therefore, the two values are correct as presented in the assessment.

Comments from the Public

Comment 1: A reviewer commented that the application of Haber's Law to chronic effects of a non-cumulative substance like phosgene is not well-founded. The sharp dose-response in the Kodavanti et al. (1997) study indicates the critical importance of exposure intensity rather than exposure duration, as illustrated by the results of Henderson et al. (1993) on effects of ozone exposure.

Response 1: The Agency agrees that it is inappropriate to use Haber's Law as the sole rationale for extrapolating the intermittent animal exposures to continuous animal dosing, as was done in the draft document. This is the default assumption used in most EPA evaluations. Since Kodavanti et al. (1997) found that variation in intermittent phosgene exposure durations in the range of 1 to 5 days per week had little influence on the events leading to lung fibrosis, the revised document deletes the 5/7 factor used in the default procedure. However, the 6/24 factor for partial day exposure was retained on the assumption that Haber's Law is valid for continuous exposures in the range of a few hours to one day, as shown by earlier continuous acute exposures of phosgene. Henderson's paper dealt with continuous exposures from 3 to 24 hours, and therefore, does not contribute to understanding the effect of intermittent phosgene exposures.

Comment 2: A reviewer observed that exposure intensity, in addition to incidence, should be taken into account in the agency's analysis. The agency should address not only whether the chronic effects are driven by (repeated) acute effects, but also that the acute threshold may be valid for chronic exposure. This suggested approach would be based on exposure intensity.

Response 2: In agreement with the commentor, the EPA did consider phosgene concentration (which is equivalent to exposure intensity) to be the dose metric critical for lung damage leading

to fibrosis. Acute phosgene experiments do not show a threshold, but do show a response dependent on $C \times T$. The threshold as analyzed in the Henderson et al. (1993) paper was actually what EPA would call a “point of departure,” which is a response level that exceeds that of the controls, rather than a threshold dose below which there is no response.

Comment 3: A reviewer commented that the draft review did not describe in sufficient detail the anatomical location of the lung lesions leading to fibrosis, the stains used to identify collagen deposition or the scoring criteria used for the pathological analysis.

Response 3: The information on the stain used and a better description of the criteria that were used to judge the severity of the lesions was added to the document.

Comment 4: A reviewer stated that the uncertainty factor for the CatReg analysis (x10) is not sufficiently justified and is overly conservative.

Response 4: The CatReg analysis has been rewritten (see above discussions regarding the relation of CatReg to the BMD and NOAEL approaches).

Comment 5: A reviewer commented that the draft does not distinguish between measured and nominal concentrations used in the various experiments and does not state the temperature and humidity conditions under which the experiments were carried out, nor the analytical procedures used.

Response 5: The major studies used in the evaluation (Kodavanti et al., 1997; Hatch et al., 2001; Selgrade et al., 1995) were conducted in the same laboratory under the same temperature and humidity conditions, and the measured concentrations closely matched the targeted concentration. Therefore, there is no need to make concentration adjustments before comparing results between the major studies. The measured concentrations for the Kodavanti et al. (1997) study were added to the document. The deviation from targeted values was generally within 10% of the mean.

Comment 6: A reviewer considered the derived RfC to be overly conservative from two points of view: (1) the BMD approach results in a lower RfC than the NOAEL approach, and although it is preferred, a better understanding of the role of exposure intensity and duration is likely to lead to a less conservative RfC, and (2) the RfC may be in the range of rural levels (non-anthropogenic sources) of phosgene.

Response 6: The agency agrees that the BMD approach is more valid because it uses more of the experimental data than the NOAEL approach, and has stated preference for that approach. However the agency is unwilling to speculate about whether better understanding of the role of exposure intensity and duration would eventually lead to a higher or lower RfC.

The RfC derived in this assessment is $3E-4 \text{ mg/m}^3 = 75 \text{ ppt}$. The current ambient levels of phosgene are not known with any degree of confidence but the 1977 phosgene concentration in clean air (rural and seacoast) locations averaged 22 ppt, which is about 0.3 times the RfC. Since the main precursors of phosgene in air are tetrachloroethylene and trichloroethylene, which have steadily decreased over the last 15 years, the current ambient air levels of phosgene are probably much less than 0.3 times the RfC. There is an obvious need for current ambient air measurements in order to answer this comment.