TOXICOLOGICAL REVIEW

OF

PHOSGENE

(CAS No. 75-44-5)

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

March 2004

NOTICE

This document is an **external review draft**. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position on this chemical. It is being circulated for peer review on its technical accuracy and science policy implications.

U.S. Environmental Protection Agency
Washington, DC

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LIST OF ABBREVIATIONS AND ACRONYMS

ARE	Acute reference exposure
BAL	Bronchoalveolar lavage
BMD	Benchmark dose
Cat Reg	Categorical regression
EC	Effective concentration
EPA	U.S. Environmental Protection Agency
HEC	Human equivalent concentration
IRIS	Integrated Risk Information System
LOAEL	Lowest-observed-adverse-effect level
mg/kg	Milligram per kilogram body weight
mg/m^3	Milligram per cubic meter
MF	Modifying factor
ng/m^3	Nanogram per cubic meter
NCTR	National Center for Toxicological Research
NOAEL	No-observed-adverse-effect level
NPSH	Nonprotein sulfhydral
NTP	National Toxicology Program
POD	Point of departure
RfC	Reference concentration
RfD	Reference dose
RGDR	Regional gas-dose ratio
SAR	Structure-activity relationship
SMR	Standard mortality ratio
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
UF	Uncertainty factor

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, EPA has characterized its overall confidence in the qualitative and quantitative aspects of hazard and dose response. Issues considered in this characterization include knowledge gaps, uncertainties, quality of data, and scientific controversies. This characterization is presented in an effort to make apparent 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 301-345-2870.

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This document and summary information on IRIS have received peer review by EPA scientists as well as reviewed by independent scientists external to EPA. External reviewers comments have been addressed. This assessment will undergo an Agency-wide consensus review process by the IRIS Program prior to entry into the Agency's IRIS database.

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1. INTRODUCTION

This document presents background and justification for the hazard and dose-response assessment summaries in EPA's Integrated Risk Information System (IRIS). IRIS summaries may include an oral reference dose (RfD), inhalation reference concentration (RfC) and a carcinogenicity assessment.

The RfD, RfC, and acute reference exposure (ARE) provide quantitative information for noncancer dose-response assessments. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as some carcinogenic responses. It is expressed in units of mg/kg/day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The inhalation RfC 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). It is generally expressed in units of mg/m^3. The ARE is analogous to the RfC, except that it protects against noncancer effects due to inhalation exposures of 24 hours or less. The ARE is generally expressed in units of mg/m^3 and is associated with specific exposure durations.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral exposure 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. Quantitative risk estimates are presented in three ways. The *slope factor* is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The *unit risk* is the quantitative estimate in terms of either risk per μg/L drinking water or risk per $\mu g/m^3$ air breathed. Another form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000; 1 in 100,000; or 1 in 1,000,000.

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), draft revised *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), *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, 2000b), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000c), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000d), and *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000e).

The literature search strategy employed for this compound was based on the CASRN and at least one common name. At a minimum, the following databases were searched: RTECS, HSDB, TSCATS, CCRIS, GENE-TOX, DART/ETIC, EMIC, EMICBACK, DART, ETICBACK, TOXLINE, CANCERLINE, MEDLINE, and MEDLINE backfiles. 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 December 2001.

2. CHEMICAL AND PHYSICAL INFORMATION PROPERTIES

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 Registry number: 75-44-5
Structural formula: $COCl_2$
Molecular weight: 98.92

Vapor pressure: 1180 mm Hg 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/m^3, 1 mg/m^3 = 0.247 ppm (25 °C, 760 mm Hg)

The primary use of phosgene is in the polyurethane industry for the production of polymeric isocyanates (U.S. EPA, 1984, 1986c; WHO, 1997, 1998). Phosgene is also used in the polycarbonate industry as well as 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 found in the ambient air at average concentrations of 80 to 130 ng/m^3 (WHO, 1997, 1998).

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 (CO_2) and hydrochloric acid (HCl), with a half life at 37 °C of approximately 0.026 seconds (Manogue and Pigford, 1960; Schneider and Diller, 1989). The American Conference of Governmental Industrial Hygienists (ACGIH, 2000) recommends a time-weighted average of 0.1 ppm (0.4 mg/m^3) 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.

Phosgene levels have been measured in ambient air (U.S. EPA, 1983; Singh et al., 1977; Singh 1976). Multiple samples (10–257) were taken from four locations in California within a 24-hour period. The average level for rural areas was 87 ng/m^3 (21.7 ppt). The average levels found in these locations were 117 ng/m^3 (29.3 ppt), 121 ng/m^3 (30 ppt), and 129 ng/m^3 (31.8

ppt), with a peak level of 244 ng/m^3 (61 ppt) for one of the samples. In the other three cities, the ambient air level was reported to be less than 80 ng/m^3 (20 ppt). These values were also reported 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 0.08 μg/m^3. The above information indicates that there is a wide range of concentrations in ambient air.

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.

3. TOXICOKINETICS

Phosgene is rapidly hydrolyzed in aqueous solution to CO_2 and HCl, which are likely to be exhaled (Diller, 1985; Schneider and Diller, 1989). Consequently, phosgene is not expected to leave the pulmonary circulation following inhalation exposure, nor is exposure by the oral route likely (U.S. EPA, 1984, 1986d; WHO, 1997, 1998). All of the effects of inhaled phosgene reported in animal and human studies have been attributed to a direct effect on the respiratory tissues or to indirect effects resulting from damage to the respiratory system; data on phosgene absorption are not available. Studies on the distribution and elimination of phosgene in animals or humans were not located in the published literature.

Phosgene is thought to directly participate in acylation reactions with amino, hydroxyl, or sulfhydral groups (Diller, 1985; Schneider and Diller, 1989; U.S. EPA, 1986c; WHO, 1997, 1998). Formation of phosgene as a metabolite of other compounds has been hypothesized (reviewed in U.S. EPA, 1984) but not directly measured, perhaps due to the rapid reaction of phosgene with tissue molecules or hydrolysis in aqueous solution. 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. EPIDEMIOLOGY STUDIES IN HUMANS

Studies on the toxicity of phosgene following oral acute or chronic exposure in humans are not available. As noted in Section 2, phosgene is a gas at room temperature, and aqueous phosgene rapidly hydrolyzes to CO_2, and HC1; consequently, exposure by the oral route is highly unlikely. Diller and Zante (1982) performed an extensive literature review of human phosgene 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 post-mortem results from human phosgene poisonings; however, exposure concentrations were not reported.

The effect of occupational exposure to phosgene on mortality was examined in workers employed from 1943 to 1945 at a uranium processing plant in the United States (Polednak, 1980; Polednak and Hollis, 1985). In the initial report (Polednak, 1980), a comparison was made between a group of 699 male workers who were exposed daily to phosgene and 9352 male controls who were employed during the same time period but not exposed to phosgene. The duration of exposure was generally 2 months to 1 year; the follow-up 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 or 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, the exposed groups were small, and exposure levels were not well documented. Consequently, evidence presented in this study is inadequate to assess the carcinogenicity of phosgene.

In the follow-up study (Polednak and Hollis, 1985), the number of subjects had decreased to 694 male workers who were exposed daily to phosgene and 9280 male controls who were employed 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 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 follow-up 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.

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, with occasional lesions of the kidney, liver, and heart due to pulmonary lesions.

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 post-exposure. One patient reported lacrimation and redness of the eyes.

4.2. ACUTE/SUBCHRONIC AND CHRONIC STUDIES IN HUMANS AND ANIMALS

4.2.1. Humans

4.2.1.1. *Acute Inhalation Exposure Studies in Humans*

The acute toxicity of phosgene inhalation has been well documented in humans and animals (Underhill, 1919; U.S. EPA, 1984, 1986c; WHO, 1997, 1998). Diller et al. (1979), Frosolono and Pawlowski (1977), and Zwart et al. (1990) examined 10 men who had been exposed to phosgene 3 to 9 years earlier for changes in pulmonary function, but they found that pulmonary function impairment in this group correlated better with smoking history than with phosgene exposure. 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.

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 (Diller, 1985; Schneider and Diller, 1989). In the initial phase, high concentrations (>3 ppm) may result in a vagal reflex action that causes frequent, shallow respiration and a decreased respiratory vital capacity and volume. This in turn leads to a decreased arterial CO_2 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 post-exposure, clinical signs and symptoms are generally lacking (Diller, 1985; Schneider and Diller, 1989). 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, resulting in this phase being termed the "clinical latent phase." The length of this phase varies inversely with the inhaled dose.

In the third clinical phase of phosgene toxicity (Diller, 1985; Schneider and Diller, 1989), 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. 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 may also be affected, resulting in cardiac failure due to pulmonary congestion. In general, this phase will peak approximately 24 hours after an acute exposure and, assuming lethality does not occur, will recede over the next 3–5 days.

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.

4.2.2. Animals

4.2.2.1. *Inhalation Exposure*

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

4.2.2.2. *Experimental Animal Studies*

A number of studies have examined the acute effects of phosgene in animals, with a similar spectrum of effects seen across the many species examined. Exposures were limited to concentrations of between 0.5 and 40 ppm (2 to 10 mg/m^3) for intervals ranging from 5 minutes to 8 hours.

Animals exposed to phosgene 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 unexposed or air-exposed animals (Lehnert, 1992). An increase in lung weight also has been observed (Jaskot et al., 1989, 1991; Sciuto, 1998). 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 bronchoalveolar lavage (BAL) parameters, including increased protein (Hatch et al., 1986; Jaskot et al., 1989; Jugg et al., 1999; Sciuto, 1998; Slade et al., 1989), phospholipid content (Jugg et al., 1999), and enzyme levels (Jaskot et al., 1991; Lehnert, 1992) as well as increases in the numbers of inflammatory cells (Lehnert, 1992).

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 estravasated erythrocytes (Durlacher and Bunting, 1947; Gross et al., 1965; Jugg et al., 1999; Keeler et al., 1990; Lehnert, 1992; 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, there is an initial increase in blood volume, 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 has also been shown to result in a decreased immune response in animals, as evidenced by an increased susceptibility to in vivo bacterial and viral infections (Ehrlich and Burleson, 1991; Selgrade et al., 1989) and injected tumor cells (Selgrade et al., 1989) as well as a decreased in vitro virus-killing and T-cell response (Burleson and Keyes, 1989; Ehrlich et al., 1989). Several studies have reported that prior acute exposure to phosgene is

protective against the effects of a later acute exposure (Box and Cullumbine, 1947; Ghio and Hatch, 1996).

Often, the magnitude of exposure to a toxic gas or vapor is quantified as the product of concentration (C) and exposure time (T) (as Haber's Law). This concept has proven to apply to exposures to phosgene of between 0.5 and 200 ppm (2 and 800 mg/m^3) and at exposure times long enough to negate the effects of an animal holding its breath (discussed in U.S. EPA, 1986c). However, it may not hold true for lower concentrations, as indicated by Jaskot et al. (1991). He reported that rats exposed to 0.5 ppm of phosgene for 4 hours (120 ppm/min) showed a significantly greater response, measured as increased lung weight and BAL Se-dependent glutathione peroxidase, glucose 6-phosphate dehydrogenase (G6PD), and superoxide dismutase enzyme levels, than did rats exposed to 0.25 ppm of phosgene for 8 hours (120 ppm/min) at various time points up to 7 days post-exposure, most often at days 2 and 3 post-exposure. This serves to illustrate that at extremes of time or concentration, the C × T product may not be an appropriate dose metric. The application of Haber's Law (Haber, 1924) to subchronic or chronic exposures to phosgene has not been adequately studied.

Kodavanti et al. (1997) exposed groups of male F344 rats to phosgene levels designed to provide equal products of concentration times time (C × T) products for all groups but the lowest exposure concentration. Groups of eight rats were exposed for 6 hours per day to 0.1 ppm (0.4 mg/m^3) for 5 days/wk, 0.2 ppm (0.8 mg/m^3) for 5 days/wk, 0.5 ppm (2 mg/m^3) for 2 days/wk or 1 ppm (4 mg/m^3) for 1 day/wk for 4 or 12 weeks. Groups of similarly exposed rats were allowed clean air recovery for 4 weeks after 12 weeks of exposure. 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 and were not analyzed. No mortality was reported for any exposure level or time examined.

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). 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 of the bronchiolar region, 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. An increase in collagen staining was seen in 0.2 and 1 ppm animals, although there was no elevation of total hydroxyproline, a measure of collagen deposition.

Similar changes were seen following 12 weeks of exposure, although 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. Pulmonary hydroxyproline 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. No changes in lung displacement volume were seen in any group following 4 weeks of air recovery. 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 post-recovery, but hydroxyproline levels in the 0.5 ppm and the 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 at 0.2 and 1 ppm.

In a later publication (Hatch et al., 2001), the same group of investigators 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. Taking these measurements as indications of chronic toxicity, a lowest-observed-adverse-effect level (LOAEL) of 0.2 ppm (0.8 mg/m^3) 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 (97 and 162 mg/m^3); pre-test 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 which time the frequency of exposure was reduced to once or twice a week. Exposures were performed for 10–12 weeks. During the fifth and sixth week, 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 dying during exposure or sacrificed were autopsied and their lungs 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 2–3 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. Due to inadequate reporting of exposure levels, no NOAEL or LOAEL could be identified from this study.

Clay and Rossing (1964) described histopathology in the same study that is described in Rossing (1964). They exposed groups of mongrel dogs (sex not specified) to phosgene at levels of between 24 and 40 ppm (97 and 162 mg/m^3) for 30 minutes for one to three exposures per week. Group 1 (n = 2) consisted of unexposed controls; group 2 dogs (n = 7) were exposed one or two times and sacrificed 1–2 days post-exposure; group 3 animals (n = 7) were exposed 4–10 times and sacrificed up to 7 days post-exposure; group 4 animals (n = 5) were exposed 15–25 times and sacrificed immediately or up to 2 weeks post-exposure; 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. At the light microscope level, these changes began as acute bronchiolitis and peribronchiolitis that affected only scattered sections of the lung at the lowest number of exposures. With increasing number of exposures, there was a progression to a chronic obliterative bronchiolitis, 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. Due to the poor design of the study and the independent 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/m^3) of phosgene for 4 hours and then sacrificed immediately after exposure or at 1, 2, 7, 14, or 38 days post-exposure. Body weights were decreased to 13% below those of controls (p<0.01) on the first day post-exposure 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 post-exposure before returning to nearly normal values. Lung wet weights were significantly elevated in exposed rats immediately after exposure and remained elevated through day 7 post-exposure.

No change in nonprotein sulfhydryl (NPSH) content was seen immediately post-exposure, but it showed an upwardly increasing trend thereafter. G6PD activity was elevated over that of controls from days 1–14 post-exposure. 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/m^3) or 0.25 ppm (1 mg/m^3) of phosgene for 4 hrs/day, 5 days/wk 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 post-exposure, 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. The 0.125 ppm dose can be considered a LOAEL for histologic alterations of the respiratory tract. No NOAEL was identified in this study.

4.3. REPRODUCTIVE/DEVELOPMENTAL TOXICITY STUDIES

No studies examining the effects of phosgene on reproduction or development for any exposure route in humans or experimental animals were located in the published literature. Given the high reactivity and rapid hydrolysis of phosgene, effects at sites other than the portal of entry are unlikely. A case report by Gerritsen and Buschmann (1960) describes a 7-month-pregnant woman who survived severe phosgene-induced pulmonary adema and went on deliver a normal, full-term infant.

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 hypertension may cause anoxic injury to the brain (Diller, 1985).

4.4.4. Genotoxicity

No relevant experimental animal or human studies examining the in vivo or in vitro genotoxic effects of exposure to phosgene were located except for one by Reichert et al. (1983), who 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 precludes a valid in vivo test of genetic toxicity.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS AND MODE OF ACTION

The acute toxicity of phosgene inhalation in humans and animals has been well documented (Underhill, 1919, as reviewed in U.S. EPA, 1984, 1986c; WHO, 1997, 1998). 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 (Diller, 1985; Schneider and Diller, 1989). If one applies Haber's Law to compute a dose-metric, the magnitude of exposure to a toxic gas or vapor is determined by the product of C × T. This concept has proven to apply, within limits, to exposures to phosgene of between 0.5 and 200 ppm (2 and 800 mg/m^3) and at exposure times long enough to negate the effects of an animal holding its breath (discussed in U.S. EPA, 1986c).

Inhalation of phosgene for subchronic or chronic durations is less well studied, with limited human data and very few well-conducted animal studies. Available studies point to the respiratory tract as the target for subchronic phosgene toxicity. The application of Haber's Law to subchronic or chronic exposures to phosgene has not been adequately studied.

Phosgene is not expected to leave the pulmonary circulation following inhalation exposure. All of 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 (Diller, 1985; Schneider and Diller, 1989, as discussed in U.S. EPA, 1986c; WHO, 1997, 1998).

4.6. MECHANISMS OF TOXICITY—SUMMARY

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 the cellular level—has not been well clarified. Fibrosis is characterized by 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 animal provides a good model for chronic pulmonary inflammation and fibrosis in humans. Connective tissue may develop both interstitial and intra-alveolar fibrosis upon short-term exposure. Hydroxyproline content and the activities of prolyl hydroxylase and galactosyl-hydroxy-lysyl glucotransferase were increased in lungs of rats exposed to phosgene. These observations were reported by Kodavanti et al. (1997) and later reported 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. A brief summary is given below.

Phosgene is a highly reactive gas capable of damaging a variety of biological materials in an oxidant-like fashion. Its activity 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 Gurtner, 1989, Schroeder and Gurtner, 1992; Jaskot et al., 1991; Sciuto et al., 1995, 1998; Sciuto and Moran, 1999). 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).

Following phosgene exposure, pulmonary cellular glycolysis and oxygen uptake are depressed, and there is a corresponding decrease in the levels of intracellular adenosine tri-phosphate and cyclic adenosine monophosphate (Currie et al., 1985; Kennedy et al., 1989; Sciuto et al., 1996) 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 (Schulz, 1959; Diller et al., 1969). 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 adenoisine monophosphate, such as treatment with phosphodiesterase inhibitors (e.g., aminophylline), B-adrenergic agonists (e.g., isoproterenol), or cyclic adenosine monophosphate analogs, markedly reduce pulmonary edema formation in animals exposed to phosgene (Kennedy et al., 1989; Sciuto et al., 1996, 1997, 1998).

Phosgene exposure has also 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 bronchoalveolar lavage fluid (Sciuto et al., 1998). Exposure also increased concentrations of leukotrienes in the lung perfusates of rabbits (Madden et al., 1991). 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 (Schroeder and Gurtner, 1992; Robinson, 1994). 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 edematrogenic doses of phosgene (Frosolono and Passarelli, 1978).

In addition to acylation, phosgene is hydrolyzed to HC1 as shown below. The formation of HCl occurs on moist membranes and may cause irritation and tissue damage (Diller, 1985).

$$COC1_2 + H_2O \rightarrow CO_2 + 2HC1$$

Because of the limited water solubility of phosgene, it is unlikely that large quantities of HC1 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 HC1

is the probable cause of immediate inflammation and discomfort after phosgene exposure at concentrations >3 ppm.

4.7. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

Available data are inadequate to evaluate and assess the carcinogenic potential of phosgene. This summary description is the appropriate characterization under the draft revised *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). Phosgene is categorized as Group D, "Not Classifiable as to Human Carcinogenicity," for the same reason.

4.7.1. Carcinogenic Potential Based on Structure-Activity Relationship (SAR) Analysis

Phosgene has been identified as a reactive intermediate in the metabolism of a number of chemical carcinogens, including carbon tetrachloride (Shah et al., 1979; Kubic and Anders, 1980) and chloroform (Pohl et al., 1977, 1981), although its role in the carcinogenesis of these compounds is not clearly understood.

The metabolism of carbon tetrachloride proceeds via cytochrome P-450-dependent dehalogenation (Sipes et al., 1977). The first step involves cleavage of one carbon-chlorine bond to yield C1 and a trichloromethyl free radical that is then oxidized to the unstable intermediate trichloromethanol, the precursor of phosgene. Hydrolytic dechlorination of phosgene yields CO_2, and HC1 (Shah et al., 1979). Although there are similarities in the metabolism of chloroform and carbon tetrachloride, metabolic activation of chloroform produces primarily phosgene, whereas the level of phosgene production from carbon tetrachloride appears to be small.

Pohl et al. (1981) compared the amount of phosgene (as diglutathionyl dithiocarbamate) produced by the aerobic metabolism of carbon tetrachloride and chloroform by liver microsomes from phenobarbital-treated rats. The results indicate that phosgene production from carbon tetrachloride was only 4% of that produced from chloroform. The reactive metabolites of both chloroform and carbon tetrachloride 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, 1985).

There is 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 CO_2 and HCl such that exposure to phosgene might not result in a reaction with nuclear DNA. At this time there are no data 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 phosgene's carcinogenicity (as discussed in U.S. EPA, 1985).

4.8. SUSCEPTIBLE POPULATIONS

4.8.1. Possible Childhood Susceptibility

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

4.8.2. Possible Gender Differences

No published studies have directly compared the effects of phosgene inhalation on male and female humans. Available data from experimental animal studies do not suggest differences in response between males and females following inhalation exposure to phosgene.

4.8.3. Other Factors

No studies are available with which 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 studies on the toxicity of phosgene following oral exposure in humans or animals were located. Because phosgene is a gas at room temperature, and because aqueous phosgene

rapidly hydrolyzes to CO_2 and HCl, exposure by the oral route is unlikely, and the consequent lack of data precludes the derivation of the RfD.

5.2. INHALATION REFERENCE CONCENTRATION (RfC)

For effects other than cancer, the risk from exposure via the inhalation route is assessed by the inhalation RfC. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime (U.S. EPA, 1994b). Like the RfD, the RfC is based on the assumption that a threshold exists for certain toxic effects. Threshold exposure limits for acute inhalation exposure are discussed in 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, 2000a); 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, 2000f). The use of these approaches has the potential to add 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)

Only one inhalation study has been reported that is considered to be suitable for the development of an RfC: the subchronic study in rats reported by Kodavanti et al. (1997). This is the only study of phosgene exposure that assessed the effects of subchronic (12 weeks or more) exposure in rats. The results of the study are summarized in Table 1. The most sensitive target organ following chronic inhalation exposure to phosgene appeared to be the lungs. The investigators observed terminal bronchial changes and interstitial thickening of the alveolar walls, inflammatory cell influx, and and epithelial alterations at 0.1 ppm after 4 and 12 weeks of exposure and lung volume changes at 0.1 ppm after 4 weeks of exposure. These effects increased in severity for the 0.2 ppm and 1 ppm exposed groups. (A different dosing regimen was used for these two concentrations; 5 days/wk and 1 day/wk, respectively.) Other effects noted at the 0.2 and 1 ppm exposure levels were an increase in collagen stain within the

thickened terminal bronchioles that was more intense at 1 ppm and persisted after a 4-week recovery period, epithelial alteration of the alveolus, and lung volume and weight changes.

Table 1. Results from an inhalation study in male F344 rats (Kodavanti et al., 1997)

Number per dose group	Duration of exposure	Critical effect	NOAEL (ppm)	LOAEL (ppm)
8–12	4 wks, 6 hrs/day, 5 days/wk	Epithelial alteration of the alveolus	–	0.1
8–12	12 wks, 6 hrs/day, 5 days/wk	Collagen staining indicative of fibrosis; alteration of epithelial cells.	0.1	0.2
6–9	12 wks, 6 hrs/day, 5 days/wk, 4-wk recovery	Collagen staining indicative of fibrosis; alteration of epithelial cells.	0.1	0.2

Lung pathology and other measures of effects, such as lung volume and weight changes were not significantly different following 4 and 12 weeks at the same level of phosgene exposure. On the other hand, higher exposure concentrations with significantly shorter exposure durations (e.g., 1 ppm 1 day/wk vs. 5 days/wk) resulted in the most severe effects. Thus, it appears that concentration rather than exposure duration is the more critical factor dictating the extent of toxic response to phosgene, even at these low exposure levels. In addition, the morphologic effects of exposure (e.g., collagen staining) appear to persist after the cessation of exposure. Because the extent to which this persistence existed after a 4-week exposure was not measured, it was deemed prudent to include a BMD and CatReg analysis of the 4-week exposure duration in this assessment. Although this exposure duration is too short to serve as the basis for the RfC, its inclusion strengthens the assessment.

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

EPA developed BMD assessment methods (U.S. EPA, 1995, 2000d) and supporting software (U.S. EPA, 2001a) to improve upon the previous NOAEL/LOAEL approach, and (2) the CatReg software (U.S. EPA, 2000f) was used to account for categorically graded lesion severity. The following sections describe how three assessment methods (NOAEL/LOAEL, BMD, 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 the derivation of an RfC for phosgene.

5.2.3. NOAEL/LOAEL Approach

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 LOAELs described above and in Table 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) = 0.1 × 98.92/24.45 = 0.405 mg/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 delivers the agent to the cells as a particular dose rate, times duration (time [T]) of exposure (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, was dependent on concentration and not on the product of C × T. The hydroxyproline data for this experiment are given in Hatch et al. (2001); Kodavanti et al. (1997) shows the 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 T) and it also increased with the product of C × 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. Therefore, the standard default method is used here to adjust the observed NOAEL from intermittent to continuous exposure. The NOAEL adjusted for continuous exposure is $NOAEL_{ADJ} = 0.405 \times 6/24 \times 5/7 = 0.0723$ mg/m^3.

3. *Extrapolating from rats to humans.* The HEC for the NOAEL ($NOAEL_{HEC}$) 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 versus 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 be 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)

$$RGDR_{TH} = (MV_a/S_a)/(MV_h/S_h) = 1.51$$

where,

MV_a (minute ventilation for F344 rats) = 0.19 m^3/day,

S_a (thoracic surface area for F344 rats) = 3423 cm^2,

MV_h (minute ventilation for humans) = 20 m^3/day, and

S_h (thoracic surface area for humans) = 543,200 cm^2.

The $NOAEL_{HEC}$ was calculated by multiplying the $NOAEL_{ADJ}$ by the $RGDR_{TH}$

$$NOAEL_{HEC} = 0.0723 \text{ mg/m}^3 \times 1.51 = 0.11 \text{ mg/m}^3$$

5.2.4. BMD Approach

Following subchronic inhalation exposure of phosgene, the most sensitive target organ in rats is the lung, as discussed in Section 5.2.1. Lung hydroxyproline content and tricrome staining for collagen are standard methods for measuring lung fibrosis and can be considered good chronic injury markers. Support for this idea is found in the present study, which showed a lack of reversibility of the collagen accumulation and possibly even a progression during the 4-week recovery period in air after termination of the 12-week exposure. Concentration rather than the

product of C × T seems to drive 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. The BMD approach assumes that the proper dose-metric is administered concentration. This assumption is uncertain for the reasons discussed in Section 5.2.3, paragraph 2. 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 a number of dose-related lung effects reported in the subchronic study by Kodavanti et al. (1997). 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 2 for 4- and 12-week exposures. The lower-bound confidence limit values reported in Table 2 represent the 95% BMDL 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). Although 4-week data are not used to derive the POD for an RfC, they are provided in Table 2 for comparison purposes.

Table 2. Bench mark 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	0.055/0.032	0.026/0.015
Inflammatory cell influx to terminal bronchiole/alveolus	0.077/0.012	0.082/0.013
Epithelial alteration of terminal bronchiole/peribronchiolar alveolus	0.078/0.026	0.017/0.0064
Increased collagen staining of terminal bronchiole/peribronchiolar	0.10/0.018	0.11/0.026
Displacement volume, left lung (mL/kg body weight × 100)	0.10/0.063[c]	0.081/0.053[c]

[a] Only endpoints for which a dose-response could be modeled are listed.
[b] EPA's Benchmark Dose Software (BMDS), version 1.3, was 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 contained 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 communication from Dr. Urmila Kodavanti, EPA/NHERL, to Dr. Jeff Gift, EPA/NCEA, dated October 22, 2001.

The BMD approach has an associated uncertainty. An element of the BMD approach is the use of several models to determine which one best fits the data[1]. The model that best fits the experimental data is used when the mode of 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, 2000d), 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 BMDL for this effect is 0.018 ppm (Appendix B). Using the same default procedures described in Section 5.2.3, an HEC of approximately 0.02 mg/m^3 (0.018 ppm × 98.92/24.45 = 0.0728 mg/m^3; 0.0728 × 6/24 × 5/7 = 0.013 mg/m^3; 0.013 x 1.51 = 0.0196) is estimated from this BMDL.

5.2.5. CatReg Approach

The BMD approach has the advantage of being able to take into account the shape of the dose-response curves for a variety of data in seeking a POD. However, it does not provide much insight into the role of the severity of effects. 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 2), yet a response at the low dose was clearly evident from severity score data (see Table 3). This illustrates how a BMD analysis is 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 used to supplement the BMD analysis. The CatReg approach has the ability to take into account responses at all severity levels when determining the probability of a response

[1]EPA's BMD Software (BMDS), version 1.3, was used for this effort. BMDS can be downloaded from the Internet at www.epa.gov/ncea/bmds.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 that are appropriate for the analysis of dichotomous (quantal) data (Gamma, Logistic, Log-Logistic, Multistage, Probit, Log-Probit, Quantal-Linear, Quantal-Quadratic, 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.

at one severity level (i.e., to determine the dose associated with a 10% severity grade 1 response, CatReg considers the complete spectrum of severity grade responses within each dose group).

Table 3. Results of CatReg analysis of severity-graded lung lesions reported by Kodavanti et al. (1997); estimates of the exposures that would cause a 10% increase in the extra risk dose (ERD_{10}) of severity grade 1 lesions.

Week	Model	Link function	ERD_{10} (ppm)	Standard error
4	Cumulative odds	Probit	0.064	0.0159
12	Cumulative odds	Logit	0.088	0.0158
4 and 12 combined	Cumulative odds	Probit	0.073	0.0106

As discussed in the previous section, the male rat lung effects from the Kodavanti et al. (1997) study provide the most appropriate endpoints for continued analysis using the CatReg Software developed by EPA (U.S. EPA, 2000f). CatReg was used to approximate ppm exposure levels that would result in a 10% increase (over background) in the probability of attaining a level of lung effect severity described by Kodavanti et al. (1997) as "minimal" or more severe[2]. All lung lesions scored for severity had to be combined and analyzed together because of the small numbers of animals used in this study. These data were supplied by the author (fax communication from Dr. Urmila Kodavanti, U.S. EPA, to Dr. Jeff Gift, U.S. EPA, dated October 23, 2001). This analysis was performed for lesions observed at 4 weeks and 12 weeks, as well as for 4 and 12 weeks combined. Although CatReg results for 4 weeks are provided in Table 3 for comparative purposes, 12-week exposures are considered a more appropriate duration for this analysis.

This CatReg analysis shows that a 0.09 ppm exposure to male rats would result in a 10% increase in the probability of minimal (severity grade 1) lung lesions. Using the same default procedures described in Section 5.2.3, an HEC of approximately 0.098 mg/m^3 (0.09 ppm × 98.92/24.45 = 0.364 mg/m^3; 0.364 × 6 hrs/24 hrs × 5 days/7 days = 0.065 mg/m^3; 0.065 mg/m^3 × 1.51 = 0.098 mg/m^3) is estimated using the CatReg approach.

[2]The 95% confidence intervals were not included because CatReg gives only graphical representation of such confidence intervals and because of the use of minimal (severity grade 1) lesions. Furthermore, many of the confidence intervals for the extra risk doses (ERDs) of these minimal lesions included zero.

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 NOAEL for lung effects is 0.1 ppm for male rats (Kodavanti et al. 1997). This value was converted to an HEC of 0.11 mg/m^3.

Application of the CatReg approach for the male rat lung effects in conjunction with the NOAEL/LOAEL and BMD approaches helps to fill gaps in knowledge that the other approaches cannot address. It should be noted that the POD derived using the CatReg approach is not a 95% lower-bound confidence limit, as is the BMDL. Thus, it would be expected to be more representative of a minimal LOAEL than a NOAEL and for this reason would be subject to application of a commensurate LOAEL-to-NOAEL UF. On the other hand, the CatReg analysis was based on the probability of a 10% increase in the incidence of all severity grade lesions, including lesions that were not considered adverse in the BMDL/NOAEL analysis. This is a limitation of the CatReg analysis.

5.2.7. RfC Derivation, Including Application of Uncertainty Factors and Modifying Factors

Uncertainty factors[3] (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

[3]RfDs 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.

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, 2001b) on the assumption that the actual values for the UFs are 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:

a. *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, including children. The default assumption of 10 is reduced only if data for the agent are already convincingly representative of sensitive subgroups (U.S. EPA, 2002). For phosgene there is only one high-quality study suitable for derivation of the RfC, and because it is in animals, it can not be regarded as representative of sensitive humans. Therefore the default value of 10 is appropriate.

b. *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.

(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 pharacodynamic 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.

c. *Subchronic-to-chronic uncertainty*: $UF_S = 3$. The POD is based on adverse effects using a subchronic inhalation study. The full factor of 10 is not appropriate because lung effects 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 a 12-week study.

d. *LOAEL-to-NOAEL uncertainty*: UF_L. In the NOAEL/LOAEL approach, the UF of 10 is not needed because the POD (0.1 ppm) represents a NOAEL. In the BMD approach, it is recognized that a BMD estimate is not the same as a NOAEL in that the BMD corresponds explicitly to an adverse effect level. Because the data represent minimal severity of lung damage and because the BMDL is a lower-bound confidence limit, the BMDL is deemed to be more representative of a NOAEL than of a LOAEL and, therefore, no explicit LOAEL-to-NOAEL UF is needed. In the CatReg approach, the dose level representing a 10% probability of a minimal severity was derived. The minimal severity of effect is regarded here as equivalent to a LOAEL and, therefore, a UF of 10 is needed in this approach. However, it is recognized that there is no Agency guidance on the application of traditional UFs to CatReg results.

e. *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 of the lung, and no effects have in fact been observed. Therefore, there is no reason to expect that reproductive or developmental effects would occur, and no UF is needed for the absence of data on these effects. There is a possibility that chronic lung toxicity of phosgene in children or the elderly is greater than in adults, but there are no animal data or human data indicating that this is the case. Data on nasal irritants with similar toxic effects (formaldehyde and ozone) do not indicate that children or the elderly are more sensitive. Therefore, there is no expectation that further data on phosgene would lead to a more protective RfC, and a database UF is not needed for phosgene.

f. *Other factors*: Modifying factor (MF) = 1. Issues that are not explicitly accounted for in the UFs named above are grouped together as "other factors."

The PODs derived using the NOAEL/LOAEL, BMD, and CatReg approaches are compared in Table 4. As explained above, the UF_L for the LOAEL-to-NOAEL UF is not needed

Table 4. Application of uncertainty factors (UFs) and modifying factor (MF) for RfC calculation

Factor	NOAEL	BMDL	CatReg
POD (mg/m^3)	0.11	0.02	0.1
UF_H	10	10	10
UF_A	3	3	3
UF_S	3	3	3
UF_L	1	1	10
UF_D	1	1	1
MF	1	1	1
$UF_{(Total)}$	100	100	1000
RfC (mg/m^3)	1E–3	2E–4	1E–4

(UF_L = 1) in the NOAEL/LOAEL or the BMD approaches, but it is needed for the CatReg approach. The other UFs are the same for all three approaches. A POD of 0.02 mg/m^3, derived from the BMD analysis of collagen staining lesions in terminal bronchioles, is chosen for the derivation of the RfC, and the result (RfC = 2E–4 mg/m^3) is similar to the RfC derived from the CatReg analysis (1E–4 $mg/m^{3)}$. The RfC is about five times higher in the NOAEL/LOAEL approach than in the BMD approach; the BMD approach is preferred because it is based on the entire dose-response data and it is similar to the CatReg approach. Using the BMD approach, the RfC is calculated as follows:

$$RfC = 0.02\ mg/m^3 \div 100 = 2E\text{-}4\ mg/m^3$$

5.3. CANCER RISK 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 following inhalation exposure in humans or animals were located. This lack of data precludes the derivation of an inhalation unit risk for phosgene.

6. SUMMARY 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 × T levels, death may

occur due to 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, but the studies are inadequate for use in a quantitative assessment of phosgene toxicity. For toxicity, the lungs are identified as the primary target organ in all species. Available data indicate that the primary cause of death is due to pulmonary edema following acute exposure. 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.

Data on the effects of phosgene on reproductive parameters or on the developing organism are not available. Due to the rapid hydrolysis of phosgene in aqueous solution, adverse effects of exposure to phosgene beyond the portal of entry are not likely.

Available data are inadequate to evaluate the carcinogenic potential of phosgene. Under the draft revised *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), data are inadequate for an assessment of human carcinogenic potential.

6.2. DOSE RESPONSE

6.2.1. Noncancer/Oral

Available data in humans and animals are inadequate to assess the potential toxicity of phosgene following oral exposure. Phosgene is a gas at room temperature and rapidly hydrolyzes to CO_2 and HCl in aqueous solution; exposure by the oral route is unlikely.

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/m^3): (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_{10} and BMDL were calculated for each of the five responses using seven different dose-response models. The model results

giving the lowest value of the BMD for each response was selected, and the lowest collagen staining data were chosen to characterize the BMD and BMDL for the entire study. Using this procedure, a BMDL 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 0.02 mg/m^3. 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 $10^{½}$, so when two factors of 3 are present, the combined UF is 10. Therefore, the RfC is 0.02/100 = 2E-4 mg/m^3.

Two additional alternative approaches were used (the LOAEL/NOAEL approach and the CatReg approach), and they resulted in RfC values of 1E–3 and 1E–4, respectively. The NOAEL/LOAEL approach uses the NOAEL of 0.1 ppm in the Kodavanti et al. (1977) study as the POD. This was adjusted for continuous human exposure by using the exposure duration and RGDR to give a POD of 0.11 mg/m^3. The total UF was 100 (10 for human variation and 3 each for animal-to-human and subchronic-to-chronic uncertainty). The resulting RfC using this approach is 0.11/100 = 1E–3 mg/m^3.

The CatReg approach uses the EPA CatReg model applied to graded severity of lung responses. The model calculated the exposure concentration that results in a 10% increase (over background) in the probability of attaining a severity of "minimal" or more severe. This level is 0.09 ppm from the 12-week study. This was adjusted for continuous human exposure by using the exposure duration and RGDR to give a POD of 0.1 mg/m^3. The total UF was 1000 (10 each for human variation and LOAEL-to-NOAEL and 3 each for animal-to-human and subchronic-to-chronic uncertainty). The resulting RfC using the CatReg approach is 0.1/1000 = 1 E–4 mg/m^3.

6.2.3. Cancer/Oral and Inhalation

Available data in humans and animals are inadequate to assess the potential carcinogenicity of phosgene.

APPENDIX A: Acute Exposure Guidelines Levels (AEGLs) for Phosgene

AEGLs 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, will be developed for each of five exposure periods (10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours) and will be 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/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, 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 $mg/^3$) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne 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 to 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 due to 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 sensitive m of phosgene toxicity (binding to macromolecules and irritation) 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 both with lethal and nonlethal endpoints after exposure to phosgene. A UF of 3 was applied to account for sensitive human subpopulations due to 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 proposed AEGL values for phosgene [ppm (mg/m ^{3})]

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	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-min or 10-min exposure (Zwart et al., 1990)

Source: NAS (2002)

APPENDIX B: CatReg and BMD Analysis

CatReg was designed and developed for the analysis of ordinal data for which the response is categorical but has a natural ordering, such as severity level. The ordinal scores are 0,...,*S*, where 0 is the lowest severity score and *S* is the highest severity score. Given a concentration *C* and duration *T*, CatReg models the distribution of Y as

$$\Pr(Y \geq s \mid C,T) = H[(\alpha_s + \beta_1 * f_1(C) + \beta_2 * f_2(T)]$$

for ordinal scores $s = 1,...,S$. This is the probability of attaining a severity score of 1 or higher at some specified concentration and duration of exposure. The parameter α_1 is the intercept for severity equals 1, and α_s is an increment in the intercept for severity equals s versus severity equals 1, for $s = 2,...,S$. β_1 and β_2 determine the relationship between the response and concentration and duration, respectively; unrestricted odds models can be chosen such that β'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 β_1 and β_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. Transformation functions, f_1 and f_2, transform *D* and *T* to another scale, usually base-10 logarithm.

The goal of this analysis is to determine the 10% extra risk dose (ERD_{10}) for a severity score equal to 1. This is defined as the dose d* that satisfies

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

Thus, the ERD_{10} is the dose that is associated with a 10% relative change from the background response at severity level 1 or greater. If the probability of a severity level 1 response or greater were 0 at 0 concentration, the ERD_{10} would be equal to the 10%

effective concentration (EC_{10}), a value that CatReg can estimate directly. Because this probability is not 0 at 0 in this case, additional calculations are necessary.[1]

This analysis used the five-level lung lesion severity grading scale of Kodavanti et al. (1997), wherein 0 = no effect, 1 = minimal effect, 2 = slight/mild effect, 3 = moderate effect, 4 = moderately severe effect, and 5 = severe effect. The doses (estimated 1-week AUC values) were not transformed to the base-10 logarithm scale for this analysis.[2]

To determine the best model for finding the ERDs, the appropriate link function and model had to be identified.[3] 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 slopes were then tested for quality. 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.

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[1]CatReg does not give ERDs directly. However, it does give the effective concentration, EC = 100*q, for any q between 0 and 1. If we want the EC-10, then q = 0.10. For example, using the logit function in CatReg, $Pr(Y \geq 1| D) = \exp[\alpha_s + \beta_1 * D]/(1+ \exp[\alpha_s + \beta_1 * D])$, where α_s is the estimated intercept associated with severity level 1, and β_1 is the estimate common slope. Similarly, the $Pr(Y \geq s \mid C)$ can be solved for the logit and log-log functions (Agresti, 1990). Then we solve:

$$Pr(Y \geq 1 \mid C = c^*) = 0.1*(1 - Pr(Y \geq 1 \mid C = 0)) + Pr(Y \geq 1 \mid C = 0)$$

where $Pr(Y \geq 1 \mid D = d^*)$ is solved by setting D to 0 in the regression equation. CatReg can then provide the EC-100*Pr(Y.1 | D = d*). This is the desired d*, the 10% ERD. Similarly, this can be done for the probit and log link functions (Agresti, 1990).

[2]The CatReg Software documentation (U.S. EPA, 2000f) recommends that concentration levels that range more than 100 should be transformed. However, background incidence is ignored when this is done. Because the baseline incidence was high for all groups, the investigators felt it was more important to utilize this information than to stabilize the dose data via base-10 logarithm transformation.

[3]See Section 2.2 of the CatReg documentation (U.S. EPA, 2000f) for the method for determining the best link function.

Table B-1. Examination of dose-response models in the BMD and CatReg approach

MALE RATS - Interstitial Thickening of the Alveolus				
Kodavanti et al. (1997)	**n**	**4 Week Exposure**	**12 Week Exposure**	
ppm				
0	12	0	0	
0.1	8	2	2	
0.2	8	5	4	
Inhalation				
LOAEL (ppm)		0.1	0.1	
LOAEL(Default HEC)[a] (mg/m^3)		0.13	0.13	
		BMD/BMDL/AIC/p	**BMD/BMDL/AIC/p**	
BMDL[b] (ppm)-Multist./Poly.[e]		0.026/0.015/22.00/.82	0.033/0.018/22.13/.98	
BMDL (ppm)-Weibull/Power[f]		0.056/0.015/23.58/1.0	0.045/0.018/24.09/1.0	
BMDL (ppm)-Gamma/Hill[g]		0.06/0.015/23.58/1.0	0.05/0.018/24.09/1.0	
BMDL (ppm)-Logistic		0.079/0.046/24.46/.43	0.085/0.050/25.29/.34	
BMDL (ppm)-Log-Logistic[h]		0.062/0.010/23.58/1.0	0.05/0.012/24.09/1.0	
BMDL (ppm)-Probit		0.075/0.043/24.16/.51	0.08/0.047/25.00/.40	
BMDL (ppm)-Log-Probit[h]		0.065/.028/23.58/1.0	**0.055/0.032/22.09/1.0**	
Selected BMDL(ppm)[k]		0.015	0.032	
BMDL(HEC) (mg/m^{3a}		0.019	0.041	
		4 Week Exposure	**12 Week Exposure**	**Combined**
CatReg ERD_{10} (ppm)[c,d]		0.064	0.088	0.073
CatReg ERD_{10} (HEC)[a] (mg/m^3)		0.08	0.11	0.09

Table B-1. Examination of dose response models in the BMD and CatReg approach (continued)

MALE RATS - Inflammatory Cell Influx to Terminal Bronchiole/Alveolus			
Kodavanti et al. (1997)	**n**	**4 Week Exposure**	**12 Week Exposure**
ppm			
0	12	2	1
0.1	8	3	3
0.2	8	8	8
Inhalation			
LOAEL (ppm)		0.1	0.1
LOAEL(Default HEC)[a] (mg/m^3		0.13	0.13
		BMDL/AIC/p	**BMDL/AIC/p**
BMDL[b] (ppm)-Multist./Poly.[e]		**0.082/0.013/25.40/.98**	**0.077/0.012/21.47/1.0**
BMDL (ppm)-Weibull/Power[f]		0.084/0.033/27.40/ZD	0.079/0.029/23.47/ZD
BMDL (ppm)-Gamma/Hill[g]		0.084/0.040/25.49/.83	0.081/0.035/21.52/.87
BMDL (ppm)-Logistic		0.031/0.018/28.00/.16	0.041/0.022/23.02/.28
BMDL (ppm)-Log-Logistic[h]		0.094/0.050/25.40/.99	0.092/0.046/21.47/.99
BMDL (ppm)-Probit		0.028/0.017/27.88/.16	0.035/0.020/23.03/.27
BMDL (ppm)-Log-Probit[h]		0.093/0.050/27.40/ZD	0.091/0.046/23.47/ZD
Selected BMDL(ppm)[k]		0.013	0.012
BMDL(HEC) (mg/m^3)[a]		0.017	0.015
CatReg ERD_{10} (ppm)[c,d]		see page 1	see page 1
CatReg ERD_{10} (HEC)[a] (mg/m^3)		see page 1	see page 1

Table B-1. Examination of dose response models in the BMD and CatReg approach (continued)

MALE RATS - Epithelial Alteration of Terminal Bronchiole/Peribronchiolar Alveolus			
Kodavanti et al. (1997)	**n**	**4 Week Exposure**	**12 Week Exposure**
ppm			
0	12	2	0
0.1	8	4	1
0.2	8	5	7
Inhalation			
LOAEL (ppm)		0.2	0.2
LOAEL(Default HEC)[a] (mg/m^3)		0.25	0.25
		BMD/BMDL/AIC/p	**BMD/BMDL/AIC/p**
BMDL[b] (ppm)-Multist./Poly.[e]		0.024/0.012/36.56/.79	**0.078/0.026/14.48/.82**
BMDL (ppm)-Weibull/Power[f]		0.024/0.012/36.56/.79	0.094/0.044/16.06/1.0
BMDL (ppm)-Gamma/Hill[g]		0.024/0.012/36.56/.79	0.096/0.050/16.06/1.0
BMDL (ppm)-Logistic		0.042/0.026/36.87/.53	0.096/0.054/16.12/.85
BMDL (ppm)-Log-Logistic[h]		**0.017/0.0064/36.49/.94**	0.096/0.055/16.06/1.0
BMDL (ppm)-Probit		0.041/0.026/36.85/.55	0.095/0.050/16.06/.95
BMDL (ppm)-Log-Probit[h]		0.043/0.023/36.66/.69	0.096/0.057/16.06/1.0
Selected BMDL(ppm)[k]		0.0064	0.026
BMDL(HEC) (mg/m^3)[a]		0.008	0.033
CatReg ERD_{10} (ppm)[c,d]		see page 1	see page 1
CatReg ERD_{10} (HEC)[a] (mg/m^3)		see page 1	see page 1

Table B-1. Examination of dose response models in the BMD and CatReg approach (continued)

MALE RATS - Increased Collagen Staining of Terminal Bronchiole/Peribronchiolar			
Kodavanti et al. (1997)	**n**	**4 Week Exposure**	**12 Week Exposure**
ppm			
0	12	1	2
0.1	8	1	2
0.2	8	8	8
Inhalation			
LOAEL (ppm)		0.2	0.2
LOAEL(Default HEC)[a] (mg/m^3)		0.25	0.25
		BMD/BMDL/AIC/p	**BMD/BMDL/AIC/p**
BMDL[b] (ppm)-Multist./Poly.[e]		**0.11/.026/16.91/1.0**	**0.10/.018/23.81/1.0**
BMDL (ppm)-Weibull/Power[f]		.068/18.91/ZD	.053/25.81/ZD
BMDL (ppm)-Gamma/Hill[g]		0.096/.071/17.66/.48	0.092/.059/24.17/.63
BMDL (ppm)-Logistic		indeterminate[i]	indeterminate[i]
BMDL (ppm)-Log-Logistic[h]		0.10/.079/16.91/.98	0.10/.068/23.81/.99
BMDL (ppm)-Probit		indeterminate[i]	indeterminate[i]
BMDL (ppm)-Log-Probit[h]		0.10/.079/18.91/ZD	0.10/.068/25.81/ZD
Selected BMDL(ppm)[k]		0.026	0.018
BMDL(HEC) (mg/m^3)[a]		0.033	0.023
CatReg ERD_{10} (ppm)[c,d]		see page 1	see page 1
CatReg ERD_{10} (HEC)[a] (mg/m^3)		see page 1	see page 1

Table B-1 Examination of dose response models in the BMD and CatReg approach (continued)

MALE RATS - Volume Displaced, Left Lung (mL/kg body weight x 100)						
Kodavanti et al. (1997)						
ppm	**4 Week Exposure**	**S.D.**	**n**	**12 Week Exposure**	**S.D.**	**n**
0	1.0715	0.12	12	1.03736	0.0937	11
0.1	1.21687	0.1614	8	1.13614	0.0725	7
0.2	1.3531	0.0767	8	1.2882	0.1428	8
Inhalation						
LOAEL (ppm)	0.1			0.2		
LOAEL(Default HEC)[a] (mg/m^3)	0.13			0.25		
	BMD/BMDL/AIC/p			**BMD/BMDL/AIC/p**		
BMDL[b] (ppm)-Multist./Poly.[e]	**0.081/.053/-88.24/.93**			**0.10/0.059/-89.16/.55**		
BMDL (ppm)-Weibull/Power[f]	0.083/0.060/-84.24/ZD			0.10/0.060/-85.52/ZD		
BMDL (ppm)-Gamma/Hill[g]	NA[i]			NA_j		
BMDL (ppm)-Logistic						
BMDL (ppm)-Log-Logistic[h]						
BMDL (ppm)-Probit						
BMDL (ppm)-Log-Probit[h]						
Selected BMDL(ppm)[k]	0.053			0.059		
BMDL(HEC) (mg/m^3)[a]	0.067			0.075		
CatReg ERD_{10} (ppm)[c,d]	NA			NA		
CatReg ERD_{10} (HEC)[a] (mg/m^3)	NA			NA		

[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 Section 5.2.2.1 in the main text).
[b] BMDLs on this page are 95% lower confidence limit estimates of the dose that would elicit a 10% extra risk
[c] ERD_{10} is an estimate of dose that would elicit a 10% extra risk of a severity grade 1 response.
[d] CatReg analysis was performed using severity grade data on all lung effects (see Section 5.2.2.3 in the main text).
[e] Betas restricted to > = 0 in multistage/polynomial models; parsimony used to select poly. order.
[f] Power always restricted to > = 1 in Weibull and Power models.
[g] Power always restricted to > = 1 in Gamma and Hill models.
[h] Slope always restricted to > = 1 in Log-Logistic and Log-Probit models.
[I] Inadequate model fit, $p<0.1$.
[j] No model was able to fit the data.
[k] Selection based on statistical (AIC, p, scaled residual values) and visual fit per BMD guidance (U.S. EPA, 2000d).

NA = Not applicable or not applied
ZD = zero degrees of freedom; p value could not be calculated

APPENDIX C: Disposition of Reviewers' Comments
Phosgene Toxicological Review and IRIS Summary

The reviewers' comments, dated May 7, 2003, pertain to the external review draft of the phosgene document dated December, 2002 (NCEA-S-1207) and the IRIS summary accompanying this draft. In this paper comments of the three reviewers are discussed separately.

Reviewer 1: Walter Piegorsch

I. Overall Document Quality

Comment: The overall quality of the Toxicological Review Document is good, but the IRIS Summary appears to be an early draft with numerous typographical errors, awkward phrases and incomplete descriptions of complex calculations.
Response: EPA agrees with the comments and has revised the IRIS Summary to correct and clarify the text.

II. RfC Derivation
2 Methods of Analysis

Comment: The reviewer recommends the inclusion of the lower 95% confidence bound on the CatReg point of departure.
Response: As explained in the external review draft, section 5.2.5, page 26, footnote, the EPA did not include the lower bound because the effect being scored is only a minimal severity effect and because the CatReg software currently being used gives only a graphical indication of the confidence limits.

3. NOAEL/LOAEL approach, section 5.2.3, item 2:

Comment: The rationale for adjusting to continuous exposure from the intermittent exposure received by the animals is problematic, but no different approach is suggested. Some adjustment for concentration is needed.
Response: EPA has used the standard assumption that toxic effects depend on the product of concentration and duration of exposure (CxT) in making the adjustment from intermittent animal exposures to continuous human exposures. Even though the data from the principal study (Kodavanti, et al., 1997) is inconsistent with Haber's Law, there is not enough data on phosgene to construct a numerical description of the dose-response surface. This issue has been discussed in section 5.2.3, item 2 of the current draft and the conclusion is that in the absence of definitive data the default Haber's Law should be used.

4. Uncertainty Factors, section 5.2.6.

Comment: Appropriate uncertainty factors have been applied and they are adequately explained.

Response: None needed

III. Cancer Weight of Evidence

Comment: All reviewers endorsed the conclusion in the document that the data on carcinogenicity are inadequate to draw conclusions about the carcinogenicity of phosgene.
Response: None

IV. Other Comments: Several editorial comments listed by the author have been corrected in the toxicological review and the IRIS summary. The rewriting of the document has eliminated much of the text that the reviewer had comments on. The rationale for not changing the text for the following comments is given below.

Page 22, middle:
Comment: For continuous data EPA should use 2 or more standard deviations from the mean to define the adverse effect, as Kodell and West (Risk Analysis, 1993) have done, whereas the agency used 1 standard deviation.
Response: This is standard practice in the agency. See Guidance for Benchmark dose analysis December, 2002

Page 24:
Comment: The CatReg point estimate of 0.088 ppm is sometimes expressed as 0.09 and sometimes as 0.1, but this should be consistent throughout the document. Another recommendation is that EPA should use the lower confidence limit of the ERD_{10} from the CatReg procedure.
Response: For the calculation of the HEC at the bottom of page 26 in the current draft document, the CatReg value of 0.088 ppm is rounded to 0.09 ppm, but the HEC is calculated as 0.098 mg/m^3 which is rounded to 0.1 mg/m^3. The latter value is a human equivalent concentration (HEC) but the CatReg value of 0.088 ppm characterizes the concentration administered to the animals. The comment did not make the distinction between the concentration given to the animals and the equivalent human concentration. The response to the lower confidence limit issue is given above (Item II 2).

Page 26:
Comment: When a partial uncertainty factor is needed, what is the justification for using the square root of 10 when the partial factors are lognormally distributed?
Response: Although this EPA convention is mentioned in the 1994 inhalation reference dose methodology document (U.S. EPA, 1994), it is described more completely in the EPA review of reference dose procedures, page 4-40 (U.S. EPA, 2001). Therefore in the current draft, (section 5.2.7, page 28, line 2) the primary reference has been changed to the 2001 document.

Page 26:
Comment: The awkward notation, “4E-5" should be replaced with the more correct notation, “4 x 10^{-5}" and three significant figures should be used in reporting these risk values.
Response: The EPA conventions used in the document were not changed and they are explained in the Carcinogen Risk Assessment Guidelines (U.S. EPA, 1999).

The editorial comments on the IRIS summary were changed where appropriate.

Reviewer #2: A. G. Salmon

I. Overall Document Quality

Comment: The characterization of exposures for several hours per day for several weeks is inaccurately referred to in the document as “acute” exposures.
Response: EPA recognizes that a 12-week exposure is not an acute study, but EPA in section 4.2.2.1 correctly cites “acute” exposures (in quotes) as a characterization that the authors used in the description of their studies.

Comment: The data in Appendix 1 of the Toxicological Review document should be included in the IRIS summary document and the Appendix 1 itself should include the actual source data from the experiment.
Response: A toxicological review is a support document for the IRIS summary, and it not current practice to include detailed data in the summary document. EPA agrees with the reviewer’s comments related to detailed information on the actual source data, assumptions used for the benchmark dose methodology, etc. The appendix does appropriately cite the published references to the source data and methodologies, so the reader does have access to this information. The revised document and IRIS summary has a better description and interpretation of the principal study (Kodavanti et al. 1997) than the draft reviewed.

Comment: The writing of the IRIS summary needs significant editing.
Response: The text of the IRIS summary has been completely rewritten with these comments in mind.

II. RfC Derivation:
1) Principal Study, section 5.2.1:

Comment: The Franch and Hatch, (1986) study could be used to support the findings of the Kodavanti et al. 1997 study.
Response: We disagree that the findings of the Franch and Hatch, (1986) study support the Kodavanti et al. 1977 study. Although the doses were similar in the two studies, different lung effects were observed.

2) Methods of analysis, section 5,2,2:
Comment: The reviewer agrees with the document's use of three approaches (NOAEL, BMD and CatReg) and with the choice of the critical study. He pointed out an error in the formula for RGDR in the IRIS summary. He also recommends a 5% response level as the point of departure (POD) for quantal endpoints in the BMD approach rather than a 10% level for the POD because the former is closer to a NOAEL, for which the standard uncertainty factors have been used previously.
Response: The error in the RGDR formula has been corrected. The comment about the 5% response level is not relevant to the collagen staining endpoint, which EPA is now using as the marker of chronic toxicity, because it is a graded severity score, not a quantal measure of effect. The reviewer's rationale for using a 5% level is based on the measurement of the incidence of a harmful event (quantal data).

3) NOAEL.LOAEL Approach, Section 5.2.3, item 2

Comment: He agrees with the agency's use of the default CxT (Haber's Law) procedure.
Response: None

4) Uncertainty Factors, Section 5.2.6

Comment 1: The uncertainty factor for subchronic to chronic studies is not explained well.
Response 1: The explanation has been expanded and appears in more detail in the current document.

Comment 2: The uncertainty factor of 10 for extrapolation of a LOAEL to a NOAEL should not be dropped from the BMD method. Instead, a BMD_{05} should be used as a surrogate NOAEL.
Response 2: The Agency disagrees with the comment. In both the reviewed document and the current draft the data on collagen staining are considered to represent minimal severity of lung damage, and the lower limit ($BMDL_{10}$)is considered more representative of a NOAEL than a LOAEL. Therefore the uncertainty factor for extrapolation from a LOAEL to a NOAEL is 1.0.

Comment 3: The reviewer states that a data base uncertainty factor of 3 should not be used and implies that a larger uncertainty factor may be necessary to protect against reproductive or developmental sequellae to respiratory impairments of mother or new-born offspring.
Response 3: The agency disagrees with the reviewer's comments. In fact the rationale for an uncertainty factor of 1.0 has been incorporated into the current draft saying that effects outside of the respiratory system are not expected because of the short half-life of phosgene in the respiratory system. There is no reason to expect that phosgene will migrate to the systemic circulation in concentrations large enough to cause reproductive or developmental effects.

III. Cancer Weight of Evidence
Comment and response: The reviewer agrees that the evidence is inadequate, and there is no issue.

IV. Other Comments
Comment and response: The minor editorial suggestions have been adopted.

Reviewer #3. H. Witschi

I. Overall Document Quality

Comment: The reviewer said the quality of the document is good, but suggested that the authors make sure that consistent concentration units are used throughout.
Response: Equivalent concentration units have been provided in the current draft so that the reader should now have no difficulty in translating between units (e.g. from ppm to mg/m^3).

II. RfC derivation:
1) Principal study, Section 5.2.1

Comment: The reviewer agreed with the Agency's selection of the Kodavanti et al., 1997 as the critical study for derivation of the RfC.
Response: None

2) Methods of analysis, Section 5.2.2

Comment: The reviewer supports the selection of three different methods used by EPA for derivation of the RfC and further notes that they are "scientifically sound and, in the present case, also gratifying"
Response: None

3) NOAEL/LOAEL approach:

Comment: The reviewer extensively discussed the advantages and disadvantages of using the CxT assumption and the difficulties in using the assumption at low doses. He is not against using the approach, but would like it to be more thoroughly discussed.
Response: In section 5.2.3, item 2 of the current document the CxT assumptions are explained in greater detail than in the review draft.

4) Uncertainty Factors:

Comment: The reviewer agrees with the EPA's use of uncertainty factors for human variation, animal to human uncertainty and for subchronic to chronic extrapolations, but he questioned whether a LOAEL to NOAEL uncertainty factor (UF_L) as large as 10 is supported by the dose-response data.

Response: The UF_L was changed from 10 to 1 in the NOAEL/LOAEL approach, so the reviewer's discomfort with the higher factor has been eliminated. The rationale for all the factors has been revised in section 5.2.7, Table 4 of the current draft.

Comment: The data base uncertainty factor of 3 was not adequately explained.
Response: EPA agrees with the comment and a discussion has been added justifying why the factor of 3 is not needed (Section 5.2.7, item e, page 29).

III. Cancer Weight of Evidence
Comment and response: Reviewer agrees with the EPA analysis; no response necessary

IV. Other comments:
Comment: Minor editorial comments were listed
Response: Most of the recommended changes were made.

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