Phosgene; CASRN 75-44-5

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

STATUS OF DATA FOR PHOSGENE

File First On-Line 10/01/1990

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	qualitative discussion	01/31/2006
Inhalation RfC (I.B.)	yes	01/31/2006
Carcinogenicity Assessment (II.)	yes	01/31/2006

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Phosgene
CASRN — 75-44-5
Section I.A. Last Revised — 01/31/2006

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of

substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

No published studies on the toxicity of phosgene following oral exposure in humans or animals were located in the literature.

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

Not applicable.

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

Not applicable.

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

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

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

Source Document — U.S. EPA (2005).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix C of the *Toxicological Review of Phosgene* (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological***

review, Appendix C, Summary of External Peer Review and Public Comments and Disposition (PDF)

Agency Completion Date -- 01/19/2006

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

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

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

Substance Name — Phosgene
CASRN — 75-44-5
Section I.B. Last Revised — 01/31/2006

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (U.S. EPA, 1994b). Since RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

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

I.B.1. Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	RfC
Collagen staining indicative of fibrosis **Subchronic inhalation study in rats (Kodavanti, et al., 1997)**	$BMDL_{10}$ = 0.018 ppm $BMDL_{10}$ (HEC) = 0.03 mg/m^3	100	3 x 10^{-4} mg/m^3

* Conversion Factor: MW = 98.9; assuming 25°C and 760 mmHg, 1 ppm = 98.9/24.45 = 4.05 mg/m^3. BMDL (ADJ) = 4.05 mg/m^3/ppm x 0.018 ppm x 6/24 = 0.0182 mg/m^3. The $BMDL_{10}$ (HEC) was calculated for a gas:respiratory effect in the pulmonary and the tracheobronchial regions. MVa = 0.19 m^3/day; MVh = 20 m^3/day; Sa (PU + PB) = 3,423 cm^2; Sh (PU + PB) = 543,200 cm^2; RGDR = (MVa/Sa)/(MVh/Sh) = 1.51; $BMDL_{10}$ (HEC) = $BMDL_{10}$ (ADJ) x RGDR = 0.0182 mg/m^3 x 1.51 = 0.0275 mg/m^3. [See the *Toxicological Review of Phosgene* (U.S. EPA, 2005) for a more detailed discussion of this conversion.]

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

No chronic studies in experimental animals on the effects of inhaled phosgene were available for developing an RfC. Therefore, two subchronic studies (Kodavanti et al., 1997 and Selgrade et al., 1995) were chosen as principal and supporting studies, respectively, as described below.

Kodavanti, UP; Costa, DL; Giri, SN; et al. (1997) Pulmonary structural and extracellular matrix alteration in Fischer 344 rats following subchronic phosgene exposure. Fundam Appl Toxicol 37(1):54-63.

Kodavanti et al. (1997) exposed groups of male F344 rats to phosgene levels designed to provide equal products of concentration times time (C x T) for all treatment groups except the lowest exposure concentration. Groups of eight rats were exposed to clean air (control) or phosgene for 6 hours per day as follows: 0.1 ppm (5 days/wk), 0.2 ppm (5 days/wk), 0.5 ppm (2 days/wk), or 1 ppm (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, but other analyses were performed (e.g., BAL, lung volume, and biochemical parameters).

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 or 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 regions, with a small but apparent thickening and mild inflammation seen at 0.1 ppm that progressed in severity with concentration to a severe inflamation and thickening of the terminal bronchiolar regions and alveolar walls at 1 ppm. An increase in collagen staining was seen in the 0.2 and 1 ppm animals, although no elevation of total hydroxyproline, a measure of collagen deposition, was observed.

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

Following 4 weeks of clean air recovery, body weights were significantly reduced only in the 1 ppm rats, with absolute lung weights also significantly increased only in the 1 ppm animals. 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 and 1 ppm groups were significantly higher than in controls. Collagen staining remained at the same level of intensity as seen in the 12-week groups dosed at 0.2 and 1 ppm.

As a followup to the same study, Hatch et al. (2001) pointed out that hydroxyproline content and collagen staining are standard measures of lung fibrosis and can be considered good markers of chronic injury. Fibrosis is accompanied by decreased lung compliance and diffusion capacity. Reversibility of the chronic injury is not known. 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-affect level (NOAEL) for this effect was 0.1 ppm.

Selgrade, MK; Gilmore, MI; Yang, YG; et al. (1995) Pulmonary host defenses and resistance to infection following subchronic exposure to phosgene. Inhal Toxicol 7:1257-1268.

Selgrade et al. (1995) administered *Streptococcus zooepidemicus* bacteria via an aerosol spray to the lungs of male Fischer 344 rats immediately after phosgene exposure and measured the subsequent clearance of bacteria. They also evaluated the immune response of uninfected rats similarly exposed to phosgene, as measured by an increase in the percentage of polymorphonuclear (PMN) leukocytes in lung lavage fluid. The exposure regimen was similar to that of the Kodavanti et al. (1997) study, in which animals inhaled phosgene at concentrations of 0, 0.1, or 0.2 ppm, 6 hrs/day, 5 days/week and 0.5 ppm, 6 hrs/day, 2 days/week for 4 and 12 weeks. For each 12-week exposure regimen, additional groups of animals were assessed at 4 weeks post exposure.

Selgrade et al. (1995) concluded that phosgene exposure at 0.1, 0.2, and 0.5 ppm impaired resistance to bacterial infection. In addition, an immune response at 0.5 ppm exposure was evident in non-infected animals. Phosgene was toxic to the immune cells in the lungs, but after the exposure stopped, other cells in the body repopulated the lung with no permanent damage to the immune system. It appeared that concentration rather than exposure duration was the more critical factor dictating the extent of toxic response to phosgene, even at low concentrations. In this study, a concentration of 0.1 ppm was established as a LOAEL for this effect.

Methods of analysis of the point of departure (POD). This assessment makes use of two dose-response modeling software suites developed by EPA, the Benchmark Dose Software (BMDS) (U.S. EPA, 2001) and CatReg (U.S. EPA, 2000b). BMD assessment methods (U.S. EPA, 2000a, 1995) and supporting BMDS software (versions 1.3 and 1.4) were developed to improve upon the NOAEL/LOAEL approach by taking into account the quality of the study and the complete dose-response, and the CatReg software was developed to allow for the evaluation of categorically graded responses over time. The *Toxicological Review of Phosgene* (U.S. EPA, 2005) contains details on how all three assessment methods (BMD, NOAEL/LOAEL, and CatReg) were used to analyze the critical effects identified from the Kodavanti et al. (1997) and Selgrade et al. (1995) rat subchronic inhalation studies. This summary focuses on the BMD approach, the preferred point of departure (POD) for use in derivation of the RfC for phosgene. [As is discussed further in the *Toxicological Review of Phosgene* (U.S. EPA, 2005), the BMD analysis was chosen for derivation of the RfC because it utilizes all dose-response data and because BMD methods are well described (U.S. EPA, 2000a) relative to the CatReg approach.]

BMD approach. A benchmark dose analysis was performed for a number of dose-related lung effects reported in the subchronic study by Kodavanti et al. (1997). A summary of the results most relevant to the development of a POD for quantification of phosgene noncancer risk is provided in Table 1 below for 4- and 12-week exposures. The lower-bound confidence limit values reported are for the 95% BMDL (lower-bound confidence limit on the benchmark

dose) on the estimated ppm exposure associated with a 10% extra risk (dichotomous endpoints) or a one-standard-deviation change from the estimated control mean (continuous endpoints, lung volume change). BMD analyses at 15, 5, and 1% were also performed and reported in Appendix B-1 of the *Toxicological Review of Phosgene* for the 4- and 12-week exposure durations. However, the exposure group size of eight rats is not conducive to obtaining response estimates below 10%. One indication of this is given by the fact that as the BMR% decreases (i.e., x = 15%, 10% to 5% to 1%) the $BMD_x/BMDL_x$ ratio increases (i.e., 3.9, 5.6 to 10.5 to 44.1) for the collagen staining, multistage model. This ratio indicates that although the BDMLx values are all 95% confidence intervals, the "variability and/or reliability" of the models are somewhat considerably worse at the BMR values below 10%. Although 4-week data are not used to derive the POD for an RfC, they are provided in Table 1 for comparison purposes.

Table 1. Benchmark dose results from a subchronic study in rats (Kodavanti et al., 1997)

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

[a] Only endpoints for which a dose-response could be modeled are listed.
[b] EPA's Benchmark Dose Software (BMDS), 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 presented in Appendix B-1 of the *Toxicological Review of Phosgene*.

[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 from an e-mail dated October 22, 2001, from Dr. Urmila Kodavanti, U.S. EPA/NHEERL, to Dr. Jeff Gift, U.S. EPA/NCEA, and from data submitted on October 21, 2004, by Dr. Urmila Kodavanti, U.S. EPA/NHEERL, to Dr. Jeff Gift, U.S. EPA/NCEA.

An element of the BMD approach is the use of several models to determine which one best fits the data. 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, 2000a), this is done by measures of fit. In this case, the multistage model provided the best fit of all the dichotomous models to the endpoint characterized as increased collagen staining of terminal bronchioles. The $BMDL_{10}$ for this effect is 0.018 ppm. These data are shown in Figure 1 of the *Toxicological Review of Phosgene* (U.S. EPA, 2005).

In the absence of a relevant physiologically based pharmacokinetic (PBPK) model, RfC default methods for lung toxicity caused by gaseous exposures (U.S. EPA, 1994b) were used to derive human equivalent concentrations (HECs) from the $BMDL_{10}$ described above. This was done in three steps by (1) converting the exposure from ppm to mg/m^3, (2) adjusting from intermittent to continuous exposure, and (3) extrapolating from rats to humans using the rat-to-human regional gas-dose ratio (RGDR):

1. *Converting from ppm to mg/m^3*. The molecular weight (MW) of phosgene is 98.92. Assuming 25°C and 760 mmHg, the NOAEL (mg/m^3) = 0.018 ppm x 98.92/24.45 = 0.0728 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 is proportional to the rate at which the agent is delivered to the cells, multiplied by duration of exposure (T) (i.e., Haber's law). A review of acute phosgene exposure studies indicates that this assumption may be valid for exposures of fractions of a day (U.S. EPA, 2005). However, the study of Kodavanti et al. (1997) directly implies that intermittent exposures to a certain concentration for 7 days per week would have the same effect as intermittent exposure for 5 days per week. For this reason, it is assumed that effects from continuous exposures for 7 days per week would not be significantly different from effects from intermittent exposures for 7 days per week. Therefore, in the standard default method for adjusting for continuous exposures, the traditional 5/7 factor is not applied. The BMDL from the Kodavanti et al. (1997) adjusted for continuous exposure is: $BMDL_{ADJ}$ = 0.0728 mg/m^3 x 6/24 = 0.0182 mg/m^3.
3. *Extrapolating from rats to humans*. The human equivalent concentration (HEC) corresponding to the $BMDL_{ADJ}$ ($BMDL_{HEC}$) was calculated for a gas:respiratory tract effect in the thoracic region, taking into account volume breathed per day and the

surface area of the thoracic region of the rat lung versus the human lung. This is the standard procedure for dose conversions from animals to humans for Category 1 gases, which are completely and irreversibly absorbed by the lung (U.S. EPA, 1994b). The 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 $BMDL_{HEC}$ was calculated by multiplying the $BMDL_{ADJ}$ by the $RGDR_{TH}$:

$$BMDL_{HEC} = 0.0182 \text{ mg/m}^3 \text{ x } 1.51 = 0.0275 \text{ mg/m}^3 \text{ (0.007 ppm)}$$

Application of the benchmark dose approach to the immune response data from Selgrade et al. (1995) is problematic because of the difficulties establishing what level of bacterial resistance adversely affects the overall health and survival of the animals. The extent, duration, and health consequences of impaired bacterial resistance from phosgene exposure is highly dependent on secondary factors such as the exposure scenario involved, the health status of the exposed individual, and the type of infection. Since the quantitative relevance of the rat model of bacterial resistance to humans is unknown, it would be inappropriate to use these results in a benchmark dose determination of the RfC. The application of a NOAEL/LOAEL approach to data from Selgrade et al. (1995) is provided in the *Toxicological Review for Phosgene* (U.S. EPA, 2005). The *Toxicological Review* presents a comparison of the resulting points of departure and RfDs based on data from Kodavanti et al. (1997) and Selgrade et al. (1995), and the rationale for selection of Kodavanti et al. (1997) as the principal study.

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

UF = 100.

UFs are applied to account for uncertainties in extrapolating from experimental conditions to the assumed human scenario (i.e., chronic exposure over a lifetime). Historically, UFs are applied as values of 10 in a multiplicative fashion (Dourson and Stara, 1983). Recent EPA practice, however, also includes the use of a partial UF of $10^{1/2}$ (3.162) (U.S. EPA, 2001) 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 of $10^{1/2}$ is rounded to 3, such that the total factor would be 30 (3 x 10). When two partial UFs are evoked, however, they are not rounded, so a UF of 3, 3, and 10 would result in total uncertainty of 100. UFs applied for this RfC assessment and the justification for their use are as follows:

1. *Human variation*: $UF_H = 10$. This factor is used to account for the variation in susceptibility within the human population and for the possibility that the data available are not representative of sensitive subgroups or lifestages, including children (U.S. EPA, 2002). For phosgene, two studies are suitable for derivation of the RfC, and because they are in animals, they cannot be regarded as representative of sensitive humans. Therefore the default value of 10 is appropriate.
2. *Animal-to-human uncertainty*: $UF_A = 3$. Use of an RGDR to estimate an HEC is deemed to largely account for the pharmacokinetic portion of this uncertainty. A threefold UF is retained to account for uncertainties regarding pharmacodynamic differences between animals and humans.
3. *Subchronic-to-chronic uncertainty*: $UF_S = 3$. The PODs are based on adverse effects in two subchronic inhalation studies. The full factor of 10 is not appropriate because the lung damage observed by Kodavanti et al. (1997) and the impairment in bacterial resistence observed by Selgrade et al. (1995) are not likely to progress significantly with further exposure. However, a partial factor of 3 is still necessary because of the remaining uncertainty in predicting full lifetime effects from both 12-week studies.
4. *LOAEL-to-NOAEL uncertainty*: $UF_L = 1$. No uncertainty factor is applied to the 0.018 ppm BMDL derived from collagen staining in the Kodavanti et al. (1997) study because this POD is consistent with the NOAEL of 0.1 ppm given the small group sizes in this study and because it represents minimal severity of lung damage.
5. *Database*: $UF_D = 1$. In general, a database UF is needed to account for the potential for deriving an underprotective RfC as a result of an incomplete characterization of the toxicity (U.S. EPA, 2002). This includes areas where there is a complete lack of information as well as areas where existing data indicate that further information on a particular subject has the potential for demonstrating effects at lower exposures. Because phosgene is a chemically reactive agent with an extremely short half-life in water and in lung tissue, its effects when inhaled are not likely to be observed outside the lung, and no effects have in fact been observed to date. While it is recognized that the investigation of systemic effects following phosgene exposure has not been the focus of existing studies, there is no reason to expect that reproductive, developmental, or other systemic effects would occur, and no uncertainty factor is needed for the absence of data on these effects. In view of the Selgrade et al. (1989) finding of increased sensitivity to bacterial infection in mice due to short-term (4 and 8 hour) phosgene exposures (section I.B.4 of this Summary) at lower concentrations

than in the sub-chronic rat experiments (Selgrade et al., 1995), there is a possibility that a longer-term study in mice might show effects at a lower concentration than in rats. That possibility would be a rationale for a data base uncertainty factor of greater than one. However the species difference between the response in mice and rats is small and adequately accounted for in the subchronic-to-chronic factor of 3 and the animal-to-human factor of 3. Therefore a separate data base uncertainty factor is not necessary.

The application of these UFs to the BMD POD is summarized in Table 2. The RfC is calculated as follows:

$$RfC = 0.03 \text{ mg/m}^3 \div 100 = 3 \text{ x}10^{-4} \text{ mg/m}^3$$

Table 2. Application of uncertainty factors (UFs) for RfC calculation

Factor	BMDL[a]
POD (mg/m^3)	**0.03**
UF_H	10
UF_A	3
UF_S	3
UF_L	1
UF_D	1
$UF_{(Total)}$	100
RfC (mg/m^3)	3E-4

[a]The $BMDL_{HEC}$, based on collagen staining in the Kodavanti et al. (1997) study.

I.B.4. Additional Studies/Comments

The effect of occupational exposure to phosgene on mortality was examined in workers employed at a uranium processing plant from 1943 to 1945 (Polednak and Hollis, 1985; Polednak, 1980). In the initial report (Polednak, 1980), a comparison was made between a group of 699 male workers exposed daily to phosgene and 9,352 male controls employed during the same time period but not exposed to phosgene. The duration of exposure was generally 2 months to 1 year; the followup period was 30 years. Exposure levels were not reported but were instead described as "low" (undetectable), with the level exceeding 1 ppm four to five times daily. Standard mortality ratios (SMRs) for respiratory diseases were not significantly different between controls (SMR = 113, 95% 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 exposed workers and controls for any other cause of death.

In the 5-year followup (Polednak and Hollis, 1985) to the Polednak (1980) study, the number of subjects had decreased to 694 male workers exposed to daily phosgene and 9,280 male controls. 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 difference in the SMRs for lung cancer were found between control (SMR = 118, 95% CL = 105-133) and exposed workers (SMR = 122, 95% CL = 72-193). No significant differences were found between exposed workers and controls for any other cause of death. The study authors pointed out, however, that because of the small sample sizes, only large differences in mortality rates would have been detected in these studies.

The Polednak and Hollis (1985) and Polednak (1980) studies 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 overall SMR for all causes was 109 (95% CL = 73-157) for exposed workers in 1980 and 121 (95% CL = 86-165) in 1985. In the respiratory disease category, the SMR increased from 219 (3 deaths reported, 1.37 expected; 95% CL not reported) in the 1980 report to 266 (95% CL = 86-622) in the 1985 report; 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 report to analyze a similar cohort of 91 female workers also exposed to approximately 50 ppm/min, but ascertainment of deaths and followup was less certain for this group and prevented a full analysis.

No chronic animal data on the effects of inhaled phosgene were located. The majority of studies of phosgene are of acute duration of exposure, spanning from minutes to several hours. Several studies (Kodavanti et al., 1997; Franch and Hatch, 1986; Clay and Rossing, 1964; Rossing, 1964) have examined the effects of repeated, short-term phosgene inhalation.

The acute toxicity of phosgene inhalation has been well documented in humans and animals (WHO, 1998, 1997; U.S. EPA, 1986, 1984; Diller et al., 1979; Underhill, 1919), with lung as the major target organ and pulmonary edema as the characteristic pathological feature. In other studies (Schneider and Diller, 1989; Diller, 1985), clinical signs and symptoms were generally lacking, but histologic examination of the lung revealed edematous swelling that resulted in damage to alveolar type 1 cells. At sufficiently high exposures, pulmonary congestion can lead to cardiac failure.

Clay and Rossing (1964) exposed five 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 animals (n = 2) consisted of unexposed controls; group 2 animals (n = 7) were exposed 1 or 2 times and sacrificed 1 to 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. Macrosections revealed little or no changes in animals exposed one or two times, with a progressing fibrosis and emphysema seen with increasing number of exposures, resulting in severe dilation of the respiratory bronchioles and increased alveolar pore size in animals exposed 30-40 times. Owing to the poor design of the study and the number of experimental animals and dose levels 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. Histology of the lungs after 17 days of exposure to 0.25 ppm phosgene revealed moderate multi focal mononuclear cell accumulations in the walls of the terminal bronchioles and a minimal type II cell hyperplasia; lesions in the groups exposed to 0.125 ppm were minimal.

Because higher concentrations of phosgene for short periods of time can have serious acute effects (Hegler, 1928; Wohlwill, 1928, both cited in U.S. EPA, 1986), the RfC cannot be directly compared to averaged air concentrations without also examining available benchmarks regarding acute effects from the inhalation of phosgene. Please see Appendix A of the *Toxicological Review of Phosgene* (U.S. EPA, 2005) for discussion of acute exposure guidelines levels (AEGLs), threshold exposure limits for the general public that are applicable to emergency exposure periods ranging from 10 minutes to 8 hours.

Selgrade et al. (1989) reported that a single 4-hour exposure to phosgene concentrations as low as 0.025 ppm significantly enhanced mortality due to streptococcal infection in mice. Furthermore when the exposure time was increased from 4 to 8 hours, a significant increase in susceptibility to streptococcus was also seen at an exposure concentration of 0.01 ppm. The authors attempted to establish a mechanism for these findings by measuring alveolar macrophage activity. With intratracheal administration of bacteria, which delivers a much larger amount of bacteria than the inhalation route used in the previous experiments, phosgene concentrations of 0.25 ppm and higher, which is 10-fold higher than the lowest observable effect level, had little or no effect on alveolar macrophage phagocytic activity and little or no effect on total cells recovered, viability or differential cell counts in lavage fluid obtained shortly after exposure. The mechanism(s) responsible for increased sensitivity to bacterial infection are unclear.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study - Medium
Database - Medium
RfC - Medium

The principal study is given a medium confidence rating because it was a well-conducted subchronic (4-12 week) study. It was performed on only one species and did identify a NOAEL. Confidence in the database can be considered medium due to lack of chronic or subchronic data in a second species and the lack of an oral study. Therefore, due to the gaseous nature and extremely short half-life, confidence in the RfC can also be considered medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)

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

Source Document -- U.S. EPA (2005).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix C of the *Toxicological Review of Phosgene* (U.S. EPA, 2005). ***To review this appendix, exit to the toxicological***

review, Appendix C, Summary of and Response to External Peer Review Comments and Disposition (PDF)

Agency Completion Date -- 01/19/2006

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

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

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Phosgene
CASRN — 75-44-5
Section II. Last Revised — 01/31/2006

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific values are presented. The "oral slope factor" is an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, the "unit risk" is an upper bound on the estimate of risk per unit concentration, either per µg/L drinking water (see Section II.B.1.) or per µg/m^3 air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. Evidence for Human Carcinogenicity

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

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005b), there is inadequate information to assess carcinogenic potential of phosgene. A single epidemiology study was not considered adequate for evaluating carcinogenic potential in humans, and no animal cancer bioassays of phosgene have been conducted.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

A comparison was made between a group of 694 male workers exposed daily to phosgene and 9,280 male cohorts who were employed during the same time period but not exposed to phosgene (Polednak and Hollis, 1985; Polednak, 1980). The duration of exposure was generally 2 months to 1 year; the followup period was 30 years. Exposure levels were not reported but were instead described as "low" (undetectable), with the level exceeding 1 ppm four to five times daily. SMRs for respiratory diseases and lung cancer were not significantly different between controls and exposed workers. No significant differences were found for any other cause of death. Because of the small sample sizes, however, this study would have detected only large differences in mortality. Therefore, these studies are not adequate for evaluating potential cancer risk in humans.

II.A.3. Animal Carcinogenicity Data

None.

II.A.4. Supporting Data for Carcinogenicity

None.

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

Not applicable.

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

Not applicable.

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

II.D.1. EPA Documentation

Source Document — U.S. EPA (2005a).

This assessment was peer reviewed by a group of external scientists. Comments from the peer reviewers were evaluated carefully and considered by the Agency during the finalization of this assessment. A record of these comments is included in Appendix C of the Toxicological Review of Phosgene (U.S. EPA, 2005a). ***To review this appendix, exit to the toxicological review, Appendix C, Summary of and Response to External Peer Review Comments (PDF)***.

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

Agency Consensus Date — 01/19/2006

II.D.3. EPA Contacts (Carcinogenicity Assessment

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

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

VI. Bibliography

Substance Name — Phosgene
CASRN — 75-44-5

VI.A. Oral RfD References

U.S. EPA (Environmental Protection Agency). (2005) Toxicological review of phosgene in support of summary information on integrated risk information system (IRIS). National Center for Environmental Assessment, Washington, DC. Available from: http://www.epa.gov/iris.

VI.B. Inhalation RfC References

Clay, JR; Rossing, RG. (1964) Histopathology of exposure to phosgene: an attempt to produce pulmonary emphysema experimentally. Arch Pathol 78:544-551.

Diller, WF. (1985) Pathogenesis of phosgene poisoning. Toxicol Ind Health 1:7-15.

Diller, WF; Schnellbaecher, F; Wuestefeld, E. (1979) Pulmonale spaetfolgen nach phosgenvergiftungbzw. Inhalationstoxischem lungenoedem [Late pulmonary sequelae of phosgene poisoning or inhalation-toxic pulmonary edema]. Zentralbl Arbeitsmed Arbeitsschutz Prophyl 29:5-16. (Cited in U.S. EPA, 1986.)

Dourson, ML; Stara, JF. (1983) Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol 3:224-238.

Franch, S; Hatch, GE. (1986) Pulmonary biochemical effects of inhaled phosgene in rats. J Toxicol Environ Health 19:413-423.

Hatch, GE; Kodavanti, U; Crissman, K; et al. (2001) An "injury-time integral" model for extrapolating from acute to chronic effects of phosgene. Toxicol Ind Health 17:1-9.

Hegler, C. (1928) Ueber eine massenvergiftung durch phosgengas in Hamburg. 1. Klinische beobachtungen [On the mass poisoning by phosgene in Hamburg: 1. chemical observations]. Dtsch Med Wochenschr 54:1551-1553. (Cited in U.S. EPA, 1986.)

Kodavanti, UP; Costa, DL; Giri, SN; et al. (1997) Pulmonary structural and extracellular matrix alterations in Fischer F344 rats following subchronic phosgene exposure. Fundam Appl Toxicol 37(1):54-63.

Polednak, AP. (1980) Mortality among men occupationally exposed to phosgene in 1943-1945. Environ Res 22:357-367.

Polednak, AP; Hollis, DR. (1985) Mortality and causes of death among workers exposed to phosgene in 1943-1945. Toxicol Ind Health 1(2):137-151.

Rossing, RG. (1964) Physiologic effects of chronic exposure to phosgene in dogs. Am J Physiol 207:265-272.

Schneider, W; Diller, W. (1989) Phosgene. In: Ullman's Encyclopedia of industrial chemistry, 5th ed. Weinheim, Germany: VCH Verlag. Vol. A 19:411-420.

Selgrade, MK; Starnes, DM; Illing, JW; et al. (1989) Effects of phosgene exposure on bacterial, viral, and neoplastic lung disease susceptibility in mice. Inhal Toxicol 1:243-259.

Selgrade, MK; Gilmore, MI; Yang, YG; et al. (1995) Pulmonary host defenses and resistance to infection following subchronic exposure to phosgene. Inhal Toxicol 7:1257-1268.

Underhill, FP. (1919) The physiology and experimental treatment of poisoning with the lethal war gases. Arch Int Med 23:753-770. (Cited in WHO, 1997, 1998.)

U.S. EPA (Environmental Protection Agency). (1984) Health and environmental effects profile for phosgene. Draft. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Solid Waste and Emergency Response, Washington, DC. ECAO-CIN-P043.

U.S. EPA. (1986) Health assessment document for phosgene. Draft. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-86/022A.

U.S. EPA. (1988) Recommendations for and documentation of biological values for use in risk assessment. EPA 600/6-87/800. Available from: National Technical Information Service, Springfield, VA. PB88-179874/AS, February 1988.

U.S. EPA. (1994a) Interim policy for particle size and limit concentration issues in inhalation toxicity: notice of availability. Federal Register 59:53799.

U.S. EPA. (1994b) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U.S. EPA. (1995) Use of the benchmark dose approach in health risk assessment. National Center for Environmental Assessment, Washington, DC. EPA/630/R-94/007.

U.S. EPA. (2000a) Benchmark dose technical guidance document [External Review Draft]. Risk Assessment Forum, Washington, DC. EPA/630/R-00/001. Available from: http://www.epa.gov/ncea/bnchmrk/bmdspeer.htm.

U.S. EPA. (2000b) CatReg software documentation. Office of Research and Development, Washington, DC. EPA/600/R-98/053F. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=18162.

U.S. EPA. (2001) Help manual for benchmark dose software version 1.3, National Center for Environmental Assessment. EPA 600/R-00/014F, March 2001. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167.

U.S. EPA. (2002) A review of the reference dose and reference concentration processes. Risk Assessment Forum, Washington, DC. EPA/630/P-02/002F.

U.S. EPA. (2005) Toxicological review of phosgene in support of summary information on Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available from: http://www.epa.gov/iris.

WHO (World Health Organization). (1997) Environmental health criteria monograph on phosgene. Monograph 193. International Programme on Chemical Safety. Geneva, Switzerland.

WHO. (1998) Phosgene health and safety guide. Health and Safety Guide No. 106. International Programme on Chemical Safety. Geneva, Switzerland.

Wohlwill, F. (1928) II. Zur pathologischen anatomie der phosgenvergiftung [II. Pathological findings of phosgene poisoning]. Dtsch Med Wochenschr 54:1153-1157. (Cited in U.S. EPA, 1986.)

VI.C. Carcinogenicity Assessment References

Polednak, AP. (1980) Mortality among men occupationally exposed to phosgene in 1943-1945. Environ Res 22:357-367.

Polednak, AP; Hollis, DR. (1985) Mortality and causes of death among workers exposed to phosgene in 1943-1945. Toxicol Ind Health 1(2):137-151.

U.S. EPA (Environmental Protection Agency). (2005a) Toxicological review of phosgene in support of summary information on integrated risk information system (IRIS). National Center for Environmental Assessment, Washington, DC. Available from: http://www.epa.gov/iris.

U.S. EPA. (2005) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Available from: http://www.epa.gov/iris/backgrd.html.

VII. Revision History

Substance Name — Phosgene
CASRN — 75-44-5
File First On-Line 10/01/1990

Date	Section	Description
10/01/1990	I.B.	Inhalation RfC message on-line
01/31/2006	I.B., II.	RfC and cancer assessment and RfD qualitative discussion added

VIII. Synonyms

Substance Name — Phosgene
CASRN — 75-44-5
Last Revised - 01/31/2006

- 75-44-5
- Carbon dichloride oxide
- Carbone (oxychlorure de) [French]
- Carbonic dichloride
- Carbonio (ossicloruro di) [Italian]
- Carbon oxychloride
- Carbonylchlorid [German]
- Carbonyl chloride
- Carbonyl dichloride
- CG
- Chloroformyl chloride
- Fosgeen [Dutch]

- Fosgen [Polish]
- Fosgene [Italian]
- Fosgeno [Spanish]
- HSDB 796
- Koolstofoxychloride [Dutch]
- NCI-C60219
- Phosgen [German]
- Phosgene
- RCRA Waste Number P095