Phosgene; CASRN 75-44-5; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Section I (Chronic Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) represent a summary of the external review draft, "Toxicological Review of Phosgene," dated February 2004. 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 at http://www.epa.gov/iriswebp/irisbackgr-d/htm.

STATUS OF DATA FOR PHOSGENE

File First on Line 10/01/1990

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	No data	
Inhalation RfC Assessment (I.B.)	On-line	2004
Carcinogenicity Assessment (II.)	No data	

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Phosgene
CASRN -- 75-44-5
Last Revised -- 00/00/0000

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. 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 effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the non-carcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.A.1. ORAL RfD SUMMARY

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

__I. B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RFC)

Phosgene
CASRN -- 75-44-5
Last Revised -- 00/00/0000

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RFC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

___I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Collagen staining indicative of fibrosis	**$BMDL_{10}$ = 0.018 ppm** **$BMDL_{10}$ (HEC) = 0.02 mg/m^3**	**100**	**1**	**2 x 10^{-4} mg/m^3**

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* Conversion Factor: MW = 98.9; assuming 25 °C and 760 mm Hg, 1 ppm = 98.9/24.45 = 4.05 mg/m^3. BMDL (ADJ) = 4.05 x 0.018 x 6/24 x 5/7 = 0.013 mg/m^3. The $BMDL_{10}$ (HEC) was calculated for a gas; respiratory effect in the pulmonary plus the tracheobronchial regions. MVa = 0.19 m^3/day; MVh = 20 m^3/day; Sa (PU+ PB) = 3423 cm^2; Sh (PU+PB) = 543,200 cm^2; RGDR= (MVa/Sa)/(MVh/Sh) = 1.51; $BMDL_{10}$ (HEC) = $BMDL_{10}$ (ADJ) × RGDR = 0.013 x 1.51 = 0.02 mg/m^3.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

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.

A subchronic inhalation study was considered to be suitable for the development of an RfC (Kodavanti et al., 1997). This is the only study of phosgene that assessed the effects of subchronic (12 weeks or more) exposures. No studies have been located that are relevant and adequately quantify developmental effects on the reproductive system. The results of the Kodavanti et al. (1997) study are summarized below.

Kodavanti et al. (1997) exposed groups of male F344 rats to phosgene levels designed to provide equal concentration times time (C × T) products for all treatment groups except the lowest exposure concentration. Groups of eight rats were exposed for 6 hours per day to 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 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 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 inflamation 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 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 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 pointed out that hydroxyproline content and collagen staining are standard measures of lung fibrosis and can be considered good markers of chronic injury. Reversibility of the chronic injury is not known. 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-affect level (NOAEL) for this effect was 0.1 ppm in this study.

No other studies with durations of longer than 4 weeks in animals have been reported, although several studies with exposure durations ranging from minutes to a few days in both humans and animals may serve to characterize the acute effects of phosgene.

Methods of analysis of the point of departure (POD). Two recent developments in risk assessment have the potential to impact the RfC for phosgene: (1) EPA has developed benchmark dose assessment methods (U.S. EPA,1995, 2000a) and supporting software (U.S. EPA, 2001) to improve upon the previous NOAEL/LOAEL approach, and (2) CatReg software (U.S. EPA, 2000b) that can be used to account for categorically graded lesion severity. Three assessment methods (NOAEL/LOAEL, benchmark dose [BMD], and categorical regression [CatReg]) were used to analyze the critical effects identified from Kodavanti et al. (1997) to obtain a POD for use in deriving an RfC for phosgene.

NOAEL/LOAEL approach. In the absence of a relevant physiologically based pharmacokinetic (PBPK) model, RfC default methods (U.S. EPA, 1994) were used to derive human equivalent concentrations (HECs) from the NOAEL of 0.1 ppm (0.4 mg/m^3) 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 of phosgene is 98.92. Assuming 25 °C and 760 mm Hg, the NOAEL is 0.1 ppm × 98.92/24.45 = 0.405 mg/m^3.

2. *Adjusting from intermittent to continuous exposure.* To adjust from 6 hrs/day to 24 hrs/day and from 5 days/wk to 7 days/wk of exposure, NOAEL (ADJ) = 0.405 mg/m^3 × 6 hrs/24 hrs × 5 days/7 days = 0.0723 mg/m^3.

3. *Extrapolating from rats to humans*. The HEC for the NOAEL 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 the human lung. The thoracic region, which consists of both the pulmonary and tracheobronchial regions of the lungs, was chosen because (1) some of these lesions have been classified as pulmonary lesions, (2) some of the assays measured would not make a distinction between the two lung regions (e.g., whole-lung

prolyl hydroxylase and hyproxyproline as an index of collagen synthesis, volume displacement measurements), and (3) some lesions appeared to be in both regions (bronchus inflammation, alveolar interstitial thickening). The regional gas-dose ratio 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 (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, and
MV_h (Minute ventilation for humans) = 20 m^3/day,
S_h (thoracic surface area for humans) = 543,200 cm^2.

The NOAEL (HEC) was calculated by multiplying the $NOAEL_{ADJ}$ by the $RGDR_{TH}$.

$$NOAEL\ (HEC) = 0.0723\ mg/m^3 \times 1.51 = 0.11\ mg/m^3$$

BMD approach. As discussed in Hatch et al. (2001), collagen staining of bronchioles is an appropriate marker of chronic toxicity. Benchmark dose modeling results for this and other endpoints of toxicity are given in the following table. The lung effects after 4 weeks of exposure are included in this analysis for comparison purposes.

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

Effects[a]	BMDL[b] (ppm)	
	12–week exposure	4–week exposure
Interstitial thickening of the alveolus	0.032	0.015
Inflammatory cell influx to terminal bronchiole/alveolus	0.012	0.013
Epithelial alteration of terminal bronchiole/peribronchiolar/ alveolus	0.026	0.0064
Increased collagen staining of terminal bronchiole/peribronchiolar	0.018	0.026
Displacement volume, left lung (mL/kg body weight × 100)	0.063[c]	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% lower confidence limit 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 A of the toxicological review document.
[c]For this continuous endpoint, the BMDL represents a one-standard-deviation change from the estimated control mean. The mean and standard deviation values for this endpoint were obtained from Dr. Urmila Kodavanti (e-mail dated 10/22/01 from Urmila Kodavanti, U.S. EPA, to Jeff Gift, U.S. EPA).

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, 2000c), this is done by measures of fit. In this case, the multistage model provided the best fit of all the dichotomous models (see Appendix A of the toxicological review document) to the endpoint characterized as increased collagen staining of terminal bronchioles. The BMDL for this effect is 0.018 ppm (Appendix A). 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 × 1.51 = 0.0196) is estimated from this BMDL.

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 for consideration of point of departure. However, it does not provide much insight into the role of 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, yet a response at the low dose was clearly evident from the severity score data (Kodavanti et al., 1997) (see Table 3 in the toxicological review document). 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, which does account for differences in severity of response. Hence, a CatReg that can explicitly account for the severity of 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 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).

The male rat lung effects from Kodavanti et al. (1997) provide the most appropriate endpoints for continued analysis using the CatReg software developed by EPA (U.S. EPA, 1999). 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. All lung lesions scored for severity were combined and analyzed together. These data were supplied by the author (fax dated 10/23/01 from Urmila Kodavanti, U.S. EPA, to Jeff Gift, U.S. EPA). This analysis was performed for lesions observed at 4 weeks, 12 weeks, and 4 and 12 weeks combined. (Appendix

[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 nested 4 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 BMC and the estimate of the BMDL.

A of the toxicological review document describes CatReg and how it was used in this assessment.)

The 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 earlier, 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.

Comparisons between each approach. Each approach considered for determination of the POD has strengths and limitations, as described above, but together they present a consistent and more appropriate determination for the POD for the phosgene RfC. The NOAEL/LOAEL allows for crude comparison of results between multiple species and results (e.g., NOAEL/ LOAEL can be determined experimentally with less dependence on the 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 a $NOAEL_{HEC}$ 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.

___I.B.3. UNCERTAINTY FACTORS (UFs) AND MODIFYING FACTORS (MFs) (INHALATION RfC)

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 $10^{1/2}$ (3.62) (U.S. EPA, 1994) 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 × 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:

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 cannot 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.

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 uncertainty factor 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. 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*: 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 three approaches are compared in the following table. As explained above, the UF_L for the LOAEL-to-NOAEL UF is not needed ($UF_L = 1$) 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 m^2/m^3). The RfC is about 5 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 agrees with the CatReg approach. Using the BMD approach, the RfC is calculated as follows:

$$\text{RfC} = 0.02 \text{ mg/m}^3 \div 100 = 2\text{E-}4 \text{ mg/m}^3 = 5\text{E-}5 \text{ ppm}$$

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

Factor	NOAEL	BMD	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

_I. B. 4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

The effect of occupational exposure to phosgene on mortality was examined in workers employed at a uranium processing plant from 1943 to 1945 (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 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% CL = 98–130) and exposed workers (SMR = 78, 95% CL = 31–161) relative to cause- and age-specific death rates for U.S. white males. 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 follow-up (Polednak and Hollis, 1985) to the Polednak (1980) study, the number of subjects had decreased to 694 male workers exposed to daily phosgene and 9280 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 cases of 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 was 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 follow-up 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 (Clay and Rossing, 1964; Franch and Hatch, 1986; Kodavanti et al, 1997; Rossing, 1964) have examined the effects of repeated, short-term phosgene inhalation. However, none of these studies meet the minimum criteria for a low-confidence RfC as defined in the RfC guidelines (U.S. EPA, 1994).

The acute toxicity of phosgene inhalation has been well documented in humans and animals (Underhill, 1919; U.S. EPA, 1984, 1986; WHO, 1997, 1998; Diller et al. 1979). In other studies (Diller 1985; Schneider and Diller, 1989), clinical signs and symptoms were generally lacking, but histologic examination revealed edematous swelling that resulted in damage to alveolar type 1 cells. The heart may also have been affected, resulting in cardiac failure due to pulmonary congestion at sufficiently high exposure.

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 (n = 2) consisted of unexposed controls; group 2 animals (n = 7) were exposed 1 or 2 times and sacrificed 1 to 3 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. Due 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 multifocal 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. The 0.125 ppm (0.5 mg/m^3) dose can be considered a LOAEL for histologic alterations of the respiratory tract; no LOAEL was identified in this study.

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, 1986c), the RfC cannot be directly compared to averaged air concentrations without also examining available benchmarks regarding acute effects from the inhalation of phosgene.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study - Medium
Database - Medium
RfC - Medium to Low

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 nonexistence of an oral study. Confidence in the RfC can also be considered medium.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- 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.

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to _____.

Other EPA Documentation -- None.

Agency Consensus Date -- __/__/__

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

__II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

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Section II 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 exposure and inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the draft revised *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999). The quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper-bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per μg/L drinking water or per μg/cu.m air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

__ II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___ II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Classification – D; not classifiable as to human carcinogenicity, based on inadequate human data and no data from animal bioassays.

___II. A.2. HUMAN CARCINOGENICITY DATA

Inadequate. A comparison was made between a group of 694 male workers exposed daily to phosgene and 9280 male cohorts who were employed during the same time period but not exposed to phosgene (Polednak, 1980; Polednak and Hollis, 1985). 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 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.

___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

None

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

None

__II..D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document - _____

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS summary. A record of these comments is included as an appendix to _____.

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date - ___/___/___

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or hotline.iris @epamail.epa.gov (email address).

_III. [reserved]

_IV. [reserved]
_V. [reserved]

__VI. BIBLIOGRAPHY

Phosgene
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__VI. A. ORAL RfD REFERENCES

None

__VI. B. INHALATION RfC REFERENCES

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__ VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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__VII. REVISION HISTORY

Phosgene
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Date	Section	Description

__VIII. SYNONYMS

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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