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Health assessment of phosgene: Approaches for derivation of reference concentration ☆

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ABSTRACT

This paper describes the derivation of the chronic reference concentration (RfC) for human inhalation of phosgene that was recently added to the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) data base (U.S. EPA, 2005. Toxicological Review of Phosgene: In Support of Summary Information on the Integrated Risk Information System (IRIS). Available online at: <http://www.epa.gov/IRIS>). The RfC is an estimate of daily phosgene exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime. [For this and other definitions relevant to EPA risk assessments refer to the glossary of terms in the US EPA IRIS website (http://www.epa.gov/IRIS).] Phosgene is a potential environmental pollutant that is primarily used as a catalyst in the polyurethane industry. It is a gas at room temperature, and in aqueous solution it rapidly hydrolyzes to CO_2 and HCl.

In the absence of chronic human health effects information and lifetime animal cancer bioassays, the RfC is based on two 12-week inhalation studies in F344 rats which measured immune response and pulmonary effects, respectively. The immune response study showed impaired clearance of bacteria that was administered into the lungs of rats immediately after exposure to phosgene at concentrations of 0.1, 0.2 and 0.5 ppm. It also showed that the immune response in uninfected rats was stimulated by phosgene exposure at all concentrations. The pulmonary effects study showed a progressive concentration-related thickening and inflammation in the bronchiolar regions of the lung that was mild at 0.1 ppm and severe at 1.0 ppm. An increase in collagen content, as observed with histological collagen stains, was observed at 0.2 ppm and above. Though there is considerable uncertainty associated with the species and exposure duration employed, this endpoint is considered an indication of chronic lung injury of potential relevance to humans.

Three different approaches for RfC derivation were taken in analyzing these studies: (1) the traditional NOAEL/LOAEL method; (2) the benchmark dose (BMD); and (3) the categorical regression for the analysis of severity-graded pulmonary damage data using the recently revised USEPA CatReg software. The BMD approach was selected as the method of choice to determine the RfC for phosgene because it has several advantages compared to the NOAEL/LOAEL: (1) it is not restricted to the set of doses used in the experiments; (2) the result is not dependent on sample size; (3) it incorporates information on statistical uncertainty. The CatReg approach allowed the incorporation of data on the severity of the pathological lesions, and therefore it complemented the other approaches. The BMD approach could not be applied to the immune response data because it was not possible to define an adverse effect level for bacterial resistance. However, NOAEL/LOAEL values for immune responses were consistent with benchmark dose levels derived from lung pathology data and used in the derivation of the RfC. The preferred RfC method and derivation involved dividing the benchmark dose from the collagen staining data (0.03 mg/m^3) by a composite uncertainty factor of 100: RfC = 0.03/100 = 3E − 4 mg/m^3.

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1. Introduction

Phosgene is primarily used in the polyurethane industry for the production of polymeric isocyanates (WHO, 1997; U.S. EPA, 1986). Phosgene is also used in the polycarbonate industry and in the manufacture of carbamates and related pesticides, dyes,

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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; Pauluhn et al., 2007).

Phosgene levels have been measured in ambient air (U.S. EPA, 1983; Singh et al., 1981, 1977; Singh, 1976). Kelly et al. (1994) reported that the phosgene ambient concentration median was 80 ng/m^3. Inhalation is the primary exposure route for phosgene (Kelly et al., 1994; WHO, 1998). Suspected sources of atmospheric phosgene are fugitive emissions, thermal decomposition of chlorinated hydrocarbons, and photo-oxidation of chloroethylenes. The purpose of this paper is to briefly review the published literature on toxicological effects of phosgene and to derive a reference concentration for its chronic inhalation exposure to human population.

Upon inhalation, phosgene is either rapidly hydrolyzed to HCl and CO_2 and exhaled (Schneider and Diller, 1989; Diller, 1985) or, as recent evidence would suggest, penetrates deep into the lungs and is eliminated by rapid reactions with nucleophilic constituents of the alveolar region (Pauluhn et al., 2007). Consequently, phosgene is not expected to leave the pulmonary circulation following inhalation exposure, and exposure by the oral route is not likely (WHO, 1998; U.S. EPA, 1986). Data on phosgene pulmonary absorption are not available. Phosgene is electrophilic and undergoes attack by a variety of nucleophiles. It also reacts with a wide variety of nucleophiles, including primary and secondary amines, hydroxy groups, and thiols. In addition, it also reacts with macromolecules, such as enzymes, proteins, or other polar phospholipids, resulting in a marked depletion of glutathione (Sciuto et al., 1996) and the formation of covalent adducts that can interfere with molecular functions.

There is little information on the distribution and elimination of phosgene in experimental animals and humans, but much has been written on local pulmonary interactions of phosgene, particularly with the surfactant system, the mixture of lipids and proteins situated at the air–liquid interface of the alveolus (Jugg et al., 1999; Pauluhn et al., 2007). Surfactant lipids are important for maintaining alveolar stability and for preventing pulmonary edema. The induction of surfactant abnormalities following phosgene exposures is presumed to be a key pathophysiological event leading to pulmonary edema and either acute respiratory failure or chronic cellular inflammation leading to the stimulation of fibroblasts and the synthesis of "abnormal" collagen in pulmonary fibrosis (Pauluhn et al., 2007).

Schneider and Diller (1989) and Diller (1985) reported that 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. Evidence from experimental studies in dogs (Cameron and Courtice, 1946), sheep (Keeler et al., 1990), and pigs (Brown et al., 2002) phosgene initially causes a permeability defect in the blood–air barrier, leading to high surface tension edema (Pauluhn et al., 2007). This appears to be associated with an imbalance of Starling forces composed of the colloid oncotic pressure and the hydrostatic hemodynamic pressure, which then results in a partial flooding of the alveolar space and the lung interstitium (Pauluhn et al., 2007).

The second phase of phosgene toxicity, when clinical signs and symptoms are generally lacking, may last for several hours after exposure. 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. Exposed individuals are unaware of these processes; thus, this phase is termed the "clinical latent phase". The length of this phase varies inversely with the inhaled dose.

In the third clinical phase of phosgene toxicity, the accumulating fluid in the lung results in the edema becoming apparent both directly and indirectly. The severity of the edema increases, potentially resulting in decreased gas exchange as the fluid gradually rises from the alveoli to the proximal segments of the respiratory tract. Agitated respiration may cause the protein-rich fluid to take on a frothy consistency. A severe edema may result in an increased concentration of hemoglobin in the blood and congestion of the alveolar capillaries. In general, this phase peaks approximately 24 h after an acute exposure and, assuming lethality does not occur, recedes over the next 3–5 days.

Increased levels of protein in bronchoalveolar lavage has been shown to be among the most sensitive endpoints characterizing the early, acute effects of phosgene exposure (Hatch et al., 1986; Sciuto, 1998; Pauluhn, 2006a,b,c). However, increased lung protein from low level, repeat exposures tends to diminish with time (Hatch et al., 2001; Kodavanti et al., 1997) and is rapidly reduced after the cessation of exposures (Pauluhn et al., 2007). With continuous, chronic low-level phosgene exposure, edema may transition to persistent cellular inflammation leading to the synthesis of abnormal, Type I collagen and pulmonary fibrosis. An increased synthesis of Type I relative to Type III collagen can lead to chronic fibrosis (Pauluhn et al., 2007).

2. Occupational epidemiology studies

Only one occupational epidemiological study of phosgene was considered for possible use in the derivation of an RfC. The effect of occupational exposure to phosgene was examined in workers employed from 1943 to 1945 at a uranium processing plant in the United States (Polednak and Hollis, 1985; Polednak, 1980). However, the exposure period covered by the study was short (generally 2 months to 1 year), exposed groups were small, and exposure levels were not well documented. Consequently, evidence presented in this study is inadequate to assess the chronic toxicity of phosgene.

3. Studies in animals

Primarily because of phosgene's early use as a war gas, many exposure studies have been performed over the past 100 years to examine the effects and mode of action of phosgene following a single, acute (less than 24 h) exposure. A brief overview of the acute exposure research, focusing on recent studies that may provide insights into the interpretation and human relevance of the few repeat exposure studies available, is provided. Only a few studies in rats (Kodavanti et al., 1997; Selgrade et al., 1995; Franch and Hatch, 1986) and dogs (Clay and Rossing, 1964; Rossing, 1964) examined the effects of repeated short-term, exposures over 2–12 weeks. These subchronic studies are more relevant to the derivation of a chronic RfC and are described separately and in more detail below.

3.1. Acute exposures

Many studies have examined the effects of acute phosgene exposure in animals and several recent reviews have been written (AEGL, 2004; U.S. EPA, 2005; Pauluhn, 2006a,b,c, Pauluhn et al., 2007). Human data are limited to case studies following accidental exposures and have been deemed less appropriate for the derivation of acute emergency exposure guidelines than controlled