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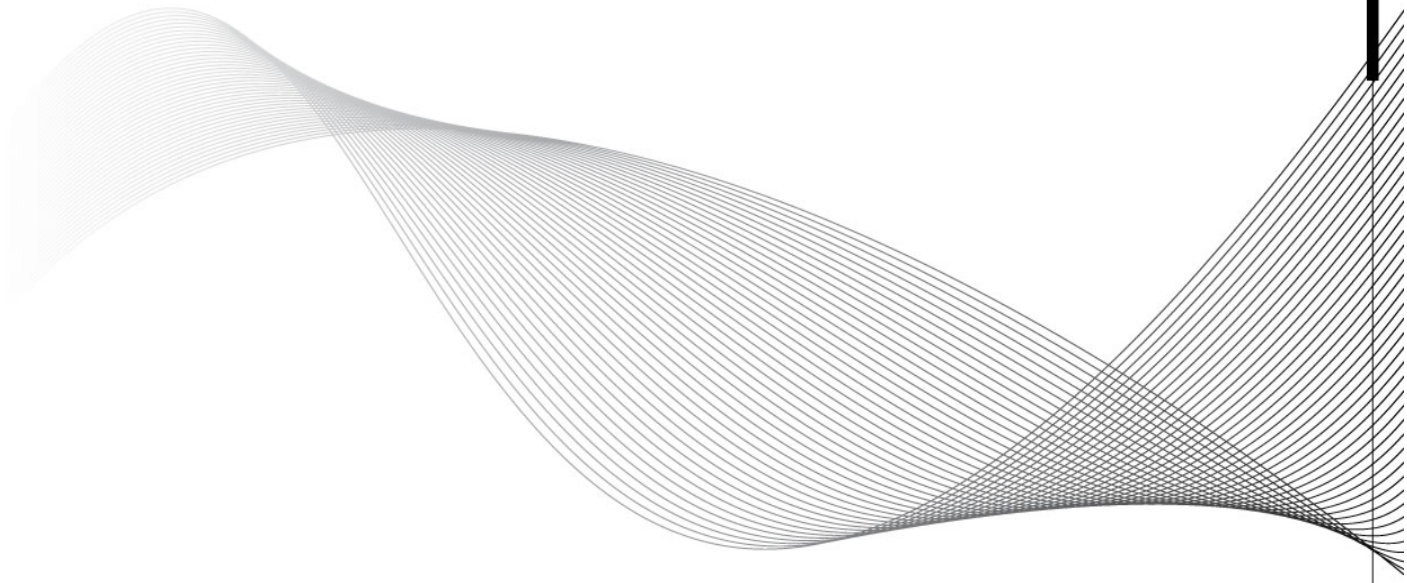

Recommendation from the Scientific Committee on Occupational Exposure Limits for phosgene

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8 hour TWA:	0.1 ppm (0.4 mg/m^3)
STEL (15 mins):	0.5 ppm (2.0 mg/m^3)
Additional classification:	-
BLV:	-

This updated evaluation of a previous assessment by SCOEL (SEG/SUM 4) is based on the MAK documentation on phosgene (Greim 2008), which includes the newest studies on acute inhalation effects of phosgene designed to verify the concentration x time = const. relationship and time-course changes in regard to pulmonary injury (lung edema probed by bronchoalveolar lavage) and to analyse species differences in rats and dogs, which are discussed extensively in this documentation. An extensive overview over the literature on the toxicity of phosgene up to 1997 is contained in IPCS (1997).

Substance identification:

Synonyms : Carbonyl chloride, carbon oxychloride

EU Classification :

Press. Gas	H330	Fatal if inhaled
Acute Tox. 2 *	H314	Causes severe skin burns and eye damage
Skin Corr. 1B		

CAS No : 75-44-5

MWt : 98.92

Conversion factor (25°C, 101.3 kPa): 4.05 mg/m^3 = 1 ml/m^{3}ml/m^3 (IPCS 1997)

Phosgene is a colourless gas with a characteristic odour like wet hay. It has a MPt of -127.8°C, a BPt of 7.5°C and a vapour pressure of 161.6 kPa at 20°C. Its vapour density is three-times that of air. It is soluble in benzene, toluene, acetic acid and most liquid hydrocarbons and reacts with ethanol. It is slightly water-soluble and hydrolyses quickly in water (IPCS 1997), therefore, a log Kow cannot be determined.

1. Occurrence/use and occupational exposure

Phosgene is a high volume substance used as an intermediate with a production rate in the European Community greater than 10,000 tonnes per annum. The global consumption in 2006 was 5 million tonnes per year (Pauluhn et al. 2007). It is used in the production of isocyanates as well as in the production of a variety of dyestuffs, polycarbonates and pharmaceuticals.

Phosgene can be generated accidentally when volatile organic chlorine compounds come into contact with flames or hot metal. During World War I, phosgene (in combination with chlorine) was used as a poison gas.

2. Health significance

2.1 Toxicokinetics

Phosgene vapour is lipophilic and penetrates the lower respiratory tract (alveoli) without any appreciable deposition in the airways and subsequent airway injury. In the lower respiratory tract reaction with nucleophils (acylation) predominates hydrolysis and HCl liberation. Lesions develop locally at the site of initial contact (lower respiratory tract). Systemic effects or accumulation are not seen (Greim 2008; Pauluhn et al. 2007).

2.2 Acute toxicity

2.2.1 Human data

The odour threshold is about 0.1 to 1 ppm (Henschler 1972). Acute intoxication in accidents can result in cough, burning of eyes and upper airways, increased sputum production, headache, vomiting, stomach pain, vertigo, and drowsiness. Lung oedema can occur 4 to 24 hours after intoxication (Henschler 1972). From human data generated in the 1940s it was estimated that a 150 minute exposure to 1 ppm (150 ppm x min) resulted in overt lung oedema with onset of mortality twice as high this dose (Borak and Diller 2001; Diller and Zante 1982). The nonlethal acute threshold dose in rats was 263 ppm x min . These data are not appropriate to derive an OEL.

2.2.2. Animal data

While in rats increased protein in bronchoalveolar lavage suggestive of early lung oedema occurred at 60 ppm x min, in dogs the exposure dose to 124 ppm x min caused only minimal protein elevations in bronchoalveolar lavage without macroscopic or microscopic evidence of oedema. Overt lung oedema occurred in this species at 263 ppm x min. At all exposure levels pulmonary injury as a result of acute lung oedema was reversible without sequelae late in onset (Pauluhn et al. 2007).

Transient changes in arachidonic acid metabolism have been reported following a 4 hour exposure of rats to 0.1 ppm (0.4 mg/m^3) phosgene (Madden et al., 1991). Time-course and dose-related changes of this very sensitive parameter were less consistent than endpoints mirroring lung oedema, such as protein in bronchoalveolar lavage. Therefore, this study was not taken as the basis for recommending the exposure limits.

A study reported by Selgrade et al. (1989) indicated that exposure of mice to 0.025 ppm (0.1 mg/m^3) phosgene for 4 hours increased their susceptibility to bacterial infection and also to lung tumour formation following inoculation of melanoma cells. However, this study design is unusual and has not been adequately validated. There is mounting experimental evidence to suggest that alterations in the level or activity of antimicrobial factors in lung surfactant contribute to deficiencies in host defense. Therefore, these findings are considered to be secondary to increased plasma extravasation. In addition, there is evidence that mice and rats may be more sensitive than humans to typical deep lung irritants due to their relatively

greater minute volume per kg body weight (Andersen, 1983; Filser, 1992). The SCOEL thus considered that the Selgrade study should not be used as the basis for proposing a limit value.

A lot of data on the acute lethality of phosgene were obtained in animals. Most of the studies are rather old and confounded by improper methodology used (see Greim 2008). Reliable studies which followed OECD test guideline 403 focussed on the dependence of mortality and early markers of lung toxicity on concentration and time of exposure (Pauluhn 2006 a, b, c) and are summarized in the following:

After acute exposure of Wistar rats (directed-flow nose-only) for 10 to 240 minutes to phosgene, LC_{50} values ranged from 8.6 mg/m³ (2.1 ppm; 240 minutes exposure) to 253 mg/m³ (62.5 ppm; 10 minutes exposure) (see Table 1).

Table 1: Acute toxicity of phosgene in Wistar rats with nose-only exposure (Pauluhn 2006 a)

Exposure duration (min)	LC_{50} (95% confidence interval) (mg/m³)	LCt_{50} (mg/m³ x min)
10	253 (194-331)	2533
30	54.5 (48-62)	1635
60	31.3 (28-35)	1878
240	8.6	2064

Mortality occurred within 24 hours and was due to acute lung oedema. LCt_{50} (LC_{50} x exposure duration) was almost constant for the 4 exposure conditions. Within the first 10 minutes of exposure a reflectory depression of the inhalation rate due to acute irritation was measured. This explains why the LCt_{50} after 10 minutes is higher than after longer exposures (Table 1). The calculated LC_{01} values were 105.3, 29.2, 21.1 and 5.0 mg/m³ (26, 7, 5, 1.3 ppm) for 10, 30, 60 and 240 min exposure, respectively. The average LCt_{50} (and confidence interval 95%) and LCt_{01} were 1741 (1547-1929) mg/m³ x min and 1075 mg/m³ x min, respectively, with a LCt_{50}/LCt_{01} ratio of 1.6., indicating a very steep exposure-mortality relationship (Pauluhn 2006 a).

Male Wistar rats were exposed (directed-flow nose-only) 30 or 240 minutes to phosgene with recovery phases of 4 and 12 weeks. In the experiment with 30 minutes exposure time, phosgene concentrations of 0.94, 2.02, 3.89, 7.35 or 15.36 mg/m³ (0.23, 0.5, 0.9, 1.8, 3.8 ppm) were used, which corresponds to c x t-products of 28.2, 60.6, 116.7, 220.5 and 460.8 mg/m³ x min. The 240 minutes exposures were conducted with 0.096, 0.387, 0.786, 1.567 or 4.2 mg/m³ (0.023, 0.1, 0.2, 0.4, 1 ppm) yielding c x t-products of 47.0, 92.9, 188.6, 376 and 1008 mg/m³ x min. The bronchoalveolar lavage (BAL) fluid of six rats/group was examined on days 1, 3, 7, 14 or 84 after exposure. Animals exposed to 1008 mg/m³ x min were investigated at days 1, 7, 14 and 28 only. None of the exposures induced lethality. The most important effect markers in the BAL fluid were increases in protein, soluble collagen and neutrophil granulocytes. The maximal changes of these parameters were seen at day 1 at 188.6 mg/m³ x min and above, whereas the total cell count in the BAL fluid and the number of alveolar macrophages with phospholipids inclusions reached their maximal value at day 3. Similar c x t-products induced slightly lesser changes in the BAL fluid after 30 minutes exposures, probably due to the hypoventilation during the first 10 minutes of exposure (see above). At 376 mg/m³ x min and above, noncollapsed lungs, focal discolorations, and/or enlarged lymph nodes were found at postexposure days 1 to 7. At 1008 mg/m³ x min frank lung oedema was observed at postexposure day 1 and a minimal to slight hypercellularity in the terminal bronchioles with focal peribronchiolar inflammatory infiltrates and focal septal thickening was found after 4 weeks recovery. At lower c x t-products, the rats were unremarkable after 12 weeks of recovery. On the basis of the most

sensitive indicators in the BAL fluid, c x t-products up to 116.7 mg/m³ x min did not lead to adverse effects whereas at 188.6 mg/m³ x min and above, protein in the BAL fluid increased significantly (Pauluhn 2006 b).

A similar study was conducted in beagle dogs (head-nose-exposure), which were exposed for 30 minutes to phosgene concentrations of 9, 16.5 or 35 mg/m³ (2.2, 4.0, 8.7 ppm) resulting in c x t-products of 270, 495 and 1050 mg/m³ x min. None of the exposures induced lethality. No effects were found at 270 mg/m³ x min (NOAEL). Slight inflammatory reactions were seen in the bronchio-alveolar region of the lungs at 495 mg/m³ x min as well as marginal increases of lung weights, protein and collagen concentrations in the BAL fluid and increased numbers of neutrophil granulocytes. At 1050 mg/m³ x min these changes were more marked and additionally, pulmonary serofibrinous exudate and oedema were seen. The threshold dose for increased protein in the BAL fluid was calculated to be 375 mg/m³ x min (Pauluhn 2006 c).

The comparative analysis (Pauluhn 2006 c) of the most sensitive endpoint "protein concentration in the BAL fluid" in the acute inhalation studies in rats (Hatch et al. 2001; Pauluhn 2006 b) with an exposure duration of 0.5 to 6 hours showed a linear dependence of this endpoint on the c x t-product. Early pulmonary changes after a single exposure are therefore dependent on the total dose and not on the concentration alone. The same is true for the study in dogs (Pauluhn 2006 c), however, similar c x t-products induced 5-fold lower increases of protein in the BAL fluid as in rats. Phosgene exposures which induced protein concentrations in the BAL fluid 70 to 100-fold higher than in controls did not lead to mortality in rats (Hatch et al. 2001, Pauluhn 2000 b, c). A 30-fold increase of the protein concentration in patients with "acute respiratory distress syndrome" is evaluated as being lethal (Pittet et al. 1997). This seemingly decreased susceptibility of rats could be due to rodent-specific reflectory bronchio-pulmonary protection mechanisms (Lee und Widdicombe 2001; Persson et al. 1996), which increase the protein concentration in the BAL fluid in addition to the irritative lesion of the blood-air-barrier. Similar changes in humans are typically not reflex-mediated but only seen in conjunction with inflammatory reactions (Folkesson et al. 1996; Persson et al. 1996). Another reason for this species-difference might be due to the specific lavage technique (lavage of the complete lung including the respiratory airways) employed in the rat study (Pauluhn 2006 c).

For some subclinical biochemical endpoints species differences exist (Sciuto 1998). Reflex-mediated neurogenic vasodilatation or the different concentration of antioxidants in the fluid films lining the airways are probably responsible. Regarding concentrations of antioxidants, the glutathione concentration in the BAL fluid of rats is 20-fold lower than that of humans (Hatch 1992).

In addition to the oro-nasal breathing patterns, also the anatomical structures of the lungs of Beagle dogs are similar to human lungs (Heyder and Takenaka 1996; Kreyling et al. 1999; Takenaka et al. 1996, 1998). Beagle dogs and humans possess mucous producing cells in the bronchial region. The centriacinar region is the principal target structure of phosgene. The acinar morphology of dogs corresponds in principal to that of humans. The rat does not posses bronchioli alveolaris. The number of alveolar pores in the dog is similar to that of humans (Greim 2008; Pauluhn et al. 2007).

Species differences in the ventilation rates between rats (1 L/kg) and dogs 0.4 L/kg) result in a higher lung exposures in rats as compared to dogs. The ventilation rate of humans (0.2 L/kg) is even lower (see Bide et al., 2000; Pauluhn and Thiel, 2007).

Therefore, the studies in dogs are more relevant to humans than the results of the studies with the more susceptible rats.

2.3 Irritation and corrosivity

2.3.1 Human data

Slight irritation of eyes and nose is noticed at 2 ppm and higher and concentrations of 5 ppm and higher are unbearable (Henschler 1971). These observations date from the 1920s and impurities like chlorine and the hydrolysis product hydrogen chloride might have been responsible for the effects (Pauluhn et al. 2007).

2.3.2 Animal data

Phosgene exposure can result in eye and skin irritation (no further information, IPCS 1997).

2.4 Sensitisation

No data.

2.5 Repeated dose toxicity

2.5.1 Human data

Epidemiological studies indicate no adverse effects following long-term exposure levels averaging about 0.1 ppm (0.4 mg/m^3) with peak exposures up to 0.5 ppm (2 mg/m^3) (Henschler 1984). However, they are not considered to be sufficiently reliable and conclusive as to be used as the basis for evaluation.

2.5.2 Animal data

Groups of 8 to 12 male F344 rats were whole body-exposed for 6 hours/day to air or phosgene. The groups inhaling phosgene concentrations of 0.1 and 0.2 ppm were exposed 5 times/week, the 0.5 ppm group twice per week and the 1 ppm-group once per week. The animals were exposed for 4 or 12 weeks and additional recovery groups were held 4 weeks without exposure. There was no mortality. Minimal thickening in the bronchio-alveolar region and influx of inflammatory cells were seen in the group exposed to 0.1 ppm. Some of the changes seen after 4 weeks exposure to 0.1 ppm were reversible after 12 weeks exposure and all were reversible after 4 weeks recovery. None of the changes increased in grade with time in this group. At 0.2 ppm and higher, the relative lung weight was increased, the histological effects were more marked and collagen deposition was noted. Body weights were diminished in the 0.5 and 1 ppm groups and collagen as well as elastin was significantly increased in the lung homogenate. Some of the lesions described were also found qualitatively in control animals (Table 2) (Kodavanti et al. 1997). A NOAEC cannot be derived from this study. The LOAEC for marginal effects is 0.1 ppm, which corresponds to a concentration-time product of 144 mg/m^3 x min. (36 ppm x min) Taking into account the C x t relationship found following single inhalation exposure of rats, 117 mg/m^3 x min (29 ppm x min) was the no-observed-adverse-effect concentration (NOAEC) based on elevated protein in bronchoalveolar lavage fluid. This similarity supports the conclusion that the threshold dose following subchronic exposure is determined by recurrent acute alveolar irritation and not chronic exacerbation.

SCOEL notes that even this repeated dose study does not contradict time and dose dependency according to Haber's law. Exposures of 0.2 ppm 5 times per week induces higher effects than 0.1 ppm 5 times per week, whereas 1 ppm once a week showed an about similar toxic potency than the 0.2 ppm exposure regimen.

Tab. 2. Histological findings and severity scores after 4 and 12 weeks whole body exposure of rats to phosgene (Kodavanti et al. 1997)

	4 weeks				12 weeks			
Phosgene-concentration (ppm)	0	0.1	0.2	1.0	0	0.1	0.2	1.0
n	12	8	8	6	12	8	8	8
alveolar effusion	0	0	0	2 (0.33)	0	0	0	1 (0.13)
alveolus, interstitial thickening	0	2 (0.25)	5 (0.63)	6 (1.83)	0	2 (0.25)	4 (0.5)	8 (2.13)
bronchus, epithelial alteration	0	1 (0.13)	2 (0.5)	2 (0.33)	0	0	1 (0.13)	1 (0.25)
bronchus, inflammation	1 (0.08)	2 (0.25)	2 (0.4)	3 (0.83)	0	0	0	1 (0.13)
terminal bronchiole/alveolus: inflammatory cell influx	2 (0.17)	3 (0.38)	8 (1.0)	6 (3.0)	1 (0.08)	3 (0.38)	8 (1.13)	8 (2.13)
terminal bronchiole/peribronchiolar alveolus, epithelial alteration	2 (0.17)	4 (0.5)	5 (0.63)	6 (2.50)	0	1 (0.13)	7 (0.88)	8 (2.38)
terminal bronchiole/peribronchiolar: increased collagen staining	1 (0.08)	1 (0.13)	8 (1.0)	6 (1.0)	2 (0.17)	2 (0.25)	8 (1.0)	8 (2.0)

n: number of animals examined;

numbers in parentheses are group means of individual severity scores: 0: not remarkable, 1: minimal, 2: slight, 3: moderate, 4: moderately severe; 5: severe; maximum severity score observed was 3

Protein concentrations in the BAL fluid of the animals used in the study of Kodavanti et al. (1997) study were compared to those of rats exposed only once to the same concentrations. Whereas the single exposure to 0.2 ml/m3 (0.8 mg/m3) induced a 10-fold increase, the repeated exposure did not increase the protein concentration (Hatch et al. 2001). This result indicates that adaptation to the effects of phosgene is possible.

Studies conducted by Franch and Hatch (1986) confirm that exposure of rats to 0.25 ppm (1.0 mg/m3) phosgene for 17 days (4 hours/day) lead to irritation of the lower respiratory tract. A NOAEL of 0.125 ppm (0.5 mg/m3, 120 mg/m3 x min) was established.

These studies show that the pulmonary effects of phosgene are in principal dose-dependent and can be described by Haber's law (cn x t = constant; n = 1). Consequently the results including the NOELs of short-term exposure studies can be extrapolated to long-term exposure, which is further supported by the results of long-term exposure studies in rats. The applicability of Haber's law is justified by the following observations:

Acute high exposure of rats for 10 to 240 minutes each at five different concentrations resulted in almost the same LC50 x time product (LC50 x exposure duration, see Table 1).

Acute exposure of rats for 30 to 240 minutes at different concentrations resulted in an NOEL of 116.7 mg/m3 x min (Pauluhn 2006b).

From a 17 days inhalation study in rats (4 hrs daily) a NOEL of 120 mg/m3 x min has been calculated (Franch and Hatch 1986).

A prolonged inhalation study in rats (4 and 12 weeks at different concentrations for different times) resulted in an LOEL of marginal effects for which the c x t product is 144 mg/m3 x min (Kodavanti et al 1997).

In dogs, which have been exposed to 30 min at different phosgene concentrations, the effects also followed Haber's law. Based on protein in BALa the NOEL was 270 mg/m3 x min (68 ppm x min) (Pauluhn 2006c).

3.6 Genotoxicity

3.6.1 In vitro

Phosgene did not induce mutations in Salmonella thyphimurium TA98 and TA100 in presence and absence of metabolic activation (Henschler 1984).

3.6.2 *In vivo*

No data.

3.7 Carcinogenicity

No data.

3.8 Reproductive toxicity

No data.

As phosgene is quickly hydrolysed (see 3.1) it is not plausible that unhydrolysed phosgene reaches the the developing fetus. Brain lesions which were seen after high exposure concentrations can be ascribed to the secondary effects of anoxia due to lung oedema (Greim 2008).

Recommendations

The target organ/critical effect of phosgene is acute irritation of the mucous membranes of the respiratory tract and direct damage of the alveolar capillary membrane and subsequently delayed pulmonary oedema. Recent studies by Pauluhn (2006 a, b,c) in rats and dogs have shown, that these effects are time and dose dependent and follow Haber's law.

It has been shown that dogs are less sensitive than rats (Pauluhn 2006 c). Since the dog lung is anatomically and physiologically closer related to the human lung compared to the rat (Pauluhn et al. 2007), studies in dogs are more relevant than studies in rats for deriving an OEL. In dogs, an exposure to 9 mg phosgene/m3 (2 ppm) for 30 minutes (270 mg/m3 x min) did not increase the protein concentration in the BAL fluid used as a sensitive marker for inflammatory reactions in the lung (Pauluhn 2006 c). According to Haber's law, this dose corresponds to 0.14 ml/m3 for an 8 hour exposure. Interindividual differences in susceptibility, which might be due to different enzyme activities are not relevant, because phosgene reacts locally without prior metabolism. This assumption is verified by the similar protein concentration in the BAL fluid of the 4 dogs exposed to 270 mg/m^3 x min. Due to the higher ventilation rate (dogs 0.4 L/kg, humans 0.2 L/kg) the same air concentration results in a higher lung exposure in dogs than in humans. This renders dogs more sensitive than humans so that an additional

assessment factor is not needed and an OEL for phosgene of 0.1 ml/m^3 (0.4 mg/m^3) is derived.

A STEL of 0.5 ppm (2.0 mg/m^3 is proposed which is based on the NOEL of 2 ppm in dogs at 30 min exposure and considering 4 events per shift during 15 min each.

There are no data, which warrant "skin" and "sensitiser" notations.

At the levels recommended no measurement difficulties are foreseen.

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