



Grunnlag for fastsettelse av administrativ norm

Grunnlagsdokument for
Fosgen (CCl₂O)

Tittel: Grunnlag for fastsettelse av administrativ norm. Grunnlagsdokument for fosgen (CCl₂O).

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av administrativ norm for fosgen (CCl₂O).



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Forord

Arbeidstilsynet har ansvaret for revisjonsprosessen og utarbeidelse av grunnlagsdokumenter for stoffene som blir vurdert. Beslutningsprosessen skjer gjennom en høring, orienteringsmøter og drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen deltar. Konklusjonene fra drøftingsmøtene forelegges Direktøren i Arbeidstilsynet som tar den endelige beslutningen.

EU-rådets direktiv 98/24/EC (Vern av helse og sikkerhet til arbeidstakere mot risiko i forbindelse med kjemiske agenser på arbeidsplassen) av 7. april 1998 stiller krav om at kommisjonen skal legge frem forslag til indikative grenseverdier for eksponering av visse kjemikalier som medlemslandene må innføre på nasjonalt nivå. De nasjonale verdiene kan være høyere, dersom et medlemsland mener at det er nødvendig av tekniske og/eller økonomiske hensyn, men landene bør nærme seg den indikative verdien. Direktivet stiller krav om at indikative grenseverdier vedtas gjennom kommisjonsdirektiv.

I hovedsak er grunnlaget for normsettingen av stoffene i denne revisjonen utarbeidet i forbindelse med implementering av kommisjonsdirektiv 2000/39/EC. Direktivet ble implementert uten at grunnlaget for at Norge hadde en høyere verdi ble begrunnet. For flere av disse har EU også foreslått en korttidsverdi som Norge på det tidspunktet manglet regelverk for å kunne innføre. I tillegg mangler Norge en administrativ norm for platina (metallisk) som var gitt i direktiv 91/322/EEC. Dette tilsier at det toksikologiske grunnlaget for disse normene bør oppdateres.

Det toksikologiske grunnlaget for stoffene i denne revisjonen baserer seg på kriteriedokumenter fra EUs vitenskapskomité for fastsettelse av grenseverdier, Scientific Committee for Occupational Exposure Limits (SCOEL). SCOEL utarbeider de vitenskapelige vurderingene som danner grunnlaget for anbefalinger til helsebaserte grenseverdier, og disse legges fram for kommisjonen.

Statens arbeidsmiljøinstitutt (STAMI) ved Toksikologisk ekspertgruppe for administrative normer (TEAN) bidrar med faglige vurderinger i dette arbeidet. TEAN vurderer og evaluerer de aktuelle SCOEL dokumentene og presiserer kritiske effekter når det er behov for det og dersom informasjonen er tilgjengelig i dokumentene. Videre søker og evaluerer TEAN nyere litteratur etter utgivelsen av dokumentet, og vurderer behov for korttidsverdier ut i fra den foreliggende dokumentasjonen. TEANs vurderinger om behov for korttidsverdier tar utgangspunkt i SCOEL's metodedokument, "Methodology for the derivation of occupational exposure limits: Key documentation (version 6)". Dette er inkludert i TEANs Metodedokument del B (Prosedyre for utarbeidelse av toksikologiske vurderinger for stoffer som skal implementeres i den norske administrative norm liste etter direktiv fra EU-kommisjonen) utarbeidet for revisjonen.

Informasjon om bruk og eksponering i Norge innhentes fra Produktregisteret, EXPO databasen ved STAMI og eventuelle tilgjengelige måldata fra virksomheter/næringer.



Innledning

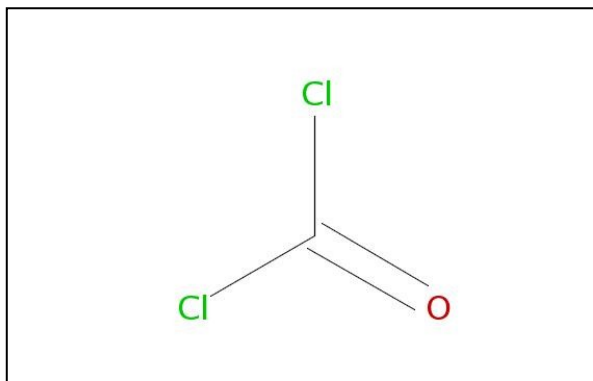
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av administrativ norm for fosgen. Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for fosgen (vedlegg 1), samt vurderinger og kommentarer fra Toksikologisk Ekspertgruppe for Administrative Normer (TEAN).

1. Stoffets identitet

Fosgen, synonymer av stoffets navn, stoffets identifikasjonsnummer i Chemical Abstract Service (CAS-nr.), European Inventory of Existing Commercial chemical Substances (EINECS-nr. el. EC-nr.) og indekseringsnummer (Indeks-nr.) i EINECS er gitt i tabell 1. Strukturformel av fosgen er vist i figur 1.

Tabell 1. Stoffets navn og identitet.

Navn	Fosgen (CCl₂O)
Synonymer	Karbonylklorid, karbonoksyklorid
CAS-nr.	75-44-5
EC-nr.	200-870-3
Indeks-nr.	006-002-00-8



Figur 1. Strukturformel av fosgen.

2. Grenseverdier

2.1. Nåværende administrativ norm

Nåværende administrativ norm i Norge for fosgen er: 0,05 ppm, 0,2 mg/m³ med anmerkning T for takverdi.

2.2. Grenseverdi fra EU

I direktiv 2000/39/EC foreslås:

IOELV (Indicative Occupational Exposure Limit Value): 0,02 ppm, 0,08 mg/m³

STEL (Short Term Exposure Limit): 0,1 ppm, 0,4 mg/m³

Den europeiske vitenskapskomiteen, SCOEL foreslår i sitt 2011 kriteriedokument:

8-timers TWA: 0,1 ppm, 0,4 mg/m³

STEL (15 minutter): 0,5 ppm, 2,0 mg/m³

2.3. Grenseverdier fra andre land og organisasjoner

Nåværende grenseverdier for fosgen fra andre land og organisasjoner er gitt i tabell 2 nedenfor.

Tabell 2. Grenseverdier for fosgen fra andre land og organisasjoner.

Land/organisasjon	Kilde	Grenseverdi	Anmerkning
Sverige	Arbetsmiljöverkets Författningssamling, AFS 2005:17 ¹	Takgrenseverdi: 0,05 ppm, 0,2 mg/m ³	
Danmark	At-vejledning, stoffer og materialer - C.0.1, 2007 ²	8-timers verdi: 0,02 ppm, 0,08 mg/m ³	
Finland	HTP-värden 2007 ³	8-timers verdi: 0,02 ppm, 0,08 mg/m ³ Korttidsverdi: 0,05 ppm, 0,2 mg/m ³	Takverdi
Storbritannia	EH40 ⁴	8-timers verdi: 0,02 ppm, 0,08 mg/m ³ Korttidsverdi: 0,06 ppm, 0,25 mg/m ³	
Nederland	The Social and Economic Council of the Netherlands (SER), Occupational exposure limits database ⁵	8-timers verdi: 0,08 mg/m ³ Korttidsverdi: 0,4 mg/m ³	
OSHA, USA	OSHA Permissible Exposure Limits, PELs	8-timers verdi: 0,1 ppm, 0,4 mg/m ³	
ACGIH, USA	ACGIH Guide to occupational Exposure Values, 2012 ⁶	8-timers verdi: 0,1 ppm, 0,4 mg/m ³	
NIOSH, USA	ACGIH Guide to occupational Exposure Values, 2012 ⁶	8-timers verdi: 0,1 ppm, 0,4 mg/m ³ Korttidsverdi:	Takverdi



		0,2 ppm, 0,8 mg/m ³	
Tyskland, MAK	DFG, 2011	8-timers verdi: 0,1 ppm, 0,4 mg/m ³	Takverdi
Tyskland, Myndighetene	BauA ⁸	8-timers verdi: 0,1 ppm, 0,41 mg/m ³	Überschreitungsfaktor 2(I)

¹ http://www.av.se/dokument/afs/AFS2005_17.pdf

² <http://www.at.dk/~media/3FA26655715740ED84EA28EC1191FB62.ashx>

³ Social og helsevårdsministeriet, HTP-værdien, Koncentrationer som befunnits skadlige, Publikationer 2007:20, Helsingfors, http://www.stm.fi/c/document_library/get_file?folderId=39503&name=DLFE-6905.pdf

⁴ <http://www.hse.gov.uk/pubns/priced/eh40.pdf>

⁵ http://www.ser.nl/en/oel_database.aspx

⁶ Guide to occupational exposure values compiled by ACGIH, 2012.

⁷ Deutsche Forschungsgemeinschaft, List of MAK and BAT values 2011, Commission for the Investigation of Health hazards of Chemical Compounds in the Work Area, report No. 47, 2011, Wiley-VCH, Tyskland.

⁸ http://www.baua.de/de/Themen-von-A-Z/Gefahrstoffe/TRGS/pdf/TRGS-900.pdf;jsessionid=EB7292E8B7DED5F0931D016EBF4ACF0B?_blob=publicationFile&v=7

2.4. Stoffets klassifisering

Forskrift om klassifisering, merking m.v. av farlige kjemikalier (merkeforskriften) blir erstattet av CLP (*Classification, Labelling and Packaging of substances and mixtures*) som er de nye reglene for klassifisering, merking og emballering av stoffer og stoffblandinger i EU. CLP vil gradvis fase ut merkeforskriften, og CLP og merkeforskriften vil gjelde parallelt fram til 1. juni 2015.

Merkeforskriften

Fosgen har følgende klassifisering i henhold til merkeforskriften: Meget giftig, T+; R26: Meget giftig ved innånding, C; R34: Etsende.

CLP

Fosgen er i henhold til CLP Annex VI, tabell 3.1 (Liste over harmonisert klassifisering og merking av farlige kjemikalier) klassifisert og merket i ulike fareklasser, med faresetninger og koder, som gitt i tabell 3 nedenfor.

Tabell 3. Fareklasse¹, kategorier² og merkekoder³ angitt for fosgen. Feill Bokmerke er ikke definert.

Fareklasse	Faresetning (R)	Merkekode
Gasser under trykk		
Akutt giftig, kategori 2	Dødelig ved innånding	H330
Etsende eller irriterende for huden, kategori 1B	Gir alvorlige etseskader på hud og øyne	H314

¹ <http://www.klif.no/no/Tema/Kjemikalier/Klassifisering-og-merking-av-kjemikalier-CLP/Klassifisering-CLP-avsnitt-I-II-og-V/>

² <http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database>

³ <http://www.klif.no/upload/arbeidsomr/kjemikalier/aktuelt/H-setninger2.pdf>



3. Fysikalske og kjemiske data

Fosgen er en svært giftig gass som virker etsende på øyne, hud og slimhinner og kan forårsake lungeskade.

Fosgen er ikke brennbart. Gassen kan fremtre som fargeløs eller hvit til svak gul og konverteres til væske ved avkjøling og trykk. Ved lave konsentrasjoner har fosgen en behagelig duft av nyslått høy, mens ved høye konsentrasjoner kan lukten være sterk og ubehagelig.

Fosgen er løselig i benzen, toluen, eddiksyre og de fleste flytende hydrokarboner. Den er noe løselig i vann og hydrolyseres lett i vann.

Det vises til tabell 4 for fysikalske og kjemiske data for fosgen.

Tabell 4. Fysikalske og kjemiske data (Amore og Huhtala, 1983) for fosgen

Kjemisk formel	CCl ₂ O
Molekylvekt	98,92
Fysisk tilstand	Fargeløs gass med lukt som fuktig høy
Smeltepunkt (°C)	- 127,8
Kokepunkt (°C)	7,5
Tetthet (20 °C)	1,381
Løselighet i vann (20 °C)	noe løselig, hydrolyseres i vann
Fordelingskoeffisient n-oktanol/vann (log Kow)	- 0,710
Damptrykk ved 20 °C (kPa)	161,6
Damptetthet (air = 1) (g/cm³)	3,48
Lukterskel (ppm)	0,90* (0,1 – 1,0 ppm)
Omregningsfaktor (20 °C, 101 kPa)	1 ppm = 4,05 mg/m ³



3.1 Forekomst og bruk

Fosgen forekommer ikke i naturen, men dannes når klorerte hydrokarboner utsettes for høy temperatur. Den kan utilsiktet dannes når flyktige organiske klorholdige forbindelser kommer i kontakt med flammer eller varmt metall.

Fosgen er en meget giftig gass som ble brukt som stridsgass under første verdenskrig.

4. Toksikologiske data og helseeffekter

Vurdering av toksikologiske data og helseeffekter av fosgen er angitt i SCOEL dokumentet på engelsk i vedlegg 1, og kommentarer fra TEAN er gitt i kapittel 4.2.

4.1. Anbefaling fra SCOEL

Anbefaling fra SCOEL er vedlagt (vedlegg 1).

4.2. Kommentarer fra TEAN

Kriteriedokumentet fra SCOEL som ble lagt til grunn for implementeringen av direktivet 2000/39/EU, er opprinnelig fra tidlig 90-tallet med siste litteraturreferanse er fra 1991. I januar 2012 ble en ny og oppdatert versjon av SCOEL's kriteriedokument for fosgen gjort tilgjengelig. Dette dokumentet er datert september 2011, og inneholder vesentlig nyere dokumentasjon med siste referanse fra 2009. Dette dokumentet blir lagt til grunn for denne vurderingen av TEAN.

Det er søkt etter nyere kriteriedokumenter for stoffet fra anerkjente institusjoner som utarbeider slike. Det er også gjort litteratursøk ved hjelp av "Pubmed" og "Web of Knowledge" for perioden 2009 til 2012. Data fra studier av fosgen publisert etter utgivelsen av siste SCOEL-dokument vil ikke endre på vurderinger som er gjort av SCOEL med hensyn på kritiske effekter og dose-respons relasjoner.

De kritiske effektene av fosgen er akutt irritasjon av slimhinner i luftveiene og direkte skade av membraner i alveolære kapillærer og påfølgende lungeødem. Nyere studier i rotter og hunder har vist at disse effektene er både tids- og doseavhengig og følger Haber's lov. På grunnlag av studiene til Pauluhn (2006 a,b,c) tar SCOEL utgangspunkt i en NOAEL i hund på 2 ppm (9 mg/m^3) eksponert for fosgen over 30 minutter, som i henhold til Haber's lov tilsvarer $67 \text{ mg/m}^3 \times \text{min}$ ($270 \text{ ppm} \times \text{min}$) eller 0,14 ppm for 8 timers eksponering. NOAEL i disse studiene blir bestemt på grunnlag av økning av proteinkonsentrasjonen i "bronchoalveolar lavage" (BAL) væsken, som er den mest sensitive markøren for inflammasjon i lungene, og som dermed danner grunnlaget for en OEL.

TEAN sier seg enig med SCOEL at fosgen bør ha en grenseverdi for korttids eksponering (STEL) for å beskytte mot skader i lungene.



5. Bruk og eksponering

I EU anvendes fosgen i stort omfang, over 10000 tonn per år. Gassen brukes i hovedsak som intermediet i kjemisk industri blant annet til fremstilling av isocyanater, polyuretan- og polykarbonater, plantevernmidler og til legemidler.

På verdensbasis var forbruket i 2006 over 5 millioner tonn per år.

5.1. Opplysning fra Produktregistret

Det er ikke funnet opplysninger om mengde og bruk av fosgen i deklareringspliktige produkter i Produktregisterets årsoppdatering for 2010.

5.2. Eksponering og måledokumentasjon

5.2.1. EXPO- data

Det foreligger ingen eksponeringsmålinger for fosgen i STAMIs eksponeringsdatabase EXPO.

5.2.2. Prøvetakings- og analysemetode

I tabell 5 er anbefalte metoder for prøvetaking og analyser av fosgen presentert.

Tabell 5. Anbefalte metoder for prøvetaking og analyse av fosgen.

Prøvetakingsmetode	Analysemetode	Referanse
Rør m/XAD-2 impregnert m12-HMP	Gasskromatografi m/NPD	OSHA metode 61 ¹
Rør m/Chromosorb W impregnert m/2-PP	Væskekromatografi m/UV	Rando et al., 1993

¹ www.osha.gov/dts/sltc/methods/toc.html

6. Vurdering

Toksikologiske data for fosgen er beskrevet i SCOEL-dokumentet i vedlegg 1, og kommentert av STAMI (TEAN) i kapittel 4. De tilgjengelige toksikologiske dataene for fosgen viser at stoffet er svært giftig. Kritisk effekt av eksponering for fosgen er akutt irritasjon av slimhinner i luftveiene og direkte skade på membraner i alveolære kapillærer og påfølgende lungeødem.

Toksikologiske data for fosgen er beskrevet i SCOEL-dokumentet i vedlegg 1, og kommentert av STAMI (TEAN) i kapittel 4. De tilgjengelige toksikologiske dataene for fosgen viser at stoffet er svært

giftig. Studier i rotter og hunder viser at disse effektene er både tids- og doseavhengig og følger Haber's lov.

Det er ingen data verken på dyr eller mennesker på reproduksjonseffekter av fosgen og tilsvarende er det manglende data på kreftfremkallende effekter. *In vitro* studier har ikke vist gentoksiske effekter av fosgen eksponering. Fordi fosgen hydrolyseres raskt er det ikke sannsynlig at fosgen kan skade foster.

Dyrestudier er hunder og rotter blir eksponert for fosgen viser at hunder er mindre sensitive enn rotter. Siden lungene til hunder er både anatomisk og fysiologisk nærmere beslektet menneskets lunger sammenlignet med rotter, er studier foretatt på hunder mer relevante enn studier på rotter for å komme frem til en OEL (occupational exposure limit eller yrkeshygienisk grenseverdi). Ved fastsettelse av OEL for fosgen har SCOEL lagt til grunn studier på hunder der en NOAEL på 9 mg/m³ eksponert for fosgen over 30 minutter 0,14 ppm for 8-timers eksponering i henhold til Haber's lov.

I tillegg foreslår SCOEL en korttidsverdi for eksponering på 0,5 ppm, 2,0 mg/m³, med inntil 4 overskridelser for å beskytte mot skader i lungene.

Ingen vitenskapelige data tilsier anmerkning for hudopptak eller sensibiliserende effekt.

Vi har ikke eksponeringsdata for fosgen fra eksponeringsdatabasen EXPO₂ og det er ikke funnet opplysninger om mengde og bruk av fosgen i deklareringspliktige produkter i Produktregisteret årsoppdatering for 2010.

7. Konklusjon med forslag til ny administrativ norm

Kommisjonens forslag til indikativ grenseverdi (IOELV) for fosgen er gitt i direktiv 2000/39/EEC. Verdiene er for 8-timer 0,02 ppm, 0,08 mg/m³ og for korttidsverdi 0,1 ppm, 0,4 mg/m³. Denne var basert på vurderinger fra 1991. Direktivet forpliktet medlemslandene til å fastsette en nasjonal verdi for stoffene gitt i direktivet. I ettertid har SCOEL foretatt en nyere vurdering av fosgen som er datert 2009. I denne vurderingen er deres forslag til en 8-timers verdi på 0,1 ppm, 0,4 mg/m³ og en korttidsverdi på 0,5 ppm, 2,0 mg/m³.

I tabell 2 er nåværende grenseverdier for fosgen fra andre land og organisasjoner oppgitt. Verdiene fra EU landene er generelt i overensstemmelse med forlaget gitt i direktivet, mens verdiene fra OSHA (USA), Tyskland, (myndighetene) samt ACGIH, NIOSH og MAK som er av nyere dato, er vesentlig høyere og i samsvar med SCOELs vurdering fra 2011.

For fosgen har vi verken opplysninger om mengde og bruk eller data om eksponering som kan brukes til vurdering av tekniske og økonomiske forhold. Forslaget til administrativ norm baserer seg derfor på en vurdering av de toksikologiske dataene.

På bakgrunn av den foreliggende dokumentasjon forslås at dagens administrative norm endres og at eksisterende anmerkning T (takverdi) utgår. I tillegg foreslås en korttidsverdi for stoffet.

Forslag til ny administrativ norm, korttidsverdi og anmerkning:

Administrativ norm (8-timers TWA): 0,1 ppm, 0,4 mg/m³

Korttidsverdi (15 min): 0,5 ppm, 2,0 mg/m³



8. Ny administrativ norm

På grunnlag av høringsuttalelser og drøftinger med partene ble ny administrativ norm for fosgen fastsatt til:

Administrativ norm (8-timer): 0,05 ppm, 0,2 mg/m³

Anmerkning: T (Takverdi)



9. Referanser

Amoore J E, Huhtala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J. Appl. Toxicol*, 1983; 3 (6), 272 – 290



Vedlegg 1: Anbefalinger fra SCOEL

Social Europe



Recommendation from the Scientific Committee on Occupational Exposure Limits for phosgene

SCOEL/SUM/004
September 2011



European Commission





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Recommendation from the Scientific Committee on Occupational Exposure Limits for phosgene

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/m³ = 1 ml/m³ml/m³ (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/m³) 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/m³) 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, LC₅₀ 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/m ³)	LCt ₅₀ (mg/m ³ 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. LCt₅₀ (LC₅₀ x exposure duration) was almost constant for the 4 exposure conditions. Within the first 10 minutes of exposure a reflexory depression of the inhalation rate due to acute irritation was measured. This explains why the LCt₅₀ after 10 minutes is higher than after longer exposures (Table 1). The calculated LC₀₁ 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 LCt₅₀ (and confidence interval 95%) and LCt₀₁ were 1741 (1547-1929) mg/m³ x min and 1075 mg/m³ x min, respectively, with a LCt₅₀/LCt₀₁ 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

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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 reflexory 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 possess 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/m³) with peak exposures up to 0.5 ppm (2 mg/m³) (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/m³ x min. (36 ppm x min) Taking into account the C x t relationship found following single inhalation exposure of rats, 117 mg/m³ 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)

Phosgene-concentration (ppm)	4 weeks				12 weeks			
	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 ($cn \times t = \text{constant}$; $n = 1$). 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/m³ 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/m³ (0.4 mg/m³) is derived.

A STEL of 0.5 ppm (2.0 mg/m³) 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.





References

- Anderson, M.E., 1983
Flow-limited clearance. In "Modelling of Inhalation Exposure to Vapours, Uptake, Distribution and Elimination" (Fiserova-Bergerova, V., ed.) CRC Press Incorp., Boca Raton, Florida, pp 67-95.
- Bide, R.W., Armour, S.J., and Yee, E. 2000. Allometric respiration/body mass data for animals to be used for estimates of inhalation toxicity to young adult humans. *J. Appl. Toxicol.* 20: 273-290.
- Borak J., Diller W.F., 2000
Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med* 43, 110-119.
- Diller W.F., Zante R. 1982
Dosis-Wirkungs-Beziehungen bei Phosgen-Einwirkung auf Mensch und Tier. *Zentralbl Arbeitsmed* 32: 360-368
- Filser, J.G., 1992
The closed chamber technique - uptake, endogenous production, excretion, steady state kinetics and rates of metabolism. *Arch. Toxicol.* 66, 1-10.
- Folkesson H.G., Matthay M.A., Weström B.R., Kim K.J., Karlsson B.W., Hastings R.H. 1996
Alveolar epithelial clearance of protein. *J Appl Physiol* 80: 1431-1445.
- Franch, S. and Hatch, G.E., 1986
Pulmonary effects of inhaled phosgene in rats. *J. Toxicol. Environ. Hlth.* 19, 413.
- Glass, D; Mark McClanahan, Loren Koller, and Femi Adeshina, 2009 Provisional Advisory Levels (PALs) for phosgene (CG; Inhalation Toxicology, 2009, 1-22, Early Online
- Greim H. (ed.), 2008
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-Arbeitsmedizinische Begründungen von MAK-Werten, Loseblattsammlung, Phosgen, x. Lieferung, Wiley-VCH, Weinheim.
- Hatch G.E. 1992
Comparative biochemistry of airway lining fluid. In: Parent RA (ed.) Treatise on pulmonary toxicology - comparative biology of the normal lung, Vol 1, CRC Press, Boca Raton, FL, USA, 617-632.
- Hatch G.E., Kodavanti U., Crissman K., Slade R., Costa D. 2001
An 'injury-time integral' model for extrapolating from acute to chronic effects of phosgene. *Toxicol Ind Health* 17: 285-293.
- Henschler, D. (ed.) 1972
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-Arbeitsmedizinische Begründung von MAK-Werten, Loseblattsammlung, Phosgen, 1. Lieferung 1972, VCH-Verlagsgesellschaft, Weinheim.
- Henschler, D. (ed.) 1984
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-Arbeitsmedizinische Begründung von MAK-Werten, Loseblattsammlung, Phosgen, 10. Lieferung 1984, VCH-Verlagsgesellschaft, Weinheim.
- Heyder J., Takenaka S. 1996
Long-term canine exposure studies with ambient air pollutants. *Eur Respir J* 9: 571-584.
- IPCS 1997
Phosgene, Environmental Health Criteria,
<http://www.inchem.org/documents/ehc/ehc/ehc193.htm>.
- Kodavanti U.P., Costa D.L., Giri S.N., Starcher B., Hatch G.E. 1997
Pulmonary structural and extracellular matrix alterations in Fischer 344 rats following subchronic phosgene exposure. *Fundam Appl Toxicol* 37: 54-63.
- Kreyling W.G., Dirscherl P., Ferron G.A., Heilmann P., Josten M., Miaskowski U., Neuner M., Reitmeir P., Ruprecht L., Schumann G., Takenaka S., Ziesenis A., Heyder J. 1999





- Health effects of sulfur-related environmental air pollution. III. Nonspecific respiratory defense capacities. *Inhalat Toxicol* 11: 391-422.
- Lee L.-Y., Widdicombe J.G. 2001
Modulation of airway sensitivity to inhaled irritants: role of inflammatory mediators. *Environ Health Perspect* 109, Suppl 4: 585-589.
- Madden, M.C., Friedmand, M., Keyes, L.L., Koren, H.S. and Burleson. G.R., 1991
Effects of phosgene exposure on lung arachidonic acid metabolism. *Inhal. Toxicol.* 3, 73.
- Pauluhn J. 2006 a
Acute nose-only exposure of rats to phosgene. Part I: Concentration x time dependence of LC_{50S}, nonlethal-threshold concentrations, and analysis of breathing patterns. *Inhalat Toxicol* 18: 423-435.
- Pauluhn J. 2006 b
Acute nose-only exposure of rats to phosgene. Part II. Concentration x time dependence of changes in bronchoalveolar lavage during a follow-up period of 3 months. *Inhalat Toxicol* 18: 595-607.
- Pauluhn J. 2006 c
Acute head-only exposure of dogs to phosgene. Part III. Comparison of indicators of lung injury in dogs and rats. *Inhalat Toxicol* 18: 609-621.
- Pauluhn J., Carson A., Costa D.L., Gordon T., Kodavanti U., Last J.A., Matthay M.A., Pinkerton K.E., Sciuto A.M., 2007
Workshop summary: phosgene-induced pulmonary toxicity revisited: appraisal of early and late markers of pulmonary injury from animal models with emphasis on human significance. *Inhal Toxicol.* 19, 789-810.
- Pauluhn, J. and Thiel, A. (2007). A simple Approach to Validation of Directed-flow Nose-only Inhalation Chambers. *J. Appl. Toxicol.* 27, 160-167.
- Persson C.G.A., Erjefält J.S., Andersson M., Greiff L., Svensson C. (1996) Extravasation, lamina propria flooding and luminal entry of bulk plasma exudate in mucosal defence, inflammation and repair. *Pulm Pharmacol* 9: 129-139.
- Pittet J.F., Mackerzie R.C., Martin T.R., Matthay M.A. (1997) Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med* 155: 1187-1205.
- Sciuto A.M. 1998
Assessment of early acute lung injury in rodents exposed to phosgene. *Arch Toxicol* 72: 283-288.
- Selgrade, M.J.K., Štarneš, D.M., Iling, J.W., Daniels, M.J. and Graham, J.A., 1989
Effects of phosgene exposure on bacterial, viral and neoplastic lung disease susceptibility in mice. *Inhal. Toxicol.* 1, 243.
- Takenaka S., Heini A., Ritter B., Heyder J. 1996
Morphometric evaluation of bronchial glands of beagle dogs. *Toxicol Lett* 88: 279-285.
- Takenaka S., Heini A., Ritter B., Heyder J. 1998
The respiratory bronchiole of beagle dogs: structural characteristics. *Toxicol Lett* 96-97: 301-308.

