Arbeidstilsynet

# Grunnlag for fastsettelse av grenseverdi

## Grunnlagsdokument for diklormetan ($CH_2Cl_2$)

## Kommisjonsdirektiv 2017/164/EU

Tittel: Grunnlag for fastsettelse av grenseverdi. Grunnlagsdokument for diklormetan ($CH_2Cl_2$).

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for diklormetan ($CH_2Cl_2$).

# Innhold

# Forord

Grunnlagsdokumenter for fastsettelse av grenseverdier utarbeides av Arbeidstilsynet i samarbeid med Statens arbeidsmiljøinstitutt (STAMI) og partene i arbeidslivet (Næringslivets hovedorganisasjon/ Norsk Industri og Landsorganisasjonen i Norge) i henhold til *Strategi for utarbeidelse og fastsettelse av grenseverdier for forurensninger i arbeidsatmosfæren*. Dette dokumentet er utarbeidet ved implementering av kommisjonsdirektiv 2017/164/EU fastsatt 31. januar 2017.

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 EU- kommisjonen skal legge frem forslag til indikative grenseverdier for eksponering av visse kjemikalier som medlemslandene må innføre på nasjonalt nivå. De nasjonale grenseverdiene kan være høyere enn de som står oppført i direktivet, dersom et medlemsland mener at det er nødvendig av tekniske og/eller økonomiske hensyn, men landene bør nærme seg den indikative grenseverdien. Direktivet stiller krav om at indikative grenseverdier vedtas gjennom kommisjonsdirektiv.

I Norge ble de indikative grenseverdiene innført som veiledende administrative normer. Da nye Arbeidsmiljøforskrifter trådte i kraft 1.1.2013 ble de veiledende administrative normene forskriftsfestet i forskrift om tiltaks- og grenseverdier og fikk betegnelsen tiltaksverdier. I 2015 ble begrepet «grenseverdi» for kjemikalier presisert og begrepet «tiltaksverdi» for kjemikalier ble opphevet i forskrift om tiltaks- og grenseverdier. I vedlegg 1 til forskriften ble det innført en tydeliggjøring av anmerkningene.

Arbeidstilsynet har ansvaret for revisjonsprosessen og utarbeidelse av grunnlagsdokumenter for stoffene som blir vurdert. Det toksikologiske grunnlaget for stoffene i denne revisjonen baserer seg i hovedsak 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, presiserer kritiske effekter og vurderer behov for korttidsverdier ut i fra den foreliggende dokumentasjonen. Videre søker og evaluerer TEAN nyere litteratur etter utgivelsen av dokumentet. TEAN bruker kriteriene gitt i SCOEL's metodedokument, "Methodology for the derivation of occupational exposure limits: Key documentation (version 7, June 2013)". Dette er inkludert i TEANs Metodedokument del B (Prosedyre for utarbeidelse av toksikologiske vurderinger for stoffer som skal implementeres i det norske regelverket for grenseverdier etter direktiv fra EU-kommisjonen) utarbeidet for denne revisjonen.

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

Beslutningsprosessen skjer gjennom drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge deltar, samt orienteringsmøter og offentlig høring. Konklusjonene fra høringen med forskriftsendringer og nye grenseverdier forelegges Arbeids- og sosialdepartementet som tar den endelige beslutningen.

# Innledning

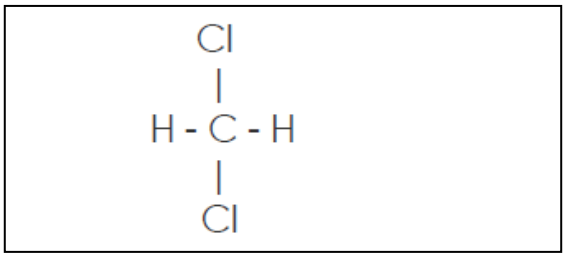
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for diklormetan. Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for diklormetan[1], samt vurderinger og kommentarer fra Toksikologisk Ekspertgruppe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

# 1. Stoffets identitet

Diklormetan og dets molekylformel, 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.) er gitt i tabell 1. Strukturformel av diklormetan er vist i figur 1.

**Tabell 1.** Stoffets navn og identitet.

| | |
|---|---|
| **Navn**<br>**Molekylformel** | diklormetan<br>$CH_2Cl_2$ |
| **Synonymer** | Metylenklorid, DCM, metandiklorid, |
| **CAS-nr.** | 75-09-2 |
| **EC-nr.** | 200-838-9 |
| **Indeks-nr.** | 602-004-00-3 |




**Figur 1.** Strukturformel av diklormetan[1].

# 2. Fysikalske og kjemiske data

Det vises til tabell 2 for fysikalske og kjemiske data for diklormetan.

**Tabell 2.** Fysikalske og kjemiske data for diklormetan.

| | |
|---|---|
| **Kjemisk formel** | $CH_2Cl_2$ |
| **Molekylvekt (g/mol)** | 84,93 |
| **Fysisk tilstand** | Fargeløs væske med en eterlignende lukt |
| **Luktterskel (ppm)** | 205-307 |
| **Smeltepunkt (°C)** | -97 |
| **Kokepunkt (°C, 101,3 kPa)** | 40 |
| **Selvantennelsestemperatur (°C)** | 605 |
| **Løselighet i vann (25 °C, g/l)**<br>**Løselighet i eter og alkohol (20 °C)** | 13,2<br>Ja |
| **Fordelingskoeffisient n-oktanol/vann (log $K_{ow}$)** | 1,25 |
| **Damptrykk ved 20 °C (kPa)** | 47,4 |
| **Damptetthet (air = 1) (g/cm$^3$)** | 2,9 |
| **Tetthet (20 °C)** | 1,3255 |
| **Omregningsfaktor (20 °C, 101 kPa)** | 1 ppm = 3,53 mg/m$^3$  1 mg/m$^3$ = 0,28 ppm |

## 2.1 Forekomst og bruk

Diklormetan framstilles vanligvis ved reaksjon mellom metanol og hydrogen til metylklorid som ved reaksjon med klor danner diklormetan (Stauffer prosess). Kloroform og karbontetraklorid er biprodukter i produksjons-prosessen. Rundt 254.000 tonn metylenklorid ble produsert i Europa i 1991, og i 1994 ble 133.000 tonn brukt. Med få unntak har forbruket av metylenklorid vært nedadgående inntil det stabiliserte seg på begynnelsen av 90-tallet (kilde: Eurochlor: http://eurochlor.org/consuption).

Stoffet brukes hovedsakelig som malingsfjerner, ellers som oppløsningsmiddel, og rensemiddel, blant annet innen elektronikkindustri (rensing av kretskort), innen metallrensing, og som ekstraksjonsmiddel i matframstilling og farmasøytiske prosesser. Diklormetan brukes videre som oppløsningsmiddel i produksjon av kjemikalier som polykarbonat, celluloseestre, triacetat og deres estre, i lim og plast og i blåsemidler i framstilling av polyuretanskum.

Restriksjon i bruk av malingfjerner som inneholder diklormetan trådte i kraft i Norge i 17.november 2011 via Forordning 276/2010 - Endring i forordning 552/2009. Malingsfjernere som inneholder diklormetan i konsentrasjon lik eller høyere enn 0,1 vektprosent skal ikke brukes av yrkesbrukere etter 06.juni 2012. I Produktregisteret var det i 2012 deklarert 33 kjemikalier som inneholder diklormetan, hvor 15 av 33 (45,5 %) deklareringene var for maling- og lakkfjernere som inneholder varierende mengde av stoffet, og 60 av 95 tonn (63,2 %) av diklormetan produsert/importert brukes i maling- og lakkfjerner.

# 3. Grenseverdier

## 3.1. Nåværende grenseverdi

Nåværende grenseverdi i Norge for diklormetan er: 15 ppm, 50 mg/m$^3$ fastsatt i 2000 med anmerkning H (hudopptak) og K (kreftfremkallende).

## 3.2. Grenseverdi fra EU

Den europeiske vitenskapskomiteen, SCOEL foreslår for diklormetan i sitt kriteriedokument fra 2009: IOELV (Indicative Occupational Exposure Limit Value) (8 timer): 100 ppm, 353 mg/m$^3$, STEL (Short Time Exposure Limit): 200 ppm, 706 mg/m$^3$, og anmerkning "Skin".

## 3.3. Grenseverdier fra andre land og organisasjoner

Tabell 3 nedenfor angir grenseverdier i andre land, med kilder angitt som fotnoter under tabell.

**Tabell 3.** Grenseverdier for diklormetan fra andre land og organisasjoner. Land og organisasjoner som ikke har grenseverdier er merket med -.

| **Land**<br>**Organisasjon** | **Grenseverdi**<br>**(8 timer)**<br>ppm, mg/m$^3$ | **Korttidsverdi**<br>**(15 min)**<br>ppm, mg/m$^3$ | **Anmerkning**<br>**Kommentar** |
|---|---|---|---|
| Sverige[1] | 35, 120 | 70, 250 | C (kreftfremkallende), H (hudopptak), V (Veiledende korttidsverdi) |
| Danmark[2] | 25, 122 | - | H (hudopptak), K (kreftfremkallende) |
| Finland[3] | 100, 350 | 350, 880 | Hud |
| Storbritannia[4] | 100, 350 | 300, 1060 | Sk, BMGV |
| Nederland[5] | 100, 350 | 500, 1740 | - |
| ACGIH, USA[6] | 50, 174 | - | - |
| NIOSH, USA[6] | 25, 125 | - | - |
| Tyskland, MAK[6] | 50, 180 | - | II(2)** (Stoffer med systemisk effekt) Skin (hudopptak); B (Reproduksjons-skadelig, gruppe B) |
| Tyskland, Myndighetene[7] | 50, 180 | - | H (hudopptak), Z (Kan være reproduksjonsskadelig) |

[1] Arbetsmiljöverkets Hygieniska gränsvärden AFS 2015:7, https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf.
[2] At-vejledning, stoffer og materialer - C.0.1, 2007, https://arbejdstilsynet.dk/da/regler/at-vejledninger/g/c-0-1-graensevaerdi-for-stoffer-og-mat.
[3] Social og hälsovårdsministeriet, HTP-värden, Koncentrationer som befunnits skadliga, Helsingfors, 2016, http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/79110/STM_9_2016_HTP-varden_2016_Ruotsi_22122016_NETTI.pdf .
[4] EH40 andre utgave, 2013, http://www.hse.gov.uk/pubns/priced/eh40.pdf
[5] http://www.ser.nl/en/oel_database.aspx; http://www.ser.nl/en/grenswaarden/2%20butyne%201%204%20diol.aspx
[6] Guide to occupational exposure values compiled by ACGIH, 2017.
[7] Baua, TRGS 900, oppdatert 2016, https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf;jsessionid=439FFF321DF2323E60F868CD08E9CD3A.s1t2?__blob=publicationFile&v=2

## 3.4. Stoffets klassifisering

Diklormetan er i henhold til CLP Forordning (EC) Nr. 1272/2008 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 4 nedenfor.

**Tabell 4.** Fareklasser, farekategori med forkortelse, merkekoder og faresetninger for diklormetan*

| Fareklasse, Farekategori, Forkortelse | Merkekode | Faresetning |
|---|---|---|
| Kreftframkallende, kategori 2 (Carc.2) | H351 | Mistenkes for å kunne forårsake kreft |

*CLP ((Forordning (EC) Nr. 1272/2008), http://www.miljodirektoratet.no/Documents/publikasjoner/M259/M259.pdf https://echa.europa.eu/information-on-chemicals/cl-inventory-database

## *3.5. Biologisk overvåking*

For å beskrive eksponering for forurensning i luften på arbeidsplassen kan man anvende konsentrasjonen av forurensningen i arbeidstakerens urin, blod eller utåndingsluft, eller annen respons på eksponeringen i kroppen. EU har satt verdier for dette, kalt biologisk grenseverdi (BLV).

SCOEL har fremmet forslag til biologisk grenseverdi (BLV) for diklormetan på 0,3 mg/l urin og 1 mg/l blod og 4% COHb.

# 4. Toksikologiske data og helseeffekter

## 4.1. Anbefaling fra SCOEL

EUs vitenskapskomite (SCOEL) har utarbeidet kriteriedokumentasjon[1] for diklormetan datert juni 2009 hvor de anbefaler en grenseverdi for stoffet lik 100 ppm, 353 mg/m$^3$ (se vedlegg).

## 4.2. Kommentarer fra TEAN

SCOEL-dokumentet er fra 2009. Det er basert på en IPCS monografi fra 1996. I tillegg er det gjennomført søk i Pubmed-databasen. I tillegg til SCOEL-dokumentet er følgende dokumenter gjennomgått: IARC monografi 110 (2016)[2], ACGIH (2001)[3], EPA (2014)[4] og MAK (2015)[5].

Diklormetan er et løsemiddel som er svært flyktig. Tørt diklormetan kan føre til dannelse av små nivåer av hydrogenklorid (HCl) i nærvær av vann og lys.

Eksponering av frivillige personer har vist at 70-75% av inhalert diklormetan blir absorbert ved eksponering for konsentrasjoner mellom 50-200 ppm. Diklormetan absorberes også gjennom huden og det er foreslått hudnotasjon på grunn av dette. Dyrestudier har vist at diklormetan blir absorbert i fordøyelsessystemet. Det er også vist distribuering av diklormetan til alle typer vev, at det skilles ut i brystmelk og at det kan krysse blod-hjerne- og placentabarrieren. Verken diklormetan eller dens metabolitter akkumuleres i vev.

Diklormetan metaboliseres hovedsakelig via to ulike enzymer, cytokrom P450 (CYP2E1) og glutation-S-transferase (GST theta 1). CYP2E1 omdanner diklormetan til karbonmonoksid (CO) og karbondioksid ($CO_2$) som videre ekshaleres. Noe av CO vil reagere med blod og danne karboksyhemoglobin (COHb).

Det er sammenhengen mellom eksponering for diklormetan og andelen COHb som er utslagsgivende for SCOELs forslag til grenseverdi. Dette kan derfor anses som den kritiske effekten av diklormetan.

Den andre metabolismeveien via GST theta 1 vil føre til dannelse av formaldehyd og format, som igjen kan omdannes til CO. Nivåene av GST som fører til omdanning av diklormetan er vesentlig høyere i mus sammenlignet med mennesker. SCOEL beskriver denne omdanningen som mindre relevant i mennesker, men den er diskutert i forbindelse med de kreftfremmende egenskapene til diklormetan.

Hvorvidt metabolismen av diklormetan går via GST theta 1 avhenger også av en vanlig polymorfi i GST theta 1-genet, hvor den ene varianten fører til at enzymet ikke metaboliserer diklormetan. IARC skriver også, i sin monografi fra 2014, at ved lavere nivåer for diklormetan eksponering vil metabolismen hovedsakelig være via CYP2E1. Ved høyere konsentrasjoner vil det også være GST theta 1-mediert metabolisme.

Eksponering for høye nivåer av diklormetan kan føre til bevisstløshet og død. Ved omdannelse av diklormetan til CO vil økt mengde COHb redusere oksygenopptaket i blodet, dette medfører symptomer som ørhet, hodepine eller bevisstløshet. Eksponering i arbeid for 250 ppm diklormetan i 7,5 timer ga en COHb på 8% (Soden et al, 1996)[1]. Det ble observert effekter på sentral nervesystemet. Blant annet fikk frivillige eksponert for 250 ppm diklormetan i 1,5-3 timer nevropsykologiske effekter. I en annen studie[1] ble det observert synsforstyrrelser hos frivillige eksponert for 290 ppm diklormetan i 95 min. Andre effekter forbundet med eksponering for diklormetan er irritasjon i øyne og luftveier, lungeødem og akutte effekter på hjerte, lever og nyrer.

Diklormetan krysser placentabarrieren og kan skilles ut via brystmelk. Det er noen få studier som har undersøkt effekter på reproduksjon, men litteraturen er vurdert som ikke tilstrekkelig til å gjøre en vurdering av potensielle effekter av diklormetan på reproduksjon.

IARC endret sin klassifisering av diklormetan i 2014[2]. De vurderte at det var tilstrekkelig bevis for å konkludere med at eksponering for diklormetan er kreftfremkallende i dyr. For mennesker mente de det var begrenset med bevis for en sammenheng mellom eksponering for diklormetan og ulike typer kreft. Ut i fra dette konkluderte IARC at diklormetan er sannsynligvis kreftfremkallende for mennesker (gruppe 2A).

SCOEL har plassert diklormetan i karsinogengruppe C (genotoksisk karsinogen hvor det er støtte for at det finnes en terskel; en helsebasert grenseverdi er derfor foreslått). IARC's endring av klassifisering indikerer at det kan være økt grunn til bekymring knyttet til diklormetans karsinogene egenskaper.

Basert på IARCs vurderinger mener TEAN at det kan være grunnlag for en grenseverdi som er lavere enn SCOELs forslag. SCOEL understreker at det er nødvendig med en korttidsverdi på bakgrunn av diklormetans prenarkotiske effekter. TEAN støtter denne vurderingen og anbefaler at det innføres en korttidsverdi. Det er rimelig at denne verdien settes i forhold til den endelige 8-timers grenseverdien.

Tilleggsinformasjon:
Det er feil i SCOEL-dokumentet: side 9, siste avsnitt. Det står beskrevet at en eksponeringsdose på 100 ppm tilsvarer utskillelse av 1 mg/L urin og blodnivåer på 0,3 mg per liter. Ifølge figur 4 på samme side bør denne beskrivelsen være motsatt (0,3 mg/L urin og 1 mg/L blod).

Det er også noe forvirrende forklaring når det gjelder effekter av diklormetan på irritasjon i lunger, under pkt 2.3 side 11 står det at det ikke finnes rapporter som beskriver irritasjonseffekter i luftveier hos mennesker eller dyr som en følge av diklormetan eksponering. Under pkt 2.5 står det at repetert eksponering over flere år gir irritasjon i luftveiene. Dette er også skrevet i anbefalingene.

# 5. Bruk og eksponering

## 5.1. Opplysning fra Produktregistret

Data fra Produktregisteret er innhentet oktober 2016, og inneholder opplysninger om mengde og bruk av diklormetan i 12 deklareringspliktige produkter. Netto maksimal mengde av diklormetan i disse produktene utgjør 29,1 tonn.

Diklormetan brukes blant annet innen produksjon av kjemikalier og kjemiske produkter, produksjon og reparasjon av møbler og boliginnredning, og i forskning og utviklingsarbeid. Stoffet inngår i reagenser og andre laboratoriekjemikalier, lim (klister) innen industrielt og håndverk, og i oppløsningsmidler, tynnere og avfettingsmidler.

Det henvises til tabell 5 for detaljert oversikt over bransjebeskrivelser med tilhørende bransjekode for de produkter det kan rapporteres på, og total mengde utgjør 26,95 tonn.

**Tabell 5.** Oversikt over bransjer hvor diklormetan benyttes og mengde forbruk i tonn.
‘

| Bransjekode | Beskrivelse | Maksimal mengde (tonn) |
|---|---|---|
| 20 | Produksjon av kjemikalier og kjemiske produkter | 22,686 |
| 31.03 og 95.24 | Produksjon av møbler og Reparasjon av møbler og boliginnredning | 2,592 |
| 72 | Forskning og utviklingsarbeid | 1,676 |

Opplysninger om produkttypekode, produkttype og maksimal mengde (over 0,4 tonn) er gitt i tabell 6 nedenfor.

**Tabell 6.** Oversikt over produkttyper som inneholder diklormetan og maksimale mengder.

| Produkttypekode | Produkttype | Maksimal mengde (tonn) |
|---|---|---|
| L05100 & L05300 | Reagenser og andre laboratoriekjemikalier | 13,5 |
| L10201 & L10202 | Lim (klister) org. løsemiddel Industrielt/Håndverk | 2,75 |
| O15100 & R10100 | Oppløsningsmidler, tynnere og Avfettingsmidler | 12,8 |

På grunn av sikkerhetsbestemmelsene i Produktregisteret kan vi ikke gi eksakte opplysninger ut over informasjon gitt i tabellene 5 og 6.

## 5.2. Eksponering og måledokumentasjon

Eksponeringene i arbeidslivet i Norge oppgis hovedsakelig å være som beskrevet i avsnitt 5.1, men målinger fra EXPO viser at arbeidstakere eksponeres for diklormetan blant annet ved laboratoriearbeid innen produksjon av farmasøytiske preparater, kjemikalier og plastprodukter, og asfalt, samt i forskning og teknisk prøving og analyse, og i sykehus og ambulansetjenester. Diklormetan finnes også i produkter som brukes ved reparasjon og vedlikehold av transportmidler og som handteres ved avfallsbehandling.

### 5.2.1. EXPO- data

Det er totalt registrert 2430 målinger av diklormetan i STAMIs eksponeringsdatabase EXPO i perioden 1973 – 2013, men kun målinger fra 2000 -2013 er tatt med i vurderingen (etter forrige revisjon av grenseverdi for stoffet i 2000), som utgjør 200 målinger.

40 av 200 målinger overskred dagens grenseverdi i Norge på 15 ppm, hvor alle overskridelsene var innen kun to bransjer (luftfart, herunder flyambulanse, og innen teknisk prøving og analyse generelt). De høyeste verdiene ble målt under avfetting og malingsfjerning, og av disse lå 6 prøver over 100 ppm. For de fleste øvrige bransjer var det ikke overskridelser, som vist i tabell 8 nedenfor.

**Tabell 7.** Målinger innen ulike bransjer og arbeidsoppgaver.

| **Bransje/arbeidsoppgaver** | **Måleområde, minste – høyeste verdi (antall prøver i parentes)** | **Gjennom-snittsverdi** |
|---|---|---|
| Laboratoriearbeid generelt* | 0 - 11,5 (**59**) | 1,4 |
| Sykehuslaboratorier | 0 - 3,4 (**13**) | 0,29 |
| Produksjon av plast og plastprodukter | 0 - 9,33 (**18**) | 4,5 |
| Avfallsbehandling (kjemikalier) | 0,8 - 10,2 (**5**) | 4,7 |

*Omfatter bransjer som bygging av veier, produksjon av kjemikalier og farmasøytiske produkter, og forskning og utvikling.

### 5.2.2. Prøvetakings- og analysemetode

I tabell 8 er anbefalte metoder for prøvetaking og analyser av diklormetan presentert.

**Tabell 8.** Anbefalte metoder for prøvetaking og analyse av diklormetan.

| **Prøvetakingsmetode** | **Analysemetode** | **Referanse** |
|---|---|---|
| Kullrør | Desorpsjon m/GC-FID* | OSHA-metode**(7), NIOSH-metode*** (1003) |
| Kullrør (2 i serie) | Desorpsjon m/GC-FID* | NIOSH-metode*** (1005) |
| Kullrør (3*350 mg) | Desorpsjon m/GC-FID* | OSHA-metode** (59) |
| Rør m/Carbosieve S-III | Desorpsjon m/CS2/1% DMF, GC-FID* | OSHA-metode** (80) |

* FID: Flame Ionisation Detector (Flammeionisasjonsdetektor)

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

***NIOSH Manual of Analytical Methods (NMAM), www.cdc.gov/niosh/docs/2003-154

# 6. Vurdering

Som angitt i kommentarer fra TEAN i avsnitt 4, er det sammenhengen mellom eksponering for diklormetan og andelen COHb som er kritisk effekt av diklormetan. Det er observert effekter på sentralnervesystemet, herunder nevropsykologiske effekter og synsforstyrrelser.

TEAN viser til at dyrestudier har vist at diklormetan blir absorbert i fordøyelsessystemet, og at det er vist distribuering av diklormetan til alle typer vev, at det skilles ut i brystmelk, og at det kan krysse blod-hjerne- og placentabarrieren. Diklormetan absorberes også gjennom huden og det er foreslått hudnotasjon på grunn av dette.

Diklormetan er et løsemiddel som er fettløselig og går derfor lett over blod-hjerne barrieren og tas opp i nervesystemet. Eksponering for høye nivåer av diklormetan kan føre til bevisstløshet og død (dvs medføre akutt fare), og må derfor holdes på laves mulig nivå. Dette også i henhold til kravene i den norske arbeidsmiljølovgivningen.

Diklormetan krysser placentabarrieren og kan skilles ut via brystmelk, og litteraturen er vurdert som ikke tilstrekkelig til å gjøre en vurdering av effekter av diklormetan på reproduksjon (men slike helseeffekter kan ikke utelukkes, noe f.eks Tyske myndigheter har tatt hensyn til i anmerkninger til grenseverdier, jf tabell 3).

IARK (2014)[2] vurderer at det er tilstrekkelig bevis for å konkludere med at eksponering for diklormetan er kreftfremkallende i dyr, og at stoffet sannsynligvis er kreftfremkallende for mennesker (gruppe 2A). SCOEL har plassert diklormetan i karsinogengruppe C.

Som fremhevet i tilleggsinformasjonen fra TEAN i deres kommentarer (4.2), er det uklare beskrivelser med hensyn til irritasjonseffekter av diklormetan. Det er også vist til andre effekter forbundet med eksponering for diklormetan, som er irritasjon i øyne og luftveier, lungeødem og akutte effekter på hjerte, lever og nyrer.

Harmonisert klassifisering og merking i EU angir kun kreftfaren med diklormetan, til tross for andre farer med eksponering for stoffet. I henhold til status i meldinger til EU (ECHA) i 2018, har produkter med diklormetan blitt vurdert å innebære farer for irritasjon av hud og øyne, akutt giftighet, systemiske effekter og kronisk skade (bl.a. på sentralnervesystem, herunder løsemiddelskade), samt mutasjoner.

Vurdering av bruk og eksponering av diklormetan i Norge

Data fra Produktregisteret viser at stoffet brukes i en del produkter i Norge, særlig innen produksjon av kjemikalier og kjemiske produkter, i produksjon og reparasjon av møbler og boliginnredning, og i forskning og utviklingsarbeid. Stoffet inngår i reagenser og andre laboratoriekjemikalier, lim (klister) innen industrielt og håndverk, og i oppløsningsmidler, som tynnere og avfettingsmidler. Dataene viser imidlertid at det er få bransjer som er berørt av bruken.

Eksponeringen for diklormetan i arbeidslivet i Norge skjer hovedsakelig ved arbeid i laboratorier (både innen FOU, sykehus og ved produksjon av materialer), samt ved arbeid med plast, og reparasjon og vedlikehold, jamfør måledata fra Expo. Eksponeringsmålinger der viser at det er begrenset antall målinger og få bransjer hvor eksponering for diklormetan overskrider dagens grenseverdi over 8 timer, og i de bransjer hvor det ellers er foretatt målinger, er gjennomsnittsnivået under 1/3 av dagens grenseverdi (se avsnitt 5.2.1).

Når det gjelder målingene innen luftfart, er det begrenset antall virksomheter som har kartlagt nivået, slik at vi ikke kan vurdere om måleresultatene er representative for bransjen. For de fleste øvrige bransjer hvor det kan forekomme eksponering for diklormetan overholdes grensene.

Det kan imidlertid være tilfelle for bransjer med høye måleverdier, men egnede tiltak (ventilasjon) bør i slike tilfeller kunne iverksettes på arbeidsplassene på lik linje med andre bransjer. Det er imidlertid generelt begrenset med målinger fra berørte bransjer.

Vurdering av grenseverdi

Grenseverdi for diklormetan ble sist fastsatt i 2000, og grunnlaget for fastsettelsen var nevrotoksisitet som kritisk effekt for diklormetan, som angitt i grunnlagsdokumentet for stoffet[6]. I vurdering av ny grenseverdi har Arbeidstilsynet tatt i betraktning både disse effekter, kritisk effekt angitt av SCOEL i 2009, samt IARC's, SCOEL's og TEAN's vurdering av kreftfare, og andre helseeffekter som er beskrevet i dette grunnlagsdokumentet.

Øvrige helseeffekter av diklormetan, og særlig nyere data om mulige kreftfremkallende egenskaper ved stoffet, at grenseverdien har vært gjeldende i mange år, og at bruken og eksponeringen i Norge er begrenset, er lagt til grunn i ny vurdering av grenseverdi. Som det framgår av avsnitt 5 er bruken i Norge begrenset, den angår få antall bransjer og virksomheter, og nivå av forurensninger er relativt lavt. I henhold til arbeidsmiljølovgivningen skal også nivå av forurensninger holdes så lavt som mulig.

Både SCOEL og TEAN anbefaler en korttidsverdi på bakgrunn av diklormetans prenarkotiske effekter, men det er ikke gitt noen nærmere helsebasert begrunnelse fra SCOEL for deres foreslåtte verdi. Denne er imidlertid sannsynligvis basert på vurdering av tilgjengelig undersøkelser av akutte effekter på sentralnervesystemet, samt nivå av COHb nivå i blod i refererte undersøkelser[1]. En korttidsverdi med overskridelsesfaktor på 3 i forhold til foreslått grenseverdi, vil gi den nødvendige sikkerhet mot akutt påvirkning av diklormetan, som også har vist akutte effekter på hjerte, lever og nyrer. Grunnlaget for bruk av denne faktor er også at grenseverdien i Norge er lavere enn SCOEL's anbefalte verdi. På dette grunnlag foreslås heller ingen biologisk grenseverdi for diklormetan i Norge.

# 7. Konklusjon med forslag til ny grenseverdi

På bakgrunn av den foreliggende dokumentasjon og en avveiing mellom de toksikologiske dataene og data om forekomst og bruk i Norge (dvs. tekniske og økonomiske hensyn), foreslås at dagens grenseverdi for diklormetan opprettholdes, at det innføres ny korttids grenseverdi for stoffet, og angis anmerkningene H og K, E og S.

Forslag til ny grenseverdi:

**Grenseverdi (8-timers TWA): 15 ppm, 50 mg/m$^3$**

**Korttidsverdi (15 min): 45 ppm, 150 mg/ m$^3$**

**Anmerkning: H (hudopptak) og K (kreftfremkallende), E (EU har fastsatt grenseverdi for stoffet), og S (korttidsverdi).**

# 8. Ny grenseverdi

På grunnlag av drøftinger med partene og høringsuttalelser ble ny grenseverdi for diklormetan fastsatt til:

**Grenseverdi (8-timers TWA): 15 ppm, 50 mg/m$^3$**

**Korttidsverdi (15 min): 45 ppm, 150 mg/ m$^3$**

**Anmerkning: H (hudopptak) og K (kreftfremkallende), E (EU har fastsatt grenseverdi for stoffet), og S (korttidsverdi).**

# 9. Referanser


1. *Recommendation from the Scientific Committee on Occupational Exposure Limits for dichlorometane SCOEL/SUM/64,*

2. *IARC, Volume 110 (2017) Some Chemicals Used as Solvents and in Polymer Manufacture. Dichloromethane. http://monographs.iarc.fr/ENG/Monographs/vol110/mono110-04.pdf. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.*

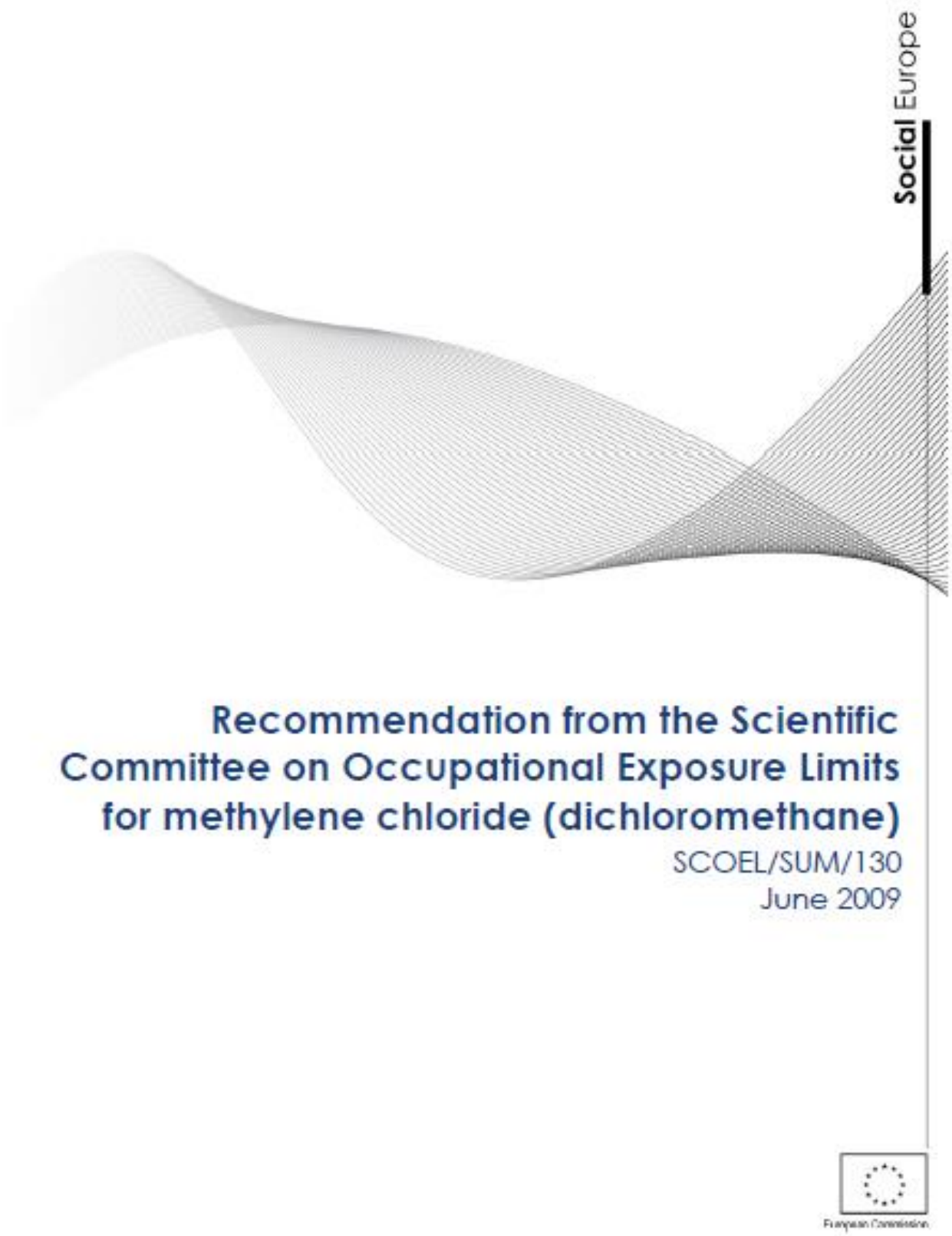
3. *ACGIH, Dichloromethane: TLV Chemical Substances 7th Edition Documentation. Product ID 7DOC-194. 2001.*

4. *EPA, TSCA Work Plan Chemical Risk Assessment. Methylene Chloride: Paint Stripping Use. EPA Document# 740-R1-4003. 2014.*

5. *Hartwig, A. and M.A.K. Commission, Dichloromethane [MAK Value Documentation, 2015], in The MAK-Collection for Occupational Health and Safety. 2002, Wiley-VCH Verlag GmbH & Co. KGaA.*

6. *Grunnlag for fastsettelse av administrativ norm for diklormetan, Direktoratet for arbeidstilsynet, 2000.*

10. **Vedlegg:** SCOEL



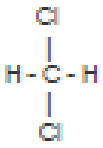
# Table of Contents

# Recommendation from the Scientific Committee on Occupational Exposure Limits for Methylene chloride (dichloromethane)

| | |
|---|---|
| 8 hour TWA: | 100 ppm [353 mg/m³] |
| STEL (15 min): | 200 ppm [706 mg/m³] |
| BLVs : | 4 % COHb (see "Recommendation") |
| | 0.3 mg methylene chloride / l urine |
| | 1 mg methylene chloride / l blood |
| Notation: | 'Skin' |
| SCOEL carcinogen group: | C (*genotoxic carcinogen for which a practical threshold is supported and a health –based OEL is proposed*) |

**SUBSTANCE IDENTIFICATION**

Methylene chloride

| | |
|---|---|
| Synonyms | DCM, dichloromethane, methane dichloride, methylene bichloride, methylene dichloride, methylenum chloratum |
| EINECS No. | 602-004-00-3 |
| CAS No. | 75-09-2 |
| Molecular formula | $CH_2Cl_2$ |
| Structural formula |  |
| MWt | 84.96 g/mol[1] |
| Conversion factor; | At 20°C and 101.3 kPa 1 ppm = 3.53 mg/m³; 1 mg/m³ = 0.28 ppm |
| EU Classification: | Carc Cat 3: R40 Limited evidence of a carcinogenic effect. |

This document is based on the International Program for Chemical Safety (IPCS) Environmental Health Criteria Monograph (1996) to which the reader is referred to for more detailed information, the references therein and studies published since the IPCS monograph, which were identified using the on-line database PubMed.

## PHYSICO-CHEMICAL PROPERTIES

Methylene chloride is a clear, colourless, highly volatile, non-flammable liquid with penetrating ether like odour. The odour threshold is 740 mg/m³. It has a boiling point of 40°C and a melting point of -95.1°C. It has a solubility in water of 13 g/L at 20°C and a vapour pressure of 47.4 kPa at 20°C. Pure methylene chloride vapour is denser than air.

Pure, dry methylene chloride is relatively stable but in the presence of water and light it slowly decomposes to produce small quantities of hydrogen chloride.

Commercial grades of methylene chloride normally contain between 0.005 and 0.02% of a stabiliser (such as methanol, ethanol, amylene, cyclohexane, phenolic compounds or tertiary butyl amine) to prevent acidification and corrosion.

# 1. Occurance/use

Methylene chloride is normally produced by the Stauffer process in which methanol is reacted with hydrogen chloride to form methyl chloride, which is then reacted with chlorine. Chloroform and carbon tetrachloride are by-products of the production process. About 254,000 tonnes were produced in Western Europe in 1991. In 1994, a total of 133,000 tonnes of methylene chloride was used in Western Europe. With the exception of 1988, which saw a slight increase in volumes sold, there had been a continuous reduction in the quantity of methylene chloride used since 1985, due largely to increased recycling by end users (Eurochlor, 1997). Since the early 1990s sales of methylene chloride have remained at a fairly stable level in Europe (Eurochlor http://www.eurochlor.org/consumption).

The main uses of methylene chloride are as a paint and varnish remover, as process solvent, in aerosols, in the electronics industry (as a photoresist stripper in the production of printed circuit boards) and in metal cleaning (vapour degreasing). It is the most commonly used solvent in paint stripping, where it is a quick-acting solvent for both wash-off and scrape-off formulations. In food and pharmaceutical processes, methylene chloride is used as an extraction medium as it offers high solvency and purity, and it can be distilled off relatively easily from the final product. In the mid-1990s, the pharmaceutical industry accounted for about 40% of the methylene chloride used in Europe. Methylene chloride is also used as a process solvent for the production of polycarbonate, cellulose esters, triacetate and triacetate esters, in adhesive formulations, plastic processing and refrigerants, and as a secondary blowing agent in polyurethane foam.

**METHODS OF EXPOSURE MONITORING AND ANALYSIS**

The UK Health and Safety Executive (1995 and 2000) have published general methods for the sampling of volatile organic compounds in workplace air and their analysis by gas chromatography that are suitable for methylene chloride (Methods for Determination of Hazardous Substances 80 and 96) and a more specific method for chlorinated hydrocarbons (MDHS 28).

The US Occupational Safety and Health Administration (OSHA) have published two fully validated methods (OSHA organic method 59, 1986; method 80, 1990) for the measurement of methylene chloride in air in workplace air. Method 59 involves collection on charcoal tubes and analysis by gas chromatography (GC/FID) where the limit of reliable quantification is 102 μg/m³ (29 ppb). Method 80 involves collection on Carbosieve S-III and analysis by GC/FID with a limit of quantification of 0.70 mg/m³ (0.196 ppm).

The US National Institute for Occupational Health and Safety (NIOSH) Analytical Method 1005, issue 3 (NIOSH, 1998) also involves collection on charcoal tubes and analysis by GC/FID. The limit of detection is stated as 0.4μg and the method has been validated for sample masses of 1.4-2600□ g corresponding to concentrations of 1.4 - 2600 mgm⁻³ (0.4 - 749 ppm) in a one litre air sample.

INRS has also published analytical methods for the determination of methylene chloride in workplace air. One is Metropol Fiche 039 (updated in 2001), which involves collection

on solbent tube containing Carboxen 564, desorption with $CS_2$ and analysis by GC/FID (Fiche Metropol C). These methods are available at http://www.inrs.fr.

Biological monitoring methods for urinary methylene chloride by gas chromatography have been described by Sakai *et al* (2002), Seno *et al* (1999) and Ukai *et al* (1998). Urinary concentrations of methylene chloride are reported to be well correlated with exposure concentrations in air. Seno *et al* (1999) also described a method for the determination of methylene chloride in blood (see also DFG 1991). It is also possible to measure methylene chloride in exhaled breath (Hatz et al., 1987). Another possibility is determination of the carboxyhaemoglobin (COHb) levels in blood. Advantages and disadvantages of the different procedures are discussed in the following chapter.

# 2 Health effects

## 2.1 Toxicokinetics

Experiments in human volunteers have established that between 70 and 75% of inhaled methylene chloride vapour is absorbed following exposure to concentrations of 50-200 ppm (176-706 $mgm^{-3}$). Experiments in humans and animals have established that methylene chloride is absorbed through the skin and animal data show that it is also absorbed from the digestive tract. Methylene chloride is distributed to all tissues and crosses the blood brain barrier and the placenta. Neither methylene chloride nor its metabolites accumulate in tissue. Methylene chloride is excreted in breast milk (IPCS, 1996).

Three skin penetration studies were found where pure methylene chloride was applied to human (Ursin et al 1995) or rat (Tsuruta 1997) skin in vitro or to mouse skin in vivo (Tsuruta 1975). The three studies reported similar results with transdermal fluxes ranging from 2.7 to 6.6 $mg/cm^2/h$. ECETOC (1993) has suggested that a skin notation should be assigned when the amount of chemical absorbed upon exposure of both hands and lower arms (2000 $cm^2$) for one hour is expected to contribute more than 10% to the systemic dose, compared to the amount absorbed via inhalation exposure at the OEL during a full work day (assuming that 10 $m^3$ air is inhaled during an 8-h workday and that 50% is absorbed). Applying this calculation to methylene chloride, the systemic dose from such skin exposure could be 3- to 7-fold greater than that from inhalation exposure at an OEL of 100 ppm.

The main route of metabolism is by cytochrome P450 mediated oxidation to form carbon monoxide and carbon dioxide that are largely exhaled. Some of the carbon monoxide binds to haemoglobin in blood. In human volunteers exposed to 150 ppm (530 $mg/m^3$) for 7.5 hours each day for five days, peak levels of carboxyhaemoglobin (COHb) were 5.3%. Exposure to 100 ppm produced peak COHb levels of 3.4%. COHb levels returned to normal within 24 hours of exposure to 200 ppm for 7.5 hours. In non-smoking workers, levels of COHb in blood following methylene chloride exposure are dose and time dependent for same day exposure but are independent of exposures on previous days (IPCS, 1996; Amsel *et al*, 2001; Soden *et al*, 1996). COHb levels in exposed workers who smoke are higher than in non-smokers and are not dose-dependent (Soden *et al*, 1996). Exposure to 496 ppm [1770 $mg/m^3$] methylene chloride for less than 1 hour is associated with COHb levels of 1 to 4%. Measured levels of COHb following exposure to 980 ppm [3500 $mg/m^3$] for two hours were 10%. COHb levels of more than 8% were found following exposure to 250 ppm [880 $mg/m^3$] for 7.5 hours. Workers exposed to average concentrations of methylene chloride of 32 ppm [114 $mg/m^3$] (8-hour TWA) had COHb

levels between 0.8 and 2.5%. At higher levels of exposure (> 250 ppm) the oxidative metabolic pathway becomes gradually saturated, the proportionate increase in COHb becomes smaller, and an increasing proportion of the received dose is exhaled unchanged.

*Figure 1* shows monitoring data of COHb in human volunteers exposed to methylene chloride, as reported by Di Vincenzo and Kaplan (1981). This set of experimental data can be opposed to data in exposed workers by Soden et al. (1996; *Figure 2*). In this data set of group means the baseline COHb level of non-exposed persons (>1.5% COHb) appears relatively high, which is likely caused by an influence of smokers in this group. Considering this, the two data sets appear basically consistent with each other.

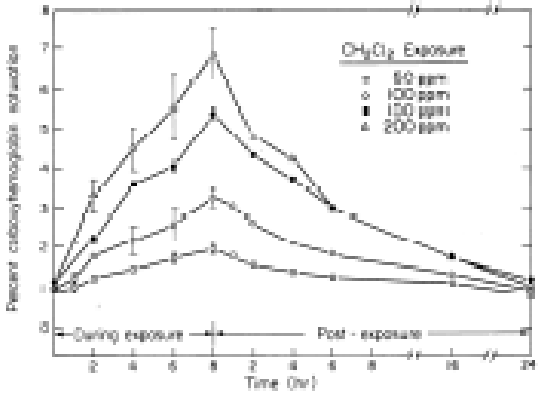



*Figure 1:* Time-course of the saturation of haemoglobin with carbon monoxide (% COHb) in volunteers exposed to different airborne levels of methylene chloride under resting conditions, according to Di Vincenzo and Kaplan (1981); means and SEM of 4-5 persons. Without exposure, a background COHb level of 1% was reported.

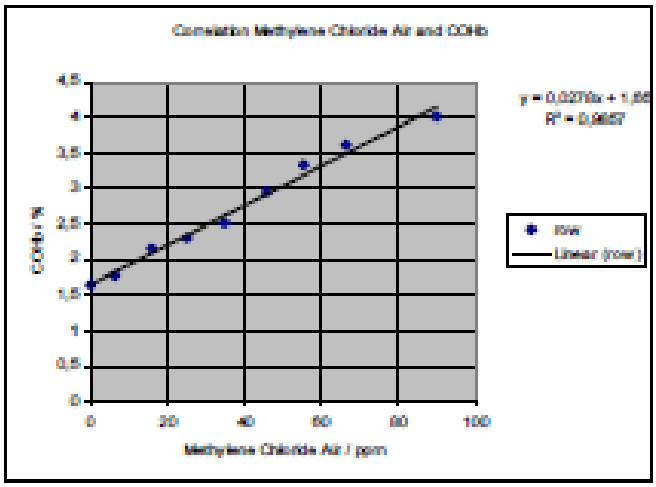



Figure 2: Correlation between airborne methylene chloride concentrations and COHb in workers (reported subgroup means); data of Soden et al. (1996)

A second (minor) metabolic pathway becomes more active at high levels of exposure, especially in mice, in which glutathione-S-transferase (GST) is involved in oxidation of

methylene chloride to formaldehyde and formate, which is further metabolised to form carbon dioxide. In vitro experiments with human cells have shown that the formation of formaldehyde from methylene chloride is influenced by the polymorphism of glutathione-S-transferase theta (*GSTT1*), and that this may influence the susceptibility of individuals to adverse effects from methylene chloride exposure (Hallier *et al*, 1994). IPCS (1996) considered this metabolic pathway to be of minor importance in humans, as concentrations of the responsible glutathione transferase in human liver tissue were only a small fraction of those in the mouse (<10%). The metabolic routes of methylene chloride are relevant for the discussions of the mode of action of tumour induction across species. For details of this discussion, see chapter 5.7 (considerations of the mode of action).

Relevant metabolic steps of the two avenues of biological activation, to carbon monoxide and to formaldehyde, are shown in Figure 3.

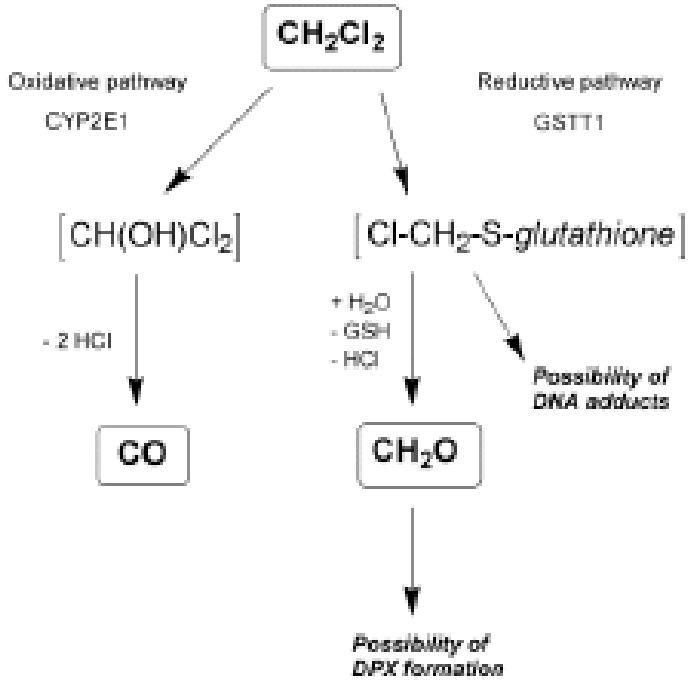



*Figure 3:* Biological activation of methylene chloride to toxic metabolites. The major oxidative (saturable) pathway leads to carbon monoxide. A minor reductive (glutathione-dependent) pathway leads to potentially reactive metabolites, such as formaldehyde.

*Biological monitoring of methylene chloride and metabolites*

The parent compound, methylene chloride, and its toxic metabolite carbon monoxide can be determined in biological media for biological monitoring. Different recommendations have been given, and there are advantages and disadvantages of the different procedures, which are compiled in *Table 1*.

Correlations between airborne methylene chloride exposures in workers and resulting methylene chloride concentrations in both blood (Lauwerys / Hoet, see also DFG 2005)

and urine (Ghittori et al. 1993, Ukai et al. 1998, Sakai et al. 2002) have been established. Taking the available data together, the functions given in *Figure 4* are resulting.

*Table 1:* Methylene chloride – existing recommendations of biological guidance values and comments (all samples collected at end of exposure). Included are the corresponding OEL proposals

| Guidance value recommended by | Analyte, matrix | Value | Advantages | Disadvantages |
|---|---|---|---|---|
| DFG (2005) (D) | DCM in Blood | 0.5mg/l (OEL 50 ppm) | No interference from smoking | Invasive, sample collection time and method critical |
| Lauwerys / Hoet (B) | DCM in Blood | 0.5mg/l (OEL 50 ppm) | No interference from smoking | Invasive, sample collection time and method critical |
| Lauwerys / Hoet (B) | DCM in breath | 15 ppm (OEL 50 ppm) | Non-invasive. No interference from smoking | Sample collection time and method critical , semi-quantitative |
| ACGIH (USA) | DCM in urine | 0.3mg/l (TLV 50 ppm) | Non-invasive. No interference from smoking | Sample collection time and method critical , semi-quantitative |
| [SCOEL discussions] | COHb | Blood | Endpoint of toxicity | Invasive, interference from smoking |
| HSE (UK) | CO | Breath (OEL 100ppm) | Non-invasive | Interference from smoking |

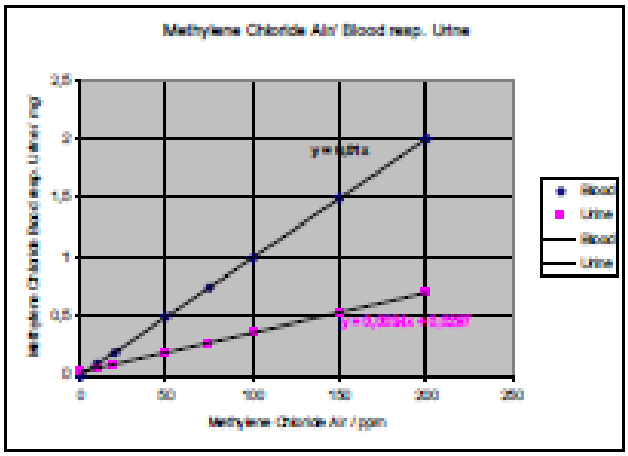



*Figure 4:* Correlation between airborne methylene chloride exposure and methylene chloride concentrations in blood and urine at end of shift (see text)

Based on these figures, an OEL of 100ppm (as proposed in this document) is equivalent to a urinary excretion of 1 mg methylene chloride per liter urine (end of shift), and to a steady-state blood level (end of the shift) of 0.3 mg per liter.

## 2.2. Acute toxicity

### 2.2.1. Human data

A number of industrial accidents involving methylene chloride have been reported (IPCS, 1996). High levels of exposure methylene chloride have led to unconsciousness and, in some cases, death. Other effects include irritation of the eyes and respiratory tract, lung oedema and acute effects on the heart, liver and kidneys. The formation of COHb as a result of methylene chloride metabolism decreases the oxygen-carrying capacity of the blood, giving symptoms of oxygen deprivation such as light-headedness, headache or loss of consciousness. Mahmud and Kales (1999) described a case in a cabinet worker who experienced intermittent headaches, consistent with both methylene chloride intoxication and carbon monoxide poisoning. In another fatal case of methylene chloride poisoning, however, COHb levels were within the normal range, suggesting that the fatal narcosis and respiratory depression were due to the direct effect of methylene chloride on the central nervous system (Zarrabeitia *et al*, 2001).

Experiments in human volunteers have established that the main effect of a single high exposure to methylene chloride is neurotoxicity (IPCS, 1996). Neurobehavioural changes (disturbed vigilance and impaired combined tracking monitoring performance) were observed following exposure to 250 ppm [894 mg/m³] for 1.5 to 3 hours. In other experiments no effects on visual performance were observed following a short exposure to 700 ppm [2500 mg/m³] (duration unknown) but effects on visual function were observed after 95 minutes exposure to 290 ppm [1040 mg/m³]. Light headedness and effects on visual function were observed after 1 hour of exposure to 672 ppm [2400 mg/m³]. A dose-related increase in serum concentrations of bilirubin was observed in volunteers exposed to 460 ppm [1650 mg/m³] together with elevated concentrations of COHb.

Chang *et al* (1999) described six cases involving oral ingestion of methylene chloride. Central nervous system depression, tachypnoea, and corrosive gastrointestinal injury were the most common effects. An elevated COHb level was documented in only two patients (35% and 8.4% COHb, respectively). Renal failure, hepatic failure, and acute pancreatitis occurred in the two most severe cases of poisoning.

### 2.2.2. Animal data

IPCS (1996) reviewed the acute toxicity of methylene chloride and concluded that it has a low acute toxicity following inhalation or oral administration. In short term inhalation experiments, 6 hour $LC_{50}$ values of 11250 ppm [40200 mg/m³] to 15650 ppm [55900 mg/m³] have been reported in rats, mice and guinea pigs. Oral $LD_{50}$ values of 1410-3000 mg/kg bodyweight have been reported. The main effects of exposure are associated with the central nervous system (CNS) and liver with CNS disturbances being reported at 3900 ppm [14000 mg/m³] or more in mice and slight changes in electroencephalographic (EEG) activity in rats at 496 [1770 mg/m³]. Slight histological changes of the liver have been reported in mice at concentrations of 15800 ppm [56500 mg/m³] or more. Exposure to 2000 ppm [7100 mg/m³] adversely affected Clara cells in the lungs of mice, but not of rats. There is inconsistent evidence for cardiovascular effects at concentrations of 9800 ppm [35000 mg/m³] in monkeys, dogs and rabbits. Some studies have reported effects on the kidneys with slight histological changes being observed in mice exposed to 15800 ppm [56500 mg/m³] for 7 hours.

### 2.3. Irritation

There are no reports linking methylene chloride to respiratory irritation in humans or animals. The IPCS (1996) cite a few case reports in which methylene chloride was caused skin and eye irritation in humans. In animals, two investigations have demonstrated that methylene chloride can cause skin irritation in rabbits including severe erythema and oedema with necrosis and acanthosis (IPCS, 1996). The IPCS (1996) also cite two investigations of the irritancy of methylene chloride to the rabbit eye. Effects were reversible and included moderate to severe changes in the conjunctiva combined with increased corneal thickness and intra-ocular tension.

### 2.4. Sensitisation

No data are available. The absence of any case reports suggests that methylene chloride is unlikely to cause respiratory or dermal sensitisation in humans.

### 2.5. Repeated dose toxicity

#### Human data

Studies of possible morbidity associated with workplace exposure to methylene chloride have all been small scale and not all included control groups (Table 2). The data suggest that no adverse effects on health are associated with workplace exposure up to concentrations of about 100 ppm [350 mg/m³] over several years. Irritation of the eyes and respiratory tract, subtle neurotoxic effects and minor effects on blood have been observed at higher levels of exposure.

With regard to the study of White et al. (1995) it should be mentioned that the persons examined in the printing industry were exposed to a mixture of solvents, including toluene, methyl ethyl ketone, mineral spirits and "beta-ether", in addition to methylene chloride.

**Table 2:** Studies of morbidity associated with methylene chloride reviewed by IPCS (1996) and more recent studies

| Exposed population | Findings | Study |
|---|---|---|
| Workers exposed to 114 mg/m³ (TWA) | No effects on clinical chemistry, haematology or electrocardiograms | Di Vincenzo & Kaplan (1981) |
| 29 men exposed for several years to concentrations "below 100 ppm" (347 mg/m³) | When compared with age matched controls, no effects on subjective symptoms, neurobehavioural tests, motor nerve conduction velocity, electrocardiograms and clinical examinations | Cherry *et al* (1981) |
| 33 workers exposed to concentrations between 100 and 17000 mg/m³ over two years (23-4800 ppm) | Irritation of the eyes and respiratory tract and neurasthenic disorders reported in half of the exposed population, digestive disorders reported by one third. No comparison with a control population | Kuzelova & Vlasak (1966) |
| 25 methylene chloride exposed retired airline maintenance workers compared against unexposed retirees (exposures not specified) | Men employed in paint stripping. No significant difference was found between exposed and unexposed workers, although subtle differences in attention and memory were detected. | Becker & Lash (1990), Lash *et al* (1991) |
| 46 subjects exposed to concentrations of 6-24 mg/m³ for several years (exposures not specified) | Non significant excess of digestive disorders and hypertonia in comparison with controls. Symptoms of gallbladder pathology and swollen liver reported, but no details of drinking or smoking habits provided | Kashin *et al* (1980) |
| Workers who had worked for at least 10 years exposed to average concentrations of 1677 mg/m³ (475 ppm) | In comparison with an unexposed group, there were no differences in selected symptoms including irregular heartbeat, dizziness or loss of memory or in SGPT (Serum Glutamic Pyruvic Transaminase), Bilirubin or haemocrit. Only noticeable difference was lower levels of SGOT (Serum Glutamic Oxaloacetic Transaminase) in the exposed group. | Soden (1993) |
| 2-year prospective study of 30 workers in a screen printing business exposed to a mixture of solvents including methylene chloride; exposures typically to about 75-100 ppm for 20 minutes, 6 times/day | Persons with higher acute exposure demonstrated significantly impaired test performance on tasks involving manual dexterity, visual memory, and mood. Those with higher chronic exposure demonstrated significantly poorer performance on visual memory tasks and mood. No obvious clinical disease. | White *et al* (1995) |

The outcome of mortality studies provide no evidence to suggest that workplace exposure to methylene chloride at concentrations of up to 1677 mg/m³ (475 ppm) has an important effect on mortality (*Table 3*). There are no indications that raised COHb levels arising from industrial exposure to methylene chloride are associated with an increased risk of ischaemic heart disease. In the Kodak, Gibbs and Tomenson studies, a ban on workplace smoking may have introduced a negative bias to the study design. The cancer studies are discussed further in section 5.7.

**Table 3:** Mortality studies reviewed by IPCS (1996), IARC (1999) and more recent studies

| Exposed population | Description of study | Findings | Study |
|---|---|---|---|
| Men exposed to methylene chloride at a Kodak photographic film production facility in New York State. Mean (8 hour TWA) exposure concentrations for different groups ranged from 35.3- 402 mg/m$^3$ (10-114 ppm) with an overall mean of 92 mg/m$^3$ (26 ppm). | Retrospective cohort mortality – 344 deaths between 1956-76 | No increase in risk from ischaemic heart disease, liver or kidney cancer or cancers at other sites | Friedlander *et al* (1978) |
| | Proportionate mortality – 754 workers employed during 1964 and followed up to 1976 | | |
| | All workers exposed for at least one year between 1964 and 1970 (1013) followed up to 1988 | No increase in risk of death from ischaemic heart disease, liver or kidney cancer, possible excess of pancreatic cancer mortality | Hearne & Friedlander (1981), Hearne *et al* (1987, 1990) |
| Update of Kodak study<br>1) 1,311 men initially employed between 1946 (when the solvent was first used) and 1970. Average exposure of 138 mg/m$^3$ (39 ppm; 8-hour time-weighted average) for 17 years<br>2) 1913 men employed between 1964 to 1970 and followed up to1994. Average exposure of 92 mgm$^{-3}$ (26 ppm) for 24 years; | Median length of follow-up from first exposure was 34 years.<br><br>Median time from first exposure - 35 years. | Mortality in both cohorts was lower than expected for all causes of death, ischaemic heart disease, and cancer. No statistically significant increases were observed for any cause of death. | Hearne and Pifer (1999) |
| Workers producing triacetate fibre in a South Carolina plant. Exposure concentrations estimated to range from 494-1677 mgm$^{-3}$ (140-475 ppm) Workers also exposed to methanol and acetone | 1271 male and female workers employed for at least 3 months between 1954 and 1977. | No excess of deaths from cardiovascular causes. Significant excess of cancers of the biliary passages and liver. Three of the four liver and biliary cancer deaths in workers with 10+ years of employment and 20+ years since first employment | Ott *et al* (1983), Lanes *et al* (1993) |
| Workers in a cellulose acetate fibre plant in Maryland. Cohort divided into 3 groups: high exposure to methylene chloride (>1300 mgm$^{-3}$; 350 ppm), low exposure (176-353 mgm$^{-3}$; 50-100 ppm) and no exposure. | Retrospective cohort mortality study of 3211 workers employed in or after 1970 and followed until 1989. | No excess mortality from cancers of the biliary tract, liver, pancreas or lung. Increased mortality from prostate cancer in men with 20+ years employment and from cervical cancer in women with 20+ years of employment. Possible increased risk of death from cardiovascular causes observed in earlier study not confirmed in 1996 study. | Gibbs (1992), Gibbs *et al* (1996) |
| 1785 employees of a factory that produced cellulose triacetate film base Subcohort of 1473 subjects with methylene chloride exposure. The mean duration of exposure was nine years at 67 mgm$^{-3}$ (19 ppm) eight hour time weighted average). | Retrospective cohort study - All male employees with a record of employment at the film factory in 1946-88; 334 deaths identified up to 31 December 1994. | In methylene chloride exposed subcohort, substantially reduced mortality for all causes, all cancers, and cancers of liver, biliary tract, lung and pancreas. Ischaemic heart disease mortality slightly increased compared with local rates but lower in active employees where a direct effect of methylene chloride exposure would be expected. No in service mortality due to ischaemic heart disease in workers with the highest cumulative exposure (2824 mgm$^{-3}$.years; 800+ ppm-years). | Tomenson *et al* (1997) |
| Workers in a chlorinated methanes production plant – exposure to a mixture of chlorinated hydrocarbons, no specific information about exposure to methylene chloride | 226 men employed for at least one year between 1940 and 1969 and followed for mortality until 1979 | No excess of respiratory cancer or circulatory disease. Three cases of pancreatic cancer were observed against 0.9 expected, no information presented about liver cancers | Ott *et al* (1985) |
| Civilian workers employed at a military aircraft maintenance facility for at least one year between 1952 and 1956; workers exposed to a mixture of solvents; exposures best characterised for trichloroethylene (methylene chloride exposures not specified) | Retrospective cohort study of 14457 workers of whom 1222 were exposed to methylene chloride | No overall excess of cancer deaths or deaths more generally; Non significant excess of non-Hodgkin lymphoma and multiple myeloma in men, increased breast cancer risk in women; no information about other cancers | Blair *et al* (1998) |
| Lamp manufacturing workers involved in coiling and wire drawing with exposures to methylene chloride (not quantitatively specified), other chlorinated solvents, strong acids and metals including arsenic and chromium | 203 women and 46 men employed for 6+ months between 1960 and 1975 | Non significant excess of all cancers and of breast cancers in women; significant excess of breast cancers in women with greater than 5 or greater than 15 years employment | Shannon *et al* (1988) |

### Animal data

The IPCS (1996) reviewed a number of inhalation studies and these are summarised in *Tables 4 and 5*. The results of these studies indicate that repeated or long-term exposure of animals to high concentrations of methylene chloride is associated with reversible CNS effects, slight eye irritation, liver effects and mortality. The lowest exposure concentration reported to cause liver effects was 25 ppm [88 $mgm^{-3}$] (continuous exposure). No effects were found on the liver following exposure to 250 ppm [880 $mgm^{-3}$] for 5 hours/day. The lowest exposure concentration associated with reversible CNS effects as 5000 ppm [17700 $mgm^{-3}$] (6 hours/day) with no effects at 1990 ppm [7,100 $mgm^{-3}$]. Effects on brain chemistry were observed following exposure to 250 $mgm^{-3}$ (6 hours/day). In a more recent investigation, no effects on immune function or thymus weight were found following exposure of rats to 5000 ppm [17700 $mgm^{-3}$] of methylene chloride for 6 hours/day, 5 days/week for 28 days, but a significant reduction in relative, but not absolute, spleen weight was observed in female rats (Warbrick *et al*, 2008).

IPCS (1996) also reviewed effects following oral administration. A study in rats established a no effects level for the liver of 125 mg/litre in drinking water. No conversion to mg/kg bodyweight per day is provided, but assuming a rat body weight of 0.35 kg and an intake of 0.049 litres water/day, this is approximately equivalent to 17.5 mg/kg/day. Another drinking water study found small effects on weight gain and indications of liver damage at intakes equivalent to 607 to 1469 mg/kg/day. In another drinking water study, mice exposed to between 226 and 1911 mg/kg/day showed subtle centrilobular fatty changes in the liver.

There is limited evidence that exposure to methylene chloride may potentiate the toxicity of other chlorinated hydrocarbons. Kim (1997) reported that methylene chloride significantly potentiated the hepatotoxicity of carbon tetrachloride in rats.

*Table 4:* Effects in rats in medium to long term repeated dose studies [conversion factor: 1 mgm$^{-3}$ = 0.28 ppm]

| Exposure regime | Concentration mgm$^{-3}$ | Observed effects | Study |
|---|---|---|---|
| 2 hours/day for 15 days | 3500 | Decreased body weight, effects on liver lipids | Ito *et al* (1990) |
| 2 hours/day for 20 days | 3500 | Effects on the liver: hypertrophic hepatocytes, increased lipid peroxidation and glutathione peroxidase activity | Takashita *et al* (1991) |
| 6 hours/day for 3 days | 250, 1100, 3500 | Effects on dopamine and noradrenaline turnover in the brain | Fuxe *et al* (1984) |
| 6 hours/day for 19 days | 5740, 11500, 22900, 45900, 56500 | Intermittent scratching, ataxia and hyperactivity in rats exposed to 22900 mgm$^{-3}$ or more, dyspnoea, anaesthesia and some death in animals exposed to 45900 mgm$^{-3}$ or more | NTP (1986) |
| 6 hours/day for 10 days | 7100, 14100 | No or limited lung or liver lesions | Hext *et al* (1986) |
| 5 hours/day for 28 days | 880 | No effects on the liver | Norpoth *et al* (1974) |
| 5 hours/day for 5 days/week for 4 weeks | 12800 | Inflammatory response and cell damage in the lungs | Sahn and Lowther (1981) |
| 6 hours/day, 5 days/week for 19 exposures | 0, 8800, 17700, 28200 | Anaesthesia, increased liver weights and reduced body weights in the two highest dose groups | Nitschke *et al* (1981) |
| 6 hours/day, 5 days/week, 13 weeks | 177, 710, 7100 | No evidence of irreversible neurological damage | Mattsson *et al* (1990) |
| 7 hours/day for 6 months | 35000 | CNS depression during period of exposure | Heppel *et al* (1944) |
| 6 hours/day for 90 days | 35000 | Slight redness of conjunctiva lasting for 1 to 10 hours after each exposure, no other signs of toxicity | Leuschner *et al* (1984) |
| 6 hours/day, 5 days/week for 13 weeks | 1850, 3700, 7400, 14800, 29700 | One rat exposed to 29700 died before the end of the study; foreign body pneumonia was observed in some rats exposed to 7400 mgm$^{-3}$ or more; mean body weights reduced in high dose group, reduced liver lipid to liver weight ratios in high dose males and females and in females at 14800 mgm$^{-3}$ | NTP (1986) |
| Continuous exposure for 100 days | 88350 | Slight cytoplasmatic vacuolisation of the liver and tubular degeneration in the kidney | Haun *et al* (1972) |
| 6 hours/day, 5 days/ week for 2 years | 0, 3500, 7100, 14100 | No effects on body weight gain | NTP (1986) |

*Table 5:* Effects in other species in repeated dose studies [conversion factor: 1 mgm$^{-3}$ = 0.28 ppm]

| Species | Exposure regime | Concentration mgm$^{-3}$ | Observed effects | Study |
|---|---|---|---|---|
| Mice | 6 hours/day, 3 weeks | 14100 | Increased liver weight and increased mitotic activity in hepacytes, a few animals showed necrosis of some epithelial cells of the bronchi and bronchioles together with reactive hyperplasia of adjacent lymphoid tissue | Eisenbrandt and Reitz (1986) |
| Mice, hamsters | 6 hours/day, 5 days/week - 18 (mice) or 19 (hamster) exposures | 0, 8800, 17700, 28200 | Anaesthesia and reduced body weights in highest dose group, effects on aspartate aminotransferase in female mice at 17,700 mgm$^{-3}$ | Nitschke *et al* (1981) |
| Mice | Continuous exposure for 7 days | 17700 | Reduced body weight, increased relative liver weights, liver damage | Weinstein *et al* (1972) |
| Mice | Continuous exposure, 30 days<br>Intermittent exposure for 1-12 hours/day, 30 days<br>Continuous exposure for 4, 8, 15, 90 days | 130-1059<br>2118-25416<br>1059 | Liver weight increased in dose-related manner, fatty accumulation and increased blood levels of butyryl cholinesterase found at 265 mgm$^{-3}$, all effects reversible | Kjellstrand *et al*, 1986 |
| Mice | 6 hours/day, 5 days/week for 13 weeks | 1850, 3700, 7400, 14800, 29700 | Some deaths and reduced body weights at 297800 mgm$^{-3}$, hepatic centrilobular hydropic degeneration in males and females at 29700 mgm$^{-3}$ and in females only at 14800 mgm$^{-3}$. | NTP (1986) |
| Mice | Continuous exposure for 100 days | 88 350 | Slight cytoplasmatic vacuolisation at both levels, decrease in microsomal P-450 content at the higher dose | Haun *et al* (1972) |
| Mice | Continuous exposure for 10 weeks | 350 | Fatty infiltration, vacuolisation and enlarged hepatocyte nuclei, reversible increase in plasma triglycerides | Weinstein and Diamond (1972) |

| | | | | |
|---|---|---|---|---|
| Dogs, monkeys, rabbits, guinea pigs | 7 hours/day, 5 days/ week for 6 months | 1,7700<br><br>35,000 | Fatty degeneration of the liver and pneumonia in 3/14 guinea pigs<br>Reduced activity in all species, fatty degeneration of the liver in dogs | Heppel *et al* (1944) |
| Dogs | Continuous exposure for up to 100 days | 3,500<br><br>17,350 | Abnormal haematology and increased activity of serum enzymes after 4 weeks<br>Oedema of the brain | Haun *et al* (1972) |
| Dogs | 6 hours/day for 90 days | 17,700 | Slight sedation and erythema lasting for up to 10 hours after exposure | Leuschner *et al* (1984) |
| Gerbils | Continuous exposure for 3 months | 340 | Decreased levels of neurotransmitter amino acids in the brain | Briving *et al* (1986) |
| Gerbils | Continuous inhalation followed by 4 months recovery | 1240<br><br>740 | Increased brain concentrations of two astroglial proteins and decreased levels of DNA in the hippocampus and cerebellum<br>Decreased hippocampal DNA levels, possibly as a result of the loss of nerve cells | Rosengren *et al* (1986) |
| Monkeys | Continuous exposure for 28 days | 88.25 | Raised COHb levels | Haun *et al*, 1972) |

### 2.6. Mutagenicity

The mutagenicity of methylene chloride has been reviewed by IARC (1999) and also IPCS (1996). Methylene chloride is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems. Methylene chloride induced sister chromatid exchanges, chromosome breakage and chromosome loss *in vitro* in human cells. *In-vitro* results in rodent cells were inconclusive or negative. Methylene chloride induced DNA single-strand breaks in mammalian cell cultures, but inconclusive or negative effects were reported for induction of gene mutations. It did not induce unscheduled DNA synthesis either *in vivo* in rodents or in human fibroblast cultures. It was genotoxic in fungi but not in *Drosophila* in the sex-linked recessive lethal assay.

### 2.7. Carcinogenicity

#### Human data

No consistent relationships between methylene chloride and cancer at any particular site have been reported in studies of workers exposed to methylene chloride (*Table 3*). Two studies observed an excess of pancreatic cancer and OjaJärvi *et al* (2001) found a small excess risk of pancreatic cancer, which was not statistically significant (RR = 1.42-0.80; 2.53). The authors could not find a relation to the level of exposure. Other individual studies reported an excess of liver and biliary tract cancers among longer-term employees, an excess of prostate cancer in men and excess of cervical cancer in women that appeared to increase with level of exposure and a possible exposure-related increase in breast cancer risk. In most studies, workers were exposed to a number of other chlorinated solvents and some were also exposed to other potential carcinogens including metals. This limited the power of published studies to detect an effect that is specific to methylene chloride. In case control studies (*Table 6*) possible associations have been reported between exposure to methylene chloride and cancers of the bladder, breast (in women), rectum and possibly the lung. Dell et al. (1999) concluded that there was no strong or consistent finding for any site of cancer, despite several studies of large occupational cohorts of workers potentially exposed to high concentrations of methylene chloride.

IARC (1999) concluded that there was not a sufficiently consistent elevation of risk across studies of any cancer type to make a causal interpretation credible. The results of more recent studies do not support a revision of this conclusion.

#### Animal data

A number of long term inhalation studies have been performed (Table ). The NTP (1986) reported clear evidence of carcinogenicity in male and female B6C3F1 mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms. Although, a high incidence of leukaemia in both exposed and unexposed rats in the NTP study is potentially a cause for concern, the outcome of the NTP studies are broadly consistent with other studies (Table 6). Maronpot *et al* (1995) found evidence that early life exposure to methylene chloride gave rise to an increased lung cancer risk in mice even in the absence of continuing exposure whereas the development of liver cancer was more closely associated with continuing exposure.

Relatively few investigations have been made of the carcinogenicity of methylene chloride following oral administration. Studies in rats and mice reviewed by IPCS (1996) did not find an excess risk of cancer at doses of up to 250 mg/kg bodyweight/day for two years or 500 mg/kg/day for 64 weeks.

IARC (1999) has concluded that there was inadequate evidence in humans for the carcinogenicity of methylene chloride, but sufficient evidence in experimental animals. The overall evaluation was that methylene chloride is possibly carcinogenic to humans (Group 2B).

*Considerations of the mode of action*

Long-term animal experiments have demonstrated that methylene chloride is associated with the development of cancers in mice whereas similar effects were not observed in rats and hamsters. Based on the formation of reactive metabolites, such as formaldehyde, through the reductive pathway of metabolism (see *Figure 3*) the paradigm has bee advanced that this pathway may be connected with carcinogenesis, and that species differences between the balance of the oxidative and reductive pathway should explain species differences in carcinogenicity (Green et al. 1988; Green 1997). Mechanistic studies have demonstrated that metabolism of methylene chloride by the glutathione-S-transferase-dependent reductive pathway is highest in the mouse. This pathway is mediated by the isoenzyme GSTT1-1 and produces reactive intermediates that are held responsible for the liver and lung tumour formation (Thier et al. 1993, 1996, 1998, Wheeler et al. 2001, Marsch et al. 2004). Upon incubation of isolated hepatocytes from mice, rats, Syrian golden hamsters and humans with methylene chloride, only mouse hepatocytes formed detectable amounts of DNA-protein crosslinks (DPX; Casanova et al. 1997). When V79 cells were transfected with the mouse enzyme (mGSTT1-1) and incubated with high concentrations (2.5-10 mM) methylene chloride, DPX were formed that were typical for formaldehyde (Hu et al. 2006). For the development of lung tumours in the mouse, damage to mouse lung Clara cells and increased cell division were seen as decisive components. The susceptibility of the mouse was seen as a consequence of very high activity and specific cellular and nuclear localisation of the theta class GST, unique to the mouse (Green 1997).

The markedly lower levels of the methylene chloride metabolising GST in rats and hamsters are consistent with the lack of liver and lung tumours in these species. The levels of this enzyme in humans are even lower than found in rats and hamsters. Hence, the mouse model may not be informative about cancer risks in humans because of the differences in the metabolism of methylene chloride (IARC, 1999).

Recently, this concept has received further experimental support. Sherratt et al. (2002) directly compared the relative capacity and locality of methylene chloride activation in mouse and human tissues. The results showed that the mouse mGSTT1-1 was more efficient in catalysing the conjugation of methylene chloride with GSH than the orthologous human enzyme (hGSTT1-1). In addition, the mouse expressed higher levels of the enzyme than humans in the liver. Histochemical analysis confirmed the presence of GSTT1-1 in the nucleus of mouse liver cells. In human liver lower levels of GSTT1-1 were detected in bile duct epithelial cells and hepatocyte nuclei, but the enzyme was also present in the cytoplasm. The species differences (mouse/humans) of a higher metabolic efficiency of mGSTT1 *vs.* hGSTT1-1 are also explained by differences in the primary structure. The amino acid residue 234 is the determinant of these differences. The replacement of $TRP^{234}$ in hGSTT1-1 by arginine, as found in the rodent enzyme, enhanced

the enzymatic activity by an order of magnitude (Shokeer et al. 2005). The enzymatic differences are paralleled by differences in the crystal structures of the proteins (Tars et al. 2005).

Some peculiarities of human GSTT1-1 are also relevant. The *hGSTT* gene is polymorphic; about 20% of the European population shows a complete deletion (*GSTT1*0*). Furthermore, GSTT1-1 metabolising methylene chloride is present in human erythrocytes, which is not the case in other species including rodents (review: Bolt and Thier 2006). Hence, part of the human population (*GSTT1*0*) does not possess the activating pathway leading to reactive metabolites, and for the rest of the population (*GSTT1*1*) the blood compartment may act as an additional "sink" to eliminate methylene chloride (Sherratt et al. 2002).

*Published assessments of carcinogenic risks*

Since the 1980s a number of articles have presented quantitative comparisons of methylene chloride metabolism, in order to derive calculations and argumentations regarding possible carcinogenic risks in humans (Andersen et al. 1987, Green et al. 1988, Liteplo et al. 1998, El Masri et al. 1999, Jonsson et al. 2001, Jonsson and Johanson 2001, Preston and Williams 2005). An improved procedure has been adopted recently (Starr et al. 2006).

Against the background of the previous developments, David et al. (2006) recently presented an updated and refined physiologically-based pharmacokinetic (PBPK) model for methylene chloride in humans. This model was based on the PBPK model developed by Andersen et al. (1987) and later developments, and it was supplemented by a Bayesian modelling using the Markov Chain Monte Carlo (MCMC) technique (Marino et al. 2006). The modelling incorporated the advances in understanding the metabolism and in statistical approaches, in order to better reflect the variability in humans. By this way, the new information on human *GSTT1* polymorphism was incorporated using the probabilistic design (El Masri et al. 1999, Jonsson and Johansson (2001). Physiological parameters for input into the MCMC analysis were selected according to current scientific evidence for each parameter. Metabolic data for individual subjects from five human studies were combined into a single data set and population values were derived. These were used for calibration of the human model. The PBPK model, using the calibrated metabolic parameters was then taken to perform a cancer risk assessment for methylene chloride, relying on the experimental tumour incidence in mice and on human exposure data of current IRIS entries. Unit risks, i.e., the risk of cancer from exposure to 1 microg/m³ over a lifetime, were estimated using the calibrated human model. The results indicated skewed distributions for liver and lung tumour risks, alone or in combination, with a mean unit risk (per microg/m³) of $1.05 \times 10^{-9}$, considering both liver and lung tumours. Adding the distribution of genetic *GSTT1* polymorphisms for metabolism to the presumed ultimate carcinogen, the unit risks ranged from 0 (which is expected given that approximately 20% of the population is estimated to be *GSTT1*0* "non-conjugators") up to a unit risk of $2.70 \times 10^{-9}$ at the 95th percentile. The median, or 50th percentile, was $9.33 \times 10^{-10}$.

If one takes such a unit risk of $10^{-9}$, the risk of exposure to 1 microg/m³ methylene chloride for human working lifetime (assumed as14% of lifetime) would be $1.4 \times 10^{-10}$. Accordingly, a lifetime risk for exposure at 100 ppm [353 mg/m³] would be $4.9 \times 10^{-8}$. This is a risk level that will never be detected in epidemiological studies. Even this estimate represents an over-estimation of the human risk, as the "sink function" of the human erythrocytes (v.s.)

in persons possessing the active GSTT1 gene and GSTT1-1 enzyme has not been considered.

Conclusion

Taking together the current knowledge on the potential of human metabolic activation of dichloromethane, it appears unlikely that this compound poses a practical carcinogenic risk to humans, under conditions of current occupational exposures. In consequence, SCOEL has decided to assign dichloromethane to the SCOEL carcinogen group C with a "practical" threshold (Bolt and Huici-Montagud 2008) and to derive an OEL based on non-cancer endpoints.

**Table 6**: Epidemiological investigations of the carcinogenicity of methylene chloride in humans

| Exposed population | Description of study | Findings | Study |
|---|---|---|---|
| 119 cases and 108 controls potentially exposed to methylene chloride | Case control study of astrocytic brain cancer | Risks increased with increased potential intensity of exposure and duration of employment; exposure assessment severely criticised by Norman (1996) | Heineman *et al* (1994) |
| Mortality records from 24 states, gathered from 1984 to 1989 coded for occupation and industry. After excluding homemakers, 33509 cases and 117794 controls remained. | Case-control study of breast cancer with separate analyses for blacks and whites. | After adjusting for socioeconomic status, suggestive associations for styrene, several organic solvents (methylene chloride, carbon tetrachloride, formaldehyde), and several metals/metal oxides and acid mists. | Cantor *et al* (1995) |
| 3630 histologically confirmed cancer cases, of whom 257 had rectal cancer, 533 population controls, 1295 subjects with cancers at sites other than the rectum, lung, colon, rectosigmoid junction, small intestine, and peritoneum | Case-control study investigating the relationship between solvent exposure and rectal cancer (building on earlier study by Siemiatycki, 1991) | Possible association between methylene chloride and rectal cancer, not possible to separate the relative importance of different potential risk factors | (Dumas *et al*, 2000) |
| 12980 female cases of CNS cancer in 24 US states in 1984-1992 and 51920 female controls who died from diseases other than malignancies and neurological disorders | Death certificate-based case-control study | 20-30% CNS cancer increase in women exposed to electromagnetic fields (EMF), methylene chloride, insecticides, fungicides, and contact with the public. Risk unrelated to probability and intensity of exposure. | Cocco *et al* (1999) |

**Table 6**: Investigations of carcinogenicity in long term animal experiments [conversion factor: 1 $mgm^{-3}$ = 0.28 ppm]

| Species | Exposure regime | Concentrations $mgm^{-3}$ | Observed effects | Study |
|---|---|---|---|---|
| Rats | for 6 hours per day, 5 days per week for 2 years | 0, 3530, 7060 and 14120 | Reduced survival of exposed and unexposed male rats due to leukaemia. Reduced survival of high dose females. Increased incidences of benign mammary gland adenomas and fibroadenomas in exposed males and females. Liver damage in exposed animals with a dose-related increase in the incidence of hepatocellular neoplastic nodules or hepatocellular carcinomas (combined) in females. Increased incidence of squamous metaplasia of the nasal cavity in high dose females. In males, increased incidence of mesotheliomas (arising primarily from the tunica vaginalis) | NTP (1986) |
| Rats | 6 hours/day, 5 days/ week for 2 years | 0, 1770, 5300, 12400 | Increase in sarcomas in the mid-cervical area in the region of the salivary gland in mid and high-dose males. Slight dose-related increase in benign mammary tumours in males, dose related increase in benign mammary tumours in females | Burek *et al* (1984) |
| Rats | 6 hours/day, 5 days/ week for 20 months (males), 24 months (females) | 0, 177, 710, 1770 | Increase in benign mammary tumours in females at 1770 $mgm^{-3}$. NOEL 710 $mgm^{-3}$ | Nitschke *et al* (1988a) |
| Rats | 4 hours/day, 5 days/week for 7 weeks, then 7 hours/day, 5 days/week for 97 weeks | 350 | No effect on incidence of benign or malignant tumours | Maltoni *et al* (1988) |
| Rats | As above for 15 and 104 weeks | 350 | No effect on incidence of benign or malignant tumours | Maltoni *et al*, 1988) |
| Mice | 6 hours/day, 5 days/week for various periods up to 104 weeks | 7100 | An excess of lung and liver tumours observed in mice exposed for over 1 year | Kari *et al* (1992) |
| Mice | 6 hours/day, 5 days/week for 26, 52, 78 or 104 weeks | 7100 | All exposed groups showed excesses of lung and liver tumours | Kari *et al* (1992) |
| Mice | 6 hours per day, 5 days per week for 2 years | 0, 7060, 14120 | The survival of exposed males and high dose females was reduced. Increased incidences of lung tumours were observed in exposed mice. Cytologic degeneration of the liver and increased Incidences of hepatocellular adenomas or hepatocellular carcinomas (combined) were observed in high dose male and exposed female mice. Dose-related increases in the numbers of mice bearing multiple lung or liver neoplasms and in the incidences of testicular atrophy in male mice and uterine and ovarian atrophy in female mice. | NTP (1986) |
| Mice | 6 h per day, for varying durations up to 104 weeks. | 7060 | Exposure caused an increase in liver and lung neoplasia in the absence of overt cytotoxicity. Measurement of replicative DNA synthesis after 13, 26, 52 and 78 weeks of exposure showed a significant decrease in the hepatocyte labelling index at 13 weeks. Replicative DNA synthesis in pulmonary airways after 1, 2, 3, 4, 13 and 26 weeks of exposure was significantly lower than in controls. | Maronpot *et al* (1995) |
| Hamster | 6 hours/day, 5 days/week for 2 years | 0, 1770, 5300, 12400 | No significant increase in tumours | Burek *et al* (1984) |

### 2.8. Reproductive toxicity

#### Humans

Methylene chloride crosses the placenta and is also excreted in breast milk.

A case control study of 44 women within a cohort of workers employed in Finnish Pharmaceutical factories reported that methylene chloride was associated with an increased risk of spontaneous abortion (Odds Ratio of 2.3 with a 95% confidence interval of 1.0-5.7). There was weak evidence that risk increased with increasing frequency with which methylene chloride was handled but the odds ratios for other solvents were also raised, so the significance of the findings for methylene chloride is uncertain (Taskinen *et al*, 1986).

A study of 50 men working on aircraft maintenance at an US Air Force installation exposed to jet fuel and solvent concentrations below 6 ppm (i.e. 21 $mgm^{-3}$ for methylene chloride) for individual solvents found some effects on sperm generation but no clear association was found between biological exposure measurements and spermatogenic changes (Lemasters *et al* 1999).

#### Animals

The IPCS (1996) reviewed several studies. Slight skeletal malformations but no significant teratogenic effects or evidence of foetal toxicity was observed in rats and mice exposed to concentrations of methylene chloride of 1230 ppm [4400 $mgm^{-3}$] for 7 hours/day on days 6 to 15 of pregnancy (Schwetz *et al*, 1975). Maternal COHb levels of 12% were measured during exposure. No teratogenic effects were observed in rats exposed to 4550 ppm [16260 $mgm^{-3}$] for 6 hours/day during 17 days of pregnancy but foetal body weights were reduced (Hardin and Manson, 1980). No effects were seen in behavioural assays but there were changes in the general activity level of pups from about 10 days that were still present at 150 days. It was unclear whether this was a result of exposure. Maternal COHb levels during exposure ranged from 7.1-10.1 %.

In a two generation study, rats were exposed to 0, 100, 500, or 1500 ppm [0, 350, 1770 or 5300 $mgm^{-3}$] for 6 hours per day for 5 days each week. No evidence was found of any adverse effect on any reproductive parameter, neonatal survival or neonatal growth in either the $F_0$ or $F_1$ generation (Nitschke *et al*, 1988a and b).

## Recommendation

High levels of exposure methylene chloride have led to unconsciousness and, in some cases, death.

The formation of COHb as a result of methylene chloride metabolism decreases the oxygen-carrying capacity of the blood, giving symptoms of oxygen deprivation such as light-headedness, headache or loss of consciousness. In non-smoking workers, COHb levels in blood of more than 8% were found following exposure to about 250 ppm [880mg/$m^3$] for 7.5 hours.

Other effects include irritation of the eyes and respiratory tract, lung oedema and acute effects on the heart, liver and kidneys. Experiments in human volunteers have found neurobehavioral changes following exposure to 250 ppm [694 mg/$m^3$] for 1.5 to 3 hours and effects on liver function at 460 ppm [1650 mg/$m^3$].

At the workplace, no evidence of adverse effects on health has been found following exposure concentrations of about 100 ppm [350 mg/m³] over several years.

In animals, repeated or long-term exposure to high concentrations of methylene chloride is associated with reversible CNS effects, slight eye irritation, liver effects and mortality. The lowest exposure concentration reported to cause liver effects is 25 ppm [88 mg/m³] (for continuous exposure). No effects were found on the liver following exposure to 250 ppm [880 mg/m³] for 5 hours per day. The lowest exposure concentration associated with reversible CNS effects is 2000 ppm [17700 mg/m³] (6 hours/day) with no effects at 500 ppm [7100 mg/m³]. Effects on brain chemistry were reported following exposure to 70 ppm [250 mg/m³] (6 hours/day).

Despite a large number of epidemiological investigations, no clear association between methylene chloride and cancer in humans has been demonstrated. The studies with the largest cohorts and longest follow up times are those published by Hearne and Pifer (1999), Lanes et al (1993) and Tomenson et al (1997).

Inhalation exposure to methylene chloride is associated with the development of cancers in mice but not in rats and hamsters. The mouse model may not be informative about cancer risks in humans because of large quantitative differences in the metabolism of methylene chloride. IARC (1999) concluded that that methylene chloride is *possibly carcinogenic to humans (Group 2B)*.

Human reproductive data are limited and do not provide clear evidence of an effect. No teratogenic effects were observed in rats exposed to 4560 ppm [16300 mg/m³] but foetal body weights were reduced. Slight skeletal malformations have been reported at 1230 ppm [4400 mg/m³]. No effects were found in a two generation study at concentrations of up to 1480 ppm [5300 mg/m³].

As mentioned above, no evidence of adverse effects on health has been found at the workplace following occupational exposure concentrations of about 100 ppm [350 mg/m³] over several years. Experimental studies appear consistent with this figure.

A relevant toxic metabolite of methylene chloride is carbon monoxide. For carbon monoxide SCOEL has recommended an OEL of 20 ppm, compatible with a biological limit (BLV) of 4% COHb (SCOEL/SUM/57D).

Experimental exposures of human volunteers to 100 ppm methylene chloride have resulted in 3% COHb at the end of an 8 h exposure period (*Figure 1*). This is basically supported by field studies in exposed workers (Soden 1993, Soden et al. 1996; *Figure 2*)

Taking these informations together, an OEL (8 h TWA) of 100 ppm is recommended for methylene chloride. Based on possible short-term prenarcotic effects, a STEL (15 min) is set to 200 ppm.

The biological limit (BLV) recommended for carbon monoxide (4%COHb) also to methylene chloride. It should be observed that this limit may be exceeded in cases of heavy smokers, due to the COHb increment by tobacco smoking. Therefore, for practical purposes the determination of methylene chloride in blood or urine (both at end of the shift) may be advantageous. According to the explanations given in chapter 5.1, BLVs are proposed for methylene chloride in blood of 1 mg/liter, and for methylenhe chloride in urine of 0.3 mg/liter.

Methylene chloride is carcinogenic to mice, producing lung and liver tumours. This carcinogenicity is conferred by a reductive, GST-dependent, metabolic pathway.

Quantitative comparisons of the toxicokinetics in several experimental animal species and in humans indicate that this toxifying pathway is not relevant in humans (see chapter 5.7 for details). This conclusion is also compatible with epidemiological data, which did not point to clear carcinogenic effects in humans, although there have been significant occupational exposures to methylene chloride since many decades. The compound is assigned to the SCOEL carcinogen group C, implying the existence of a "practical threshold (see chapter 5.7).

As specified in chapter 5.1, there may be a significant contribution of skin to the total uptake of methylene chloride under workplace conditions. Consequently, a skin notation is applied.

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