



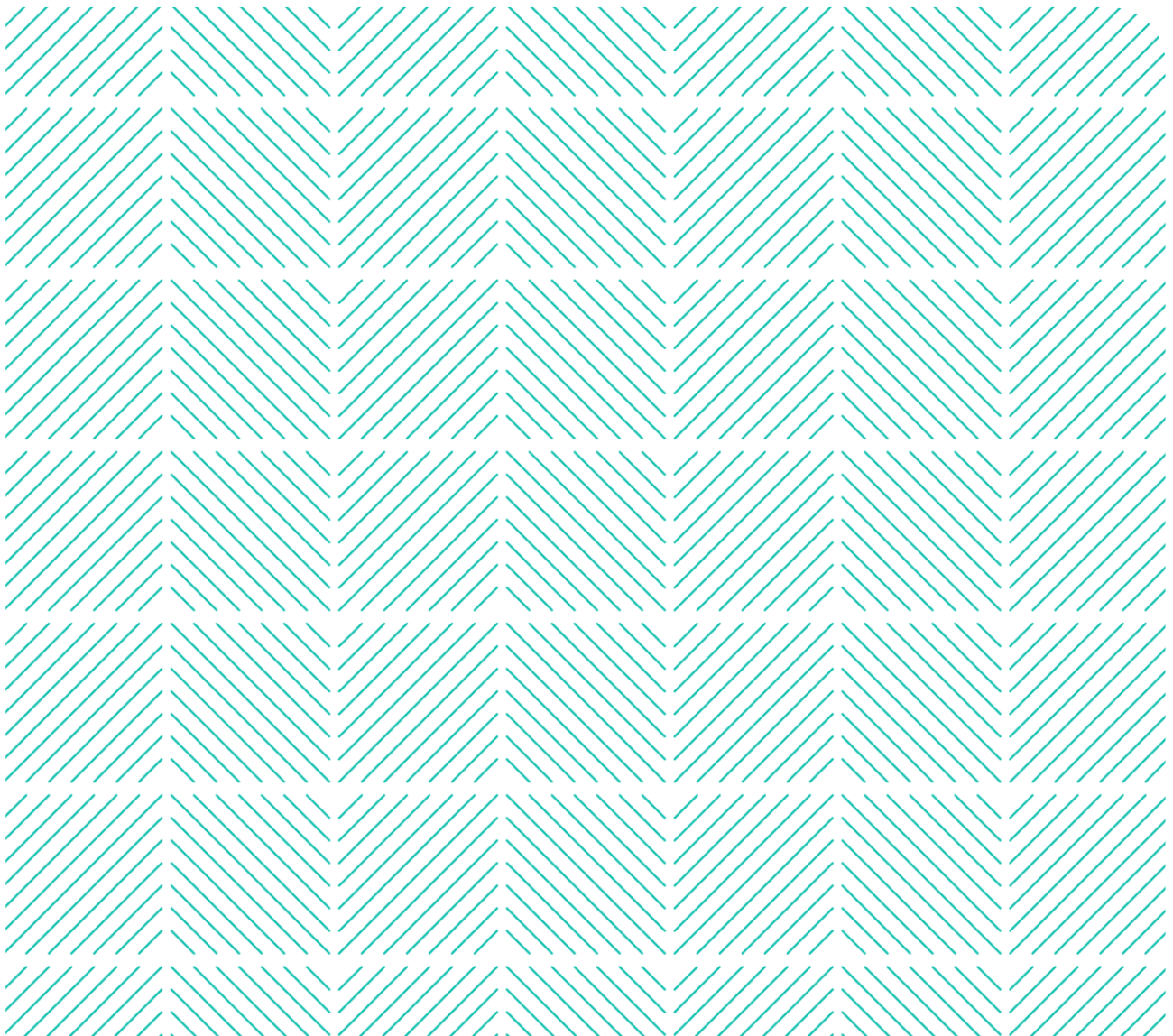
Arbeidstilsynet

Grunnlag for fastsettelse av grenseverdi

# 1-klor-2,3-epoksypropan (epiklorhydrin)

September 2020

Revisjon av direktiv 2019/130/EU – Høringsutkast



September 2020  
Arbeidstilsynet  
Postboks 4720 Torgarden  
7468 Trondheim

Tittel: Grunnlag for fastsettelse av grenseverdi for 1-klor-2,3-epoksypropan (epiklorhydrin)

Revisjon av direktiv 2019/130/EU – Høringsutkast

Dette dokumentet omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for 1-klor-2,3-epoksypropan (epiklorhydrin).

# Innhold

Innhold	3
Forord	4
Innledning	5
1. Stoffets identitet	5
2. Fysikalske og kjemiske data	5
2.1 Forekomst og bruk	6
3. Grenseverdier	6
3.1 Nåværende grenseverdi	6
3.2 Grenseverdi fra EU	7
3.3 Grenseverdier fra andre land og organisasjoner	7
3.4 Stoffets klassifisering	8
3.5 Biologisk overvåking	8
3.6 Andre reguleringer	9
4. Toksikologiske data og helseeffekter	9
4.1 Anbefaling fra SCOEL	9
4.2 Kommentarer fra TEAN	9
5. Bruk og eksponering	11
5.1 Opplysning fra Produktregistret	11
5.2 Eksponering og måledokumentasjon	11
6. Vurdering	12
7. Konklusjon med forslag til grenseverdi og anmerkninger	12
8. Grenseverdi og anmerkninger	13
Referanser	14
Vedlegg 1: SCOEL	15

# 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 direktiv 2019/130/EU fastsatt 16. januar 2019, og er den andre endringen av karsinogen-mutagen-direktivet 2004/37/EC om vern av arbeidstakere mot risiko ved å være utsatt for kreftfremkallende eller arvestoffskadelige stoffer (arbeidsmiljødirektivet). EU har som mål å fastsette juridisk bindende grenseverdier for 50 kreftfremkallende stoff gjennom fire endringsdirektiv til karsinogen-mutagen-direktivet. Når bindende grenseverdier er vedtatt i EU må medlemslandene/EØS-landene innføre samme verdi eller lavere. De bindende grenseverdiene tar hensyn til tekniske, økonomiske vurderinger i tillegg til de helsebaserte vurderingene.

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). EU-kommisjonen kan også velge kriteriedokumenter fra andre vitenskapskomiteer, som ECHA sin vitenskapskomite Risk Assessment Committee (RAC). Statens arbeidsmiljøinstitutt ved toksikologisk ekspertgruppe for grenseverdier, TEAN, bidrar med toksikologiske vurderinger i dette arbeidet.

Informasjon om bruk og eksponering i Norge innhentes fra Produktregisteret, og tilgjengelige eksponeringsdata fra virksomheter i ulike næringer fås fra eksponeringsdatabasen EXPO ved Stami.

Beslutningsprosessen skjer gjennom drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge deltar, samt orienteringer i møte med Regelverksforum eller per e-post, og med påfølgende offentlig høring. Konklusjonene fra høringen med forskriftsendringer og nye grenseverdier forelegges Arbeids- og sosialdepartementet som tar den endelige beslutningen om forskriftsfastssettelse av grenseverdiene.

# Innledning

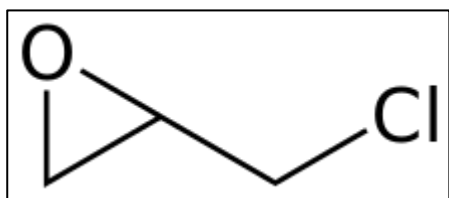
Dette dokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for 1-klor-2,3-epoksypropan (epiklorhydrin). Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for dette stoffet (vedlegg 1), samt vurderinger og kommentarer fra toksikologisk ekspertgruppe for grenseverdier, TEAN, ved Statens arbeidsmiljøinstitutt.

## 1. Stoffets identitet

1-klor-2,3-epoksypropan (epiklorhydrin) og dets molekylformel, stoffets identifikasjonsnummer i Chemical Abstract Service (CAS-nr.), European Inventory of Existing Commercial Chemical Substances (EINECS-nr. el. EC-nr.) er gitt i tabell 1. Strukturformler av epiklorhydrin er vist i figur 1.

Tabell 1. 1-klor-2,3-epoksypropan (epiklorhydrin) og dets identitet.

Kjemisk navn	1-klor-2,3-epoksypropan
Molekylformel	C <sub>3</sub> H <sub>5</sub> ClO
Synonymer	epiklorhydrin
CAS-nr.	106-89-8
EC-nr.	203-439-8
Index-nr.	603-026-00-6



Figur 1. Strukturformel av 1-klor-2,3-epoksypropan (epiklorhydrin), <https://en.wikipedia.org/wiki/Epichlorohydrin>.

## 2. Fysikalske og kjemiske data

1-klor-2,3-epoksypropan (epiklorhydrin) er en reaktiv, etsende og brannfarlig fargeløs væske med skarp søtlig lukt. Væsken er uløselig i vann, men blandbar med polare organiske løsningsmiddel. Det vises til tabell 2 for fysikalske og kjemiske data for epiklorhydrin.

Tabell 2. Fysikalske og kjemiske data for 1-klor-2,3-epoksypropan (epiklorhydrin).

Molekylformel	C <sub>3</sub> H <sub>5</sub> ClO
Molekylvekt (g/mol)	92,52
Fysisk tilstand	Fargeløs væske med skarp lukt
Smeltepunkt (°C)	-47
Kokepunkt, kPa (°C)	111
Flammepunkt (°C)	27,6
Selvantennelsestemperatur (°C)	411
Tetthet, 20 °C (g/cm <sup>3</sup> )	1,21
Damp tetthet (luft=1)	3,29
Damptrykk, 20 °C (mmHg)	16,4
Fordelingskoeffisient n-oktanol/vann (logK <sub>ow</sub> )	0,54
Løselighet i vann (mol/l)	0,712
Ekspljosjonsgrenser (%)	
Nedre (UEL)	3,8
Øvre (LEL)	21
Lukterskel (ppm)	10
Omregningsfaktor, 20 °C	1 ppm = 3,85 mg/m <sup>3</sup>

Data er gitt av TEAN.

## 2.1 Forekomst og bruk

Epiklorhydrin er en kjemikalie som i hovedsak blir brukt til produksjon av andre kjemikalier, for eksempel glyserin (C<sub>3</sub>H<sub>5</sub>(OH)<sub>3</sub>). Stoffet blir også brukt til produksjon av epoksy ved alkylering av bisfenol A og harpiks av fenoksy, til herding av propylenbasert gummi, og som løsemiddel for cellulose, estere og etere samt i harpiks med høy våtfasthet for papirindustrien.

# 3. Grenseverdier

## 3.1 Nåværende grenseverdi

Nåværende grenseverdi (8 timer) i Norge med anmerkninger for 1-klor-2,3-epoksypropan (epiklorhydrin) er:

0,5 ppm (1,9 mg/m<sup>3</sup>) med anmerkninger H (kjemikalier som kan tas opp gjennom huden), A (kjemikalier som skal betraktes som at de fremkaller allergi eller annen overfølsomhet i øynene eller luftveier, eller som skal betraktes som at de fremkaller allergi ved hudkontakt) og K (kjemikalier som skal betraktes som kreftfremkallende).

Denne grenseverdien ble revidert og fastlagt som administrativ norm med anmerkning H i 1978, med anmerkning K i 1988 og med anmerkning A i 1994. Denne administrative normen ble senere forskriftsfestet i 2013 i den da nye forskrift om tiltaks- og grenseverdier.

### 3.2. Grenseverdi fra EU

Den europeiske vitenskapskomiteen, SCOELs kriteriedokument av september 2011 [1] anbefaler ingen helsebasert grenseverdi for epiklorhydrin, men henviser til DECOS. EU har fastsatt en bindende grenseverdi for epiklorhydrin basert på anbefalinger fra DECOS. Dagens grenseverdi i EU, etter implementering av direktiv 2019/130/EU fastsatt 16. januar 2019 (andre endring av karsinogen-mutagen-direktivet 2004/37/EC) er:

BOELV (Binding Occupational Exposure Limit Value): 1,9 mg/m<sup>3</sup> (TWA 8 timer) med anmerkning «skin».

### 3.3. Grenseverdier fra andre land og organisasjoner

Grenseverdier fra andre land og organisasjoner er gitt i tabell 3.

Tabell 3. Grenseverdier for 1-klor-2,3-epoksypropan (epiklorhydrin) fra andre land og organisasjoner.

Land Organisasjon	Grenseverdi (8 timer)		Korttidsverdi (15 min)		Anmerkning Kommentar
	ppm	mg/m <sup>3</sup>	ppm	mg/m <sup>3</sup>	
Sverige <sup>1</sup>	0,5	1,9	1	4	C (kreftfremkallende), H (hudopptak), S (sensibiliserende)
Danmark <sup>2</sup>	0,5	1,9			H (hudopptak), K (kreftfremkallende)
Finland <sup>3</sup>	0,5	1,9			hud
Storbritannia <sup>4</sup>	0,5	1,9	1,5	5,8	Carc (kreftfremkallende)
Nederland <sup>5</sup>		0,19			
Tyskland, The German Committee on Hazardous Substances (Ausschuss für Gefahrstoffe, AGS) <sup>6</sup>	2 (1) 0,6 (2)	8 (1) 2,3 (2)	4 (1)	16 (1)	(1) - foreslått tolererbar kreftisiko (2) - foreslått foreløpig akseptabel kreftisiko
OSHA, USA <sup>6</sup>	5	19			
Tyskland, Myndighetene, Baua <sup>7</sup>	0,6 (b) 2 (2)	2,3 (b) 8 (2)			(b) Akseptabel konsentrasjon forbundet med risikoen 4:10000 (2) Tolererbar konsentrasjon på grunnlag av en ikke-kreftfremkallende effekt. H (hudopptak)
ACGIH, USA <sup>8</sup>	0,5				Skin (hudopptak)

<sup>1</sup> Arbetsmiljöverkets Hygieniska gränsvärden AFS 2018:1,

<https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2018-1.pdf>,5

<sup>2</sup> At-vejledning, stoffer og materialer - C.0.1, 2007, <https://at.dk/media/5941/c-0-1-graensevaerdilisten-2007-t.pdf>

<sup>3</sup> Social og helsøvsrdsministeriet, HTP-värden, Koncentrationer som befunnits skadliga, Helsingfors, 2016,

[http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/160972/STM\\_10\\_2018\\_HTPvarden\\_2018\\_WEB.pdf?sequence=1&isAllowed=y](http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/160972/STM_10_2018_HTPvarden_2018_WEB.pdf?sequence=1&isAllowed=y).

<sup>4</sup> EH40 andre utgave, 2013, <https://www.hse.gov.uk/pubns/priced/eh40.pdf>

<sup>5</sup> <https://www.ser.nl/nl/thema/arbeidsomstandigheden/Grenswaarden-gevaarlijke-stoffen/Grenswaarden/Epichloorhydrine>

<sup>6</sup> AGS, GESTIS International limit values, [https://limitvalue.ifa.dguv.de/WebForm\\_ueliste2.aspx](https://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx)

<sup>7</sup> Baua, TRGS 910, 2014 revidert 1.7.2020, [https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/pdf/TRGS-910.pdf?\\_\\_blob=publicationFile&v=2](https://www.baua.de/EN/Service/Legislative-texts-and-technical-rules/Rules/TRGS/pdf/TRGS-910.pdf?__blob=publicationFile&v=2)

<sup>8</sup> ACGIH, TLVs and BEIs, Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices, 2020.

### 3.4. Stoffets klassifisering

1-klor-2,3-epoksypropan (epiklorhydrin) er klassifisert og merket i henhold til CLP Annex VI (Europaparlaments og rådsforordning (EF) nr. 1272/2008 av 16. desember 2008), tabell 3.1 (Liste over harmonisert klassifisering og merking av farlige kjemikalier). Epiklorhydrin er klassifisert og merket med koder i henhold til fareklasse, kategori og faresetninger, som gitt i tabell 4.

Tabell 4. Fareklasser, farekategori med forkortelse, merkekoder og faresetninger for 1-klor-2,3-epoksypropan (epiklorhydrin).<sup>1,2</sup>

Fareklasse Farekategori Forkortelse	Merkekode	Faresetning
Brannfarlige væsker Kategori 3 Flam. Liq. 3	H226	Brannfarlig væske og damp
Akutt giftighet Kategori 3 Acute Tox. 3	H301	Giftig ved svelging
Akutt giftighet Kategori 3 Acute Tox. 3	H311	Giftig ved hudkontakt
Etsende/irriterende for huden Kategori 1 (underkategori 1A, 1B og 1C) Skin Corr. 1B	H314	Gir alvorlige etseskader på hud og øyne
Sensibiliserende ved innånding eller hudkontakt Hudsensibilisering Kategori 1 (underkategori 1A og 1B) Skin Sens. 1	H317	Kan utløse en allergisk hudreaksjon
Akutt giftighet Kategori 3 Acute Tox. 3	H331	Giftig ved innånding
Kreftfremkallende egenskaper Kategori 1A Kategori 1B Carc. 1B	H350	Kan forårsake kreft <sup>3</sup>

<sup>1</sup> CLP ((Forordning (EC) Nr. 1272/2008), <http://www.miljodirektoratet.no/Documents/publikasjoner/M259/M259.pdf>

<sup>2</sup> <https://echa.europa.eu/information-on-chemicals/cl-inventory-database>

<sup>3</sup>Angi eksponeringsvei dersom det med sikkerhet er fastslått at ingen andre eksponeringsveier er årsak til faren.

### 3.5 Biologisk overvåking

For å vurdere grad av 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 ikke fremmet et forslag til biologisk grenseverdi for epiklorhydrin.



## 3.6 Andre reguleringer

Det europeiske kjemikaliebyrået ECHA har samlet 40 regelverk i en database med informasjon om hvordan kjemiske stoffer er regulert, og regelverk for de stoffene er søkbare: [ECHA-søk](#).

I tillegg til regelverk for grenseverdi og klassifisering som er omtalt i dette dokumentet, kan man søke andre gjeldende regelverk for epiklorhydrin her: [Epiklorhydrin](#).

# 4. Toksikologiske data og helseeffekter

## 4.1 Anbefaling fra SCOEL

SCOEL vurderer epiklorhydrin som kreftfremkallende gruppe A (sannsynlig kreftfremkallende for mennesker) med en virkningsmekanisme uten en terskel for effekt, og SCOEL anbefaler derfor ingen bindende grenseverdi for epiklorhydrin. I tillegg anbefales en hudnotasjon «skin». Se anbefalingene fra SCOEL i vedlegg 1.

## 4.2 Kommentarer fra TEAN

### Grunnlag for bindende grenseverdi for epiklorhydrin

Epiklorhydrin oppfylder kriteriene for klassifisering som kreftfremkallende (kategori 1B) i samsvar med forordning EF nr. 1272/2008 (harmonisert CLP) og er derfor definert som et kreftfremkallende stoff i henhold til direktiv 2004/37/EF.

### Kreftklassifisering

IARC (1999) har klassifisert epiklorhydrin som kreftfremkallende i gruppe 2A [2] og NTP konkluderer som «*Reasonably anticipated to be a human carcinogen*» i sitt dokument «Reports on Carcinogens» (ROC), 2016.[3] De epidemiologiske dataene er ikke tilstrekkelige for å evaluere kreftfremkallende egenskaper av epiklorhydrin hos mennesker. Den nåværende kreft-klassifiseringen bygger på data fra forsøksdyr, som viser tilstrekkelig evidens for kreftfremkallende egenskaper.

EU-kommisjonen har brukt SCOEL (2011) som et viktig toksikologisk underlag for epiklorhydrin i forbindelse med innføring av den andre revideringen av CMD. Andre komiteer som har foretatt vurderinger av epiklorhydrin, er MAK, 2015 [4], ACGIH, 1997 [5], DECOS, 2000 [6] samt BAUA, 2012 [7]. Det er søkt etter nyere litteratur for epiklorhydrin, men TEAN har ikke funnet studier som vil endre de vurderingene som er gjort av disse vitenskapskomiteene.

### Helseeffekter og dose-respons relasjoner

Det er bred enighet om de kreftfremkallende egenskapene til epiklorhydrin, og at virkningsmekanismen for epiklorhydrin er gentoksisitet uten terskelnivå ved sin direkte alkylende egenskap på DNA. På grunn av de kjemiske egenskapene som et reaktivt epoxid, vil epiklorhydrin hovedsakelig virke kreftfremkallende lokalt avhengig av eksponeringsveien, men epiklorhydrin ser også ut til å kunne virke systemisk.

SCOEL vurderer også epiklorhydrin som kreftfremkallende gruppe A, med en virkningsmekanisme uten en terskel for effekt, og at det derfor ikke er mulig å utlede en helsebasert OEL. Det er knyttet risiko til ethvert eksponeringsnivå, og det anbefales derfor at enhver yrkesmessig eksponering for epiklorhydrin bør unngås. SCOEL henviser for øvrig til DECOS (2000) sine kvantitative risikovurderinger av de kreftfremkallende

egenskapene til epiklorhydrin. Siden det epidemiologiske datagrunnlaget for å gjøre en kvantitativ risikovurdering er utilstrekkelig, så har DECOS basert sine vurderinger på dyre-eksperimentelle data. Det antas at toksikokinetikken for epiklorhydrin og virkningsmekanismene for de kreftfremkallende egenskapene hos dyr er relevante for mennesker.

Den kvantitative risikomodellen fra DECOS er basert på lineær ekstrapolering, og gir følgende sammenhenger mellom epiklorhydrin-eksponering og ekstra kreftrisiko ved daglig yrkeseksponering over 40 år som presentert i tabell 5.

Tabell 5. Oversikt over eksponering og ekstra kreftrisiko ved yrkeseksponering over 40 år for 1-klor-2,3-epoksypropan (epiklorhydrin).

Epiklorhydrin (mg/m <sup>3</sup> )	Epiklorhydrin (ppm)	Risiko ved 40 års yrkeseksponering
0.19	0.05	4: 100 000 (4x10 <sup>-5</sup> )
1,9*	0.5	4: 10 000 (4x10 <sup>-4</sup> )
19	5	4: 1000 (4x10 <sup>-3</sup> )

\* Grenseverdien slik den er fastsatt i direktiv: 2004/37/EF

BAUA utførte sin egen kvantitative risikovurdering av epiklorhydrin i 2012 basert på det samme datagrunnlaget, og kom frem til lignende risikomatrise som DECOS gjorde i 2000.

#### Andre helseeffekter enn kreft

På grunn av de kjemiske egenskapene som et reaktivt epoxid, virker epiklorhydrin sterkt korrosivt både mot hud, øyne og slimhinnene i luftveiene.

#### TEANs vurdering

De kreftfremkallende egenskapene for epiklorhydrin, samt at stoffet virker med ikke-terskel mekanisme er godt dokumentert. Ut fra den eksisterende kunnskapen om epiklorhydrin vurdere TEAN risikovurderingen som er presentert i tabellen ovenfor som et godt grunnlag for å kunne fastsette en bindende grenseverdi for epiklorhydrin.

TEAN støtter en hudnotasjon (H) for opptak av epiklorhydrin gjennom hud, men det kan ikke utelukkes at opptak delvis kan skje etter korrosiv skade. Systemisk toksisitet som oppstår etter gjentatte appliseringer av fortynnet epiklorhydrin på hud, indikerer at opptak gjennom hud kan være viktig (MAK, 2015).

Det er visse holdepunkter for at epiklorhydrin kan gi hud-sensibilisering, slik at relevant anmerkning for dette bør beholdes i norsk regelverk.

## 5. Bruk og eksponering

### 5.1. Opplysning fra Produktregistret

Data fra Produktregisteret er innhentet fra 2020, og inneholder opplysninger om mengde og bruk av 1-klor-2,3-epoksypropan (epiklorhydrin) i deklareringspliktige produkter. Netto maksimal mengde av epiklorhydrin i 90 deklareringspliktige produkter utgjør totalt 4160,2041 tonn hvorav 4160,2035 tonn av disse utgjør import.

Epiklorhydrin inngår i produksjon av bl.a. skotøy, kjemikalier, maling og lakk, farmasøytiske råvarer og metaller, og til bygging av skip og flytende materiell, malerarbeid, gulvlegging og tapetsering.

På grunn av sikkerhetsbestemmelsene i Produktregisteret kan vi ikke gi eksakte opplysninger om produkttypekode, produkttype (<4 produkter) og netto mengde (< 0,4 tonn) for epiklorhydrin.

### 5.2. Eksponering og måledokumentasjon

#### 5.2.1. EXPO-data

Rapporterte eksponeringsmålinger av 1-klor-2,3-epoksypropan (epiklorhydrin) er hentet fra Stamis eksponeringsdatabase EXPO, se tabell 6 for eksponeringsmålinger. Målingene er utført i 2012 og resultatene viser totalt 10 personbårne prøver oppgitt med konsentrasjonsangivelse ppm som alle er svært lave (<0,01 ppm). Målingene er foretatt i næringen produksjon av andre organiske kjemiske råvarer.

Tabell 6. Oversikt over næring hvor det er foretatt eksponeringsmålinger av 1-klor-2,3-epoksypropan (epiklorhydrin) og måleresultater for disse målingene. Næringer hvor det er registrert færre enn 4 målinger er utelatt fra tabellen. GV = grenseverdi.

Næringskode /Næring	Antall virksomheter	Antall prøver	Gjennomsnitt (ppm)	Minimum	Maksimum
20.140 Produksjon av andre organiske kjemiske råvarer	1	10	< 0,01	< 0,01	< 0,01

#### 5.2.2. Prøvetakings- og analysemetode

I tabell 7 er anbefalte metoder for prøvetaking og analyser av 1-klor-2,3-epoksypropan (epiklorhydrin) presentert.

Tabell 7. Anbefalte metoder for prøvetaking og analyse av 1-klor-2,3-epoksypropan (epiklorhydrin).

Prøvetakingsmetode	Analysemetode	Referanse
Prøven samles opp på kullrør og ekstraheres med CS <sub>2</sub>	GC-FID <sup>1</sup>	NIOSH metode 1010 <sup>2</sup>

<sup>1</sup> GC-FID: gasskromatografi med en flammeionisasjonsdetektor

<sup>2</sup> NIOSH metode 1010: <https://www.cdc.gov/niosh/docs/2003-154/pdfs/1010.pdf>

## 6. Vurdering

Epiklorhydrin er anbefalt klassifisert som kreftfremkallende (gruppe 2A karsinogen) av IARC, som betyr at de er sannsynlig kreftfremkallende for mennesker. Den nåværende klassifiseringen for kreft bygger på data fra forsøksdyr, som viser tilstrekkelig evidens for kreftfremkallende egenskaper, og ikke fra epidemiologiske data hvor grunnlaget er utilstrekkelig.

Epiklorhydrin er klassifisert som som Carc. 1B (kan forårsake kreft) og merket i henhold til CLP Annex VI (Forordning EF nr. 1272/2008), se tabell 4.

I TEANs vurdering blir det vist til vurderinger gitt av SCOEL og DECOS og TEAN oppgir et estimat på eksponering for epiklorhydrin og antall ekstra krefttilfeller ved ulike eksponeringer av epiklorhydrin. Risikoestimatet fra DECOS, som TEAN viser til, tilsier at eksponering for 1,9 mg/m<sup>3</sup> eller 0,5 ppm antas å føre til en risiko for ekstra krefttilfeller på 4:10 000 beregnet for en 8 timers arbeidsdag og over en 40-års eksponeringsperiode. Dette samsvarer med direktivets forslag til grenseverdi for epiklorhydrin.

Epiklorhydrin er sterkt korrosivt både mot hud, øyne og slimhinnene i luftveiene og TEAN støtter vurderinger gitt av SCOEL (2011) og MAK (2015) om en hudnotasjon (H) for opptak av epiklorhydrin gjennom hud, og direktivet foreslår også en slik anmerkning. Det er også visse holdepunkter for at epiklorhydrin kan gi hudsensibilisering, slik at relevant anmerkning for dette bør beholdes i norsk regelverk. I Norge har epiklorhydrin fått anmerkninger H (kjemikalier som kan tas opp gjennom huden), A (kjemikalier som skal betraktes som at de fremkaller allergi eller annen overfølsomhet i øynene eller luftveier, eller som skal betraktes som at de fremkaller allergi ved hudkontakt) og K (kjemikalier som skal betraktes som kreftfremkallende) og som med fordel kan opprettholdes.

Data fra Produktregisteret gir opplysninger om mengde og bruk av epiklorhydrin i 90 deklareringspliktige produkter, men det er ingen av disse deklareringspliktige produkter som utgjør total mengde > 0,4 tonn og det kan derfor ikke gis ytterligere opplysninger om produkttyper.

Eksponeringsdatabasen inneholder for få målinger (< 40) og virksamheter (< 4) i en næring til å kunne gi en oversikt over eksponeringsnivået for epiklorhydrin i Norge. De gjennomsnittlige eksponeringsmålingene som er presentert er registrert å ligge under dagens grenseverdi.

EUs konsekvensutredning vurderer at dagens eksponeringsnivåer allerede er lavere enn foreslått bindende grenseverdi, og det forventes derfor ingen ytterligere investerings- eller driftskostnader. [8]

Arbeidstilsynet kan ikke se at det foreligger tekniske eller økonomiske argumenter for å ikke beholde nåværende grenseverdi basert på den helsebaserte anbefalingen fra TEAN.

## 7. Konklusjon med forslag til grenseverdi og anmerkninger

På bakgrunn av den foreliggende dokumentasjonen og en avveining mellom de toksikologiske dataene og eksponeringsdata (dvs. tekniske og økonomiske hensyn) for epiklorhydrin, forslås det at dagens grenseverdi (tilsvarende direktivverdi) og anmerkninger beholdes (anmerkning H tilsvarende direktivnotasjon).

Forslag til grenseverdi og anmerkning for 1-klor-2,3-epoksypropan (epiklorhydrin:

Grenseverdi (8-timers TWA): 0,5 ppm, 1,9 mg/m<sup>3</sup>

Anmerkninger: H (kjemikalier som kan tas opp gjennom huden), A (kjemikalier som skal betraktes som at de fremkaller allergi eller annen overfølsomhet i øynene eller luftveier, eller som skal betraktes som at de fremkaller allergi ved hudkontakt), K (kjemikalier som skal betraktes som kreftfremkallende) og G (EU har fastsatt en bindende grenseverdi for stoffet).

## 8. Grenseverdi og anmerkninger

*Dette kapitlet utarbeides etter at ASD har fastsatt den nye grenseverdien – altså etter drøftingene med partene, høringen og endelig forslag fra Arbeidstilsynet.*

# Referanser

1. SCOEL (2011), vedlegg 1.

IARC (1999). Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part 1, Part 2, Part 3), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 71.

[https://publications.iarc.fr/\\_publications/media/download/2306/f03545f32ff8144402516d2364fd313e25863279.pdf](https://publications.iarc.fr/_publications/media/download/2306/f03545f32ff8144402516d2364fd313e25863279.pdf)

2. National Toxicology Program (NTP) Report on Carcinogens, Fourteenth Edition (RoC). (2016). Epichlorohydrin. Office of the Report on Carcinogens, US Department of Health and Human Services.
3. MAK 2015: The MAK-Collection for Occupational Health and Safety © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Epichlorohydrin, 2015.
4. American Conference of Governmental Industrial Hygienists (ACGIH®), Threshold Limit Values (TLVs®) and Biological Exposure Indices (BEIs®) 1330 Kemper Meadow Drive | Cincinnati, Ohio; Epichlorohydrin, 1997.
5. DECOS, 2000. Epichlorohydrin, Health based calculated cancer risk values, No. 2000/10OSH, The Hague: the Health Council of the Netherlands, September 06, 2000.
6. Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). (2012). Exposure-risk-relationship for epichlorohydrin in BekGS 910. Dortmund, Germany.  
[https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/910/910-epichlorhydrin.pdf?\\_\\_blob=publicationFile&v=1](https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/910/910-epichlorhydrin.pdf?__blob=publicationFile&v=1)
7. European Commission, Second study to collect updated information for a limited number of chemical agents with a view to analyse the health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC, final report, Januar 2017.

# Vedlegg 1: SCOEL

Social Europe



**Recommendation from the Scientific  
Committee on Occupational Exposure  
Limits for epichlorohydrin**

SCOEL/SUM/169  
September 2011



European Commission



## Table of content

1 Occurrence/use and occupational exposure .....	4
2 Health significance.....	4
2.1 Toxicokinetics.....	4
2.1.1 Human data.....	4
2.1.2 Animal data .....	4
2.1.3 Biological monitoring .....	4
2.2 Acute toxicity .....	5
2.2.1 Human data.....	5
2.2.2 Animal data .....	5
2.3 Irritation and corrosivity.....	5
2.3.1 Human data.....	5
2.3.2 Animal data .....	6
2.4 Sensitisation.....	6
2.4.1 Human data.....	6
2.4.2 Animal data .....	6
2.5 Repeated dose toxicity .....	7
2.5.1 Human data.....	7
2.5.2 Animal data .....	7
2.6 Genotoxicity .....	7
2.6.1 <i>In vitro</i> .....	8
2.6.2 <i>In vivo</i> - human data .....	8
2.6.3 <i>In vivo</i> – animal data .....	8
2.7 Carcinogenicity .....	9
2.7.1 Human data.....	9
2.7.2 Animal data .....	10
2.7.3 Mode of action and cancer risk assessment .....	11
2.8 Reproductive toxicity .....	12
2.8.1. Human data.....	12
2.8.2 Animal data .....	12
Recommendation .....	13
References.....	15





## Recommendation from the Scientific Committee on Occupational Exposure Limits for Epichlorohydrin

8-hour TWA:	not assigned (see "Recommendation" page 11)
STEL (15 min):	not assigned (see "Recommendation" page 11)
Additional classification:	skin notation (see "Recommendation" page 11)
BLV:	not assigned
SCOEL carcinogen group:	A (non-threshold carcinogen)
Carcinogenic risk assessment:	see "Recommendation" (page 11)

Substance identification: 1-chloro-2,3-epoxypropane

Synonyms: chloropropylene oxide, chloromethyl-oxirane

Structural formula:

$$\text{H}_2\text{C} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{---} \text{CH} \text{---} \text{CH}_2\text{Cl} \end{array}$$

CAS no.: 106-89-8  
Molecular formula: C<sub>3</sub>H<sub>5</sub>ClO  
Molecular weight: 92.53  
Melting point: -48°C  
Boiling point: 116°C

EU-Classification:

Fam. Liq. 3	H226	Flammable liquid and vapour
Carc. 1B	H350	May cause cancer
Acute Tox. 3 *	H331	Toxic if inhaled
Acute Tox. 3 *	H311	Toxic in contact with skin
Acute Tox. 3 *	H301	Toxic if swallowed
Skin Corr. 1B	H314	Causes severe skin burns and eye damage
Skin Sens. 1	H317	May cause an allergic skin reaction

Conversion factor: 1 ppm = 3.84 mg/m<sup>3</sup>; 1 mg/m<sup>3</sup> = 0.260 ppm (DFG 2009)

Criteria documents used: This summary is mainly based on the recent documentation of DFG (2009), which includes data reported earlier by BUA (1992), IARC (1999) and DFG (2003). This was supplemented by a recent literature search by SCOEL.



## 1 Occurrence/use and occupational exposure

Epichlorohydrin is a major raw chemical for the production of epoxy and phenoxy resins. It and is also used in the manufacture of glycerine, in curing propylene-based rubbers, as a solvent for cellulose esters and ethers, and in resins with high wet-strength for the paper industry (IARC 1999, NTP 2002).

## 2 Health significance

Epichlorohydrin is a directly acting alkylating agent. With nucleophiles it reacts preferably with the epoxide ring, but also with the chlorine function. The biological properties of the compound are related to this reactivity.

### 2.1 Toxicokinetics

#### 2.1.1 Human data

Incubation of epichlorohydrin in the presence of human cells of lung and bronchial parenchyma led to a decrease of mutagenicity, which is likely to be related to rapid metabolic inactivation (De Flora *et al.* 1984).

#### 2.1.2 Animal data

After both inhalation and oral administration, more than 90% epichlorohydrin was rapidly absorbed and distributed in the organism of rats within 2–4 hours (CMA 1979a; Gingell *et al.* 1985; Weigel *et al.* 1978). After application of radiolabeled epichlorohydrin, the highest systemic tissue concentrations were reached in the kidneys, intestine, liver, lacrimal glands, pancreas and spleen. The highest level of radioactivity was found in the stomach after oral administration and in the nasal mucosa after inhalation. Lower radioactivity was detected in the blood, lungs, brain and sex organs (Weigel *et al.* 1978). At different dose levels and with various types of administration of <sup>14</sup>C-labelled epichlorohydrin, 90% of the activity was excreted within 72 hours, i.e. 46–54% in the urine, 25–40% via the lungs and maximally 4% via the faeces (CMA 1979a; Gingell *et al.* 1985).

After initial reaction with glutathione, epichlorohydrin is metabolized, leading to metabolites that are detected in the urine. These are the mercapturic acid derivatives N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine, S-(2,3-dihydroxypropyl)-L-cysteine and N-acetyl-S-(2,3-dihydroxypropyl)-L-cysteine. In addition, a likewise excretable 3-chloro-1,2-propanediol is formed from hydrolysis. N-Acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine (36% of the dose) and 3-chloro-1,2-propanediol (4%) are considered to be the main metabolites (Gingell *et al.* 1985). According to Fakhouri and Jones (1979), 3-chloro-1,2-propanediol *in vivo* leads to the formation of  $\beta$ -chlorolactic acid, which in turn yields oxalic acid. The latter metabolite was however not detected in other studies.

#### 2.1.3 Biological monitoring

The analysis of haemoglobin adducts derived from epichlorohydrin has been proposed as a means of biological monitoring. As epichlorohydrin is a bifunctional alkylating agent (Romano *et al.* 2007), the reaction with the N-terminal valine of haemoglobin occurs either with its chlorine or with its epoxide moiety. N-(2,3-Dihydroxypropyl)valine was first described as haemoglobin adduct. This was also detected in rats after intraperitoneal administration of 40 mg/kg body weight. An increased amount of it was found in smokers (Hindsø Landin *et al.* 1996).

Later, Bader *et al.* (2009) described a method of quantitation of the adduct N-(3-chloro-2-hydroxypropyl)valine in human haemoglobin. This adduct was found in the blood of persons exposed to epichlorohydrin at a freight train accident.

These methods could provide a basis for biomonitoring in the future. However, more detailed occupational field studies are lacking so far.

## 2.2 Acute toxicity

### 2.2.1 Human data

An airborne concentration of 20 ppm epichlorohydrin caused corrosion to the eyes and nasal mucosa after one hour. 40 ppm led to irritation to the eyes and throat, which lasted for 48 hours (no other details on exposure period). 100 ppm was intolerable even for the shortest period. Exposure of the eyes to the liquid substance led to opacity and necrosis of the cornea (no other details; Lefaux 1966).

Cases of severe skin burns after contact with epichlorohydrin were described. Erythema, oedema and papules were observed during some days after direct skin contact. The persons affected complained about agonizing itching. The symptoms had subsided in all persons only after about two weeks (Ippen and Mathies 1970).

Schultz (1964) reported a person who had developed chronic asthmatic bronchitis after inhalation exposure to epichlorohydrin. Severe fatty degeneration of the liver was diagnosed biopsically.

### 2.2.2 Animal data

After exposure periods between 2 and 8 hours, the LC<sub>50</sub> was 3000 to 250 ppm and the 4-hour LC<sub>50</sub> for rats was 500 ppm (Hine *et al.* 1981; Pallade *et al.* 1967; Pozzani and Carpenter 1960; Srám *et al.* 1981). An oral LD<sub>50</sub> of about 220 mg/kg body weight was determined in rodents (Hine *et al.* 1981; Lawrence *et al.* 1972; Pozzani and Carpenter 1960), and the dermal LD<sub>50</sub> established in rabbits was 754 (Lawrence *et al.* 1972) and 1038 mg/kg body weight (Hine *et al.* 1981). CNS, respiratory tract or renal lesions were specified as causes of death depending on the type of administration (Laskin *et al.* 1980; Pallade *et al.* 1967; Weigel *et al.* 1978).

In an inhalation study, the respiratory rate of rats was clearly reduced within 15 minutes at a concentration of 363 ppm, and halved at 1342 ppm. Marked discharge from the nasal mucosa was observed at 1963 ppm (Gardner *et al.* 1985).

## 2.3 Irritation and corrosivity

### 2.3.1 Human data

A 46-year-old pharmaceutical company worker developed severe erythema and oedema on the face, neck, back and hands after having continuously been exposed to epichlorohydrin for 11 months. The symptoms subsided after the worker left the workplace for two weeks, but returned when he resumed work at his former workstation. They cannot be assigned to epichlorohydrin with certainty since there was co-exposure to other substances in the synthesis of propranolol and oxprenolol (Rebandel and Rudzki 1990).

Luo *et al.* (2004) investigated the influence of the glutathione S-transferase *hGSTM1* and *hGSTT1* genes on the toxic effect of epichlorohydrin. In *hGSTM1* null genotype workers, there was a dose-response of lung function tests (FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, MMEF) for epichlorohydrin exposure, but not in the *hGSTM1* non-null genotype workers. The exposure was found to be significantly associated with a decreased FEV<sub>1</sub> value ( $p = 0.09$ ) and a decreased MMEF value ( $p = 0.053$ ) after adjusting for other factors. The *hGSTM1* null genotype was found to be significantly associated with a decreased FEV<sub>1</sub> value ( $p = 0.038$ ), decreased FEV<sub>1</sub>/FVC value ( $p = 0.056$ ), and decreased MMEF value ( $p = 0.012$ ) after adjusting for other factors. The study was interpreted to indicate that obstructive lung abnormalities and small airway lung damage are associated with epichlorohydrin exposure.

The irritancy of epichlorohydrine to the respiratory tract is in accordance with human experience after an accidental release of epichlorohydrine (Basting *et al.* 2006)





### 2.3.2 Animal data

Experimental exposures of rats and rabbits to 25 or 50 ppm epichlorohydrine (6h/d, 5d/wk for 10 weeks) caused severe irritating effects to the nasal turbinates (John *et al.* 1983a). In mice, the RD<sub>50</sub> concentration was assessed to be 687 ppm. In addition to the nasal cavity, this concentration induced lesions in the lower respiratory tract, when applied 6h/d for 5 days (Buckley *et al.* 1984).

## 2.4 Sensitisation

### 2.4.1 Human data

In a Dutch plant for the production of epoxy resins, 26 cases of eczema were observed among 228 male workers. All workers were occupationally exposed to epichlorohydrin and bisphenol A, the starting materials of the manufacturing process. The authors reported that the workers had unintentional skin contact with bisphenol A epoxy resins, for example during maintenance operations, although closed systems were used for manufacturing the epoxy resins and protective measures such as wearing gloves had been taken. A patch test was carried out with 19 of the 26 workers. In addition to other substances, the two epoxy resins (molecular weight 385 and 980), which were the main production products, and bisphenol A, 1% epichlorohydrin in petrolatum and 1% in isopropanol, were tested. In the patch test, a positive reaction to 1% epichlorohydrin in petrolatum was obtained in 8 cases; it was isolated in 4 cases and occurred together with reactions to epoxy resins in 4 cases. The observed delayed-type sensitization to epichlorohydrin may have been caused by two routes of sensitization: first by direct skin contact and second aerogenically by increased airborne concentrations due to the volatility of epichlorohydrin (Prens *et al.* 1986).

The same research group reported another 6 cases (5 workers of a plant for the production of epoxy resins and a vehicle painter) of occupational contact dermatitis, which was considered to be caused by exposure to epichlorohydrin or bisphenol A epoxy resins. In addition to other substances, an epoxy resin with an average molecular weight of 385 as well as bisphenol A and 1% epichlorohydrin in solvent were patch-tested. All patients showed delayed-type reactions to epichlorohydrin, two of them to epichlorohydrin alone (van Joost 1988).

Another publication by this research group focussed on 5 workers of a plant for the production of epoxy resins who had developed contact dermatitis at their workplace. Here, too, the authors saw a connection with the delayed-type reaction to 1% epichlorohydrin in petrolatum, which they detected in the patch test in all 5 patients. A reaction to epichlorohydrin alone was found in 2 patients (van Joost *et al.* 1990).

Moreover, other research groups described case reports of contact sensitization to epichlorohydrin that had not been acquired in epoxy resin production (for a detailed description, see DFG 2009).

### 2.4.2 Animal data

Skin sensitization was examined in a Guinea pig maximization test in 15 Guinea pigs (20 animals in the control group). Intra-dermal and dermal inductions were carried out with 5% epichlorohydrin in ethanol, and 1% epichlorohydrin in ethanol was used for dermal challenge. A positive reaction was observed in 9 of 15 animals (Thorgeirsson and Fregert 1977).

No sensitization was found in another, insufficiently documented maximization test in 5 Guinea pigs at a test concentration of 0.01% epichlorohydrin in vegetable oil (Lawrence *et al.* 1972). However, this study has only limited applicability for assessment since the number of animals was too small, the test substance concentration might have been too low and insufficient information was provided on range finding. Another study in which none of 18 Guinea pigs reacted after 8 intracutaneous injections during challenge (Weil *et al.* 1963)



cannot be assessed either because of inadequate documentation (e.g. test substance concentrations not specified).

In a modified test carried out according to Landsteiner in 10 guinea pigs dermally treated four times with epichlorohydrin for induction (as well as a single intradermal treatment with Freund's adjuvant), all 10 animals reacted positively in the dermal challenge (no other details for example on the test substance concentration used; Rao *et al.* 1981).

## 2.5 Repeated dose toxicity

### 2.5.1 Human data

No published data are available.

### 2.5.2 Animal data

In a 90-day study (CMA 1979b; Quast *et al.* 1979), 20 female and 20 male B6C3F1 mice, Fischer 344 rats and Sprague-Dawley rats were exposed to epichlorohydrin for 6 hours on 5 days per week at concentrations of 5, 25 and 50 ppm. Whereas no effects were recorded at 5 ppm, hyperplasia, metaplasia and inflammatory infiltrates were found in the nose, the most sensitive organ, at the higher concentrations. Damage to the kidneys, liver and adrenals of varying severity was observed in the different animal strains.

In a study described by BUA (1992), continuous inhalation of 5 ppm by rats over 98 days led to weight loss and morphological changes to the liver, heart, kidneys and CNS, to increased urinary coproporphyrin and an increase of leukocytes in the peripheral blood. After inhalation of 0.05 and 0.5 ppm, these effects were not found or were only slight as compared with the controls. The validity of this study is unclear.

Four applications of 600 mg/kg body weight were fatal for 10/10 rats and three applications of 1200 mg/kg body weight were fatal for 4/10 rats (Freuder and Leake 1941). After intraperitoneal injection of 11, 22 and 56 mg/kg body weight three times a week over a period of 12 weeks, there was a dose-dependent, significant decrease of haemoglobin in the blood, an increase of eosinophils in all treated animals and a reduction of lymphocytes in the two groups treated with the highest doses. The weights of heart, liver and kidneys increased in the animals treated with 56 mg/kg body weight (Lawrence *et al.* 1972).

Adult male and female Sprague-Dawley rats received epichlorohydrin via gavage in distilled water for 10 consecutive days at dose levels of 3, 7, 19, and 46 mg/kg per day, and for 90 days at dose levels of 1, 5, and 25 mg/kg per day. Epichlorohydrin did not adversely affect mortality, but toxicity, at the higher doses, was evident by losses in body weight gain and organ weights, reductions in food and water consumption, and in the hematological and microscopic examinations in both study periods. Significant decreases in erythrocyte count, hemoglobin, and hematocrit levels were found in the high dose level in males after 10 and 90 days. Dose-related increases in kidney and liver weights were observed in both sexes at 25 mg/kg per day in the 90-day study and in various organs for both 19 and 46 mg/kg per day in the 10-day study. Histopathological examination identified the forestomach as the primary target organ for both sexes and in both studies with significant dose-related increases in mucosal hyperplasia (acanthosis) and hyperkeratosis. Based on the data presented, a lowest observable adverse effect level (LOAEL) for oral exposure of Sprague-Dawley rats to epichlorohydrin was 3 mg/kg per day for 10 days and 1 mg/kg per day was suggested as the no observed adverse effect level (NOAEL) for a 90 day oral exposure (Daniel *et al.* 1996).

## 2.6 Genotoxicity

Detailed reviews on the genotoxic effects of epichlorohydrin are available by Giri (1997), IARC (1999) and Kolman *et al.* (2002). The main results are summarized below.



### 2.6.1 *In vitro*

In most of the *in vitro* test systems used, epichlorohydrin induced genotoxic effects that were almost always observed even in the absence of an added metabolic activation system. Studies in bacterial test systems showed that epichlorohydrin led to DNA lesions in *E. coli* and *B. subtilis* and induced gene mutations in *S. typhimurium* and *E. coli* strains and in *Klebsiella pneumoniae*. It caused DNA lesions, recombinations, gene mutations and aneuploidies in yeasts. Epichlorohydrin induced DNA single strand breaks and SCE in mammalian cells. Induction of gene mutations at different loci and of chromosome mutations was detected in numerous studies (IARC 1999).

The main adduct obtained after reaction of epichlorohydrin with 2'-deoxynucleosides *in vitro* is 7-[3-chloro-2-hydroxypropyl]guanine, resulting from reaction of the epoxide ring of epichlorohydrine (Singh *et al.* 1996). Another aspect of DNA interaction is the formation of interstrand DNA-cdrosslinks (Romano *et al.* 2007).

Holzer *et al.* (2008) incubated rat and human nasal mucosa cells with epichlorohydrin and used the COMET assay as an endpoint of genotoxicity. In contrast to the cells derived from rats, pronounced interindividual differences in susceptibility were found with the human samples.

### 2.6.2 *In vivo* - human data

The DNA adduct 7-[3-chloro-2-hydroxypropyl]guanine (vs.) was detected at a concentration of 0.8–7.1 adducts/10<sup>9</sup> nucleotides in the lymphocytes of workers who were classified as exposed to epichlorohydrin on account of the fact that they worked in an epichlorohydrin-processing plant. No details are available about the level of exposure. This adduct was not found in non-exposed control persons (Plna *et al.* 2000).

Significantly increased sister chromatid exchange (SCE) frequencies were detected in the lymphocytes of 21 workers with high exposure to epichlorohydrin (4.5 years; 1.1–3.9 ppm) compared with 29 non-exposed control persons adjusted for age. Smoking was excluded as the only cause of the increase. The SCE frequency in 35 workers with low exposure (4.2–7.0 years; 0.1–0.2 ppm) was not significantly increased compared with the control persons (Cheng *et al.* 1999).

The lymphocytes of workers who were exposed to 0.4–0.86 mg/m<sup>3</sup> (0.11–0.23 ppm) during a 12-hour shift showed no increased frequency of hprt mutations, a slight increase of micronuclei and a significant increase of SCE and high frequency cells (> 10 SCE per cell) (Hindsø Landin *et al.* 1997).

Kucerová *et al.* (1977) found significantly increased frequencies of structural chromosomal aberrations (chromatid and chromosome breaks) in the lymphocytes of workers occupationally exposed to epichlorohydrin concentrations of 0.125 to 1.25 ppm. The workers were examined before the beginning of exposure (1.37 aberrations/cell), one year (1.91 aberrations/cell) and two years (2.69 aberrations/cell; *p* < 0.001) after the beginning of exposure. Šrám *et al.* (1980) re-examined 23 of these workers after 4-year exposure (3.02 aberrations/cell) and compared them with an adjusted control group (for age, smoking and drinking habits; *n* = 34; 2.06 aberrations/cell; *p* < 0.01) and with the general population (*n* = 21; 1.33 aberrations/cell; *p* < 0.01).

In another study of Picciano (1979), 93 exposed persons (no concentrations specified; presumably 5 ppm TWA; age 35.8 years) and 75 control persons (age 25.2 years) were examined. The frequencies of cells with chromatid breaks, chromosome breaks and marker chromosomes (rings, dicentric chromosomes and translocations), of severely damaged cells and of the total number of damaged cells were significantly higher (*p* < 0.005) in the exposed group than in the control group.

### 2.6.3 *In vivo* – animal data

In a study on the ability of epichlorohydrin to bind covalently to macromolecules, the [2-<sup>14</sup>C]-labelled substance (6.35 micromol/kg body weight) was intraperitoneally injected into mice and rats. In mice, an association of radioactivity with the purified DNA from liver,





lung, kidney and stomach, which was quantitatively similar for all organs, was observed 22 hours after administration. A covalent binding index (CBI) of 23 was determined for rat liver DNA. The corresponding value for benzene was 7 and that for 1,2-dibromoethane was 515 (Prodi *et al.* 1986).

In another study in rats, a quantitatively similar binding to the DNA of various organs was detected 6 and 24 hours after intraperitoneal injection of [2-<sup>3</sup>H]epichlorohydrin (0.97 µmol/kg body weight), and N7-(3-chloro-2-hydroxypropyl)guanine was identified as the main DNA adduct. A CBI value of 0.6 was determined. A CBI value of 2 was found by the same working group for the chemically less reactive propylene oxide. This discrepancy was attributed to a relatively more rapid elimination of epichlorohydrin (Hindsø Landin *et al.* 1999).

Epichlorohydrin induced X chromosomal recessive lethal mutations in the fruit fly *Drosophila melanogaster* (Knaap *et al.* 1982; Vogel *et al.* 1981). A third test had a negative result (Würgler and Graf 1981).

Epichlorohydrin (50 and 100 mg/kg body weight) was administered intramuscularly or subcutaneously in a host-mediated assay with NMRI mice and the *Salmonella* strains G46, TA100, TA1950, TA1951 and TA1952 (Srám *et al.* 1976). An increased rate of revertants was found for the strains G46, TA100 and TA1950. In another assay with *Schizosaccharomyces pombe* (after intraperitoneal administration of the yeast suspension and intraperitoneal treatment or intrasanguinous administration of the yeast suspension and intravenous treatment) and two different mouse strains [CD1 and (CD1xC57BL)F1], negative results were reported by Rossi *et al.* (1983b) for doses between 2 and 100 mg/kg body weight.

A third assay with NMRI mice and *Escherichia coli* strains K-12 uvrB/recA (mainly cell death of the repair-deficient bacterial strains) yielded negative results after orally administered 240 mg/kg body weight or intraperitoneally injected 140 mg/kg body weight (Hellmér and Bolcsfoldi 1992).

Increased sperm head anomalies were described in a study in mice (11 days after a single oral administration of 50 mg/kg body weight; Cassidy *et al.* 1983). This finding was however not confirmed in a second study with intraperitoneal injection of 0.025–0.2 ml/kg body weight and day for 5 days (Topham 1980). Since morphological sperm anomalies are generally not interpreted as mutations, these results are not relevant.

Epichlorohydrin induced chromosomal aberrations in the bone marrow of ICR mice in a dose range of 1–50 mg/kg body weight (in DMSO) after single or several (on 5 consecutive days) intraperitoneal and oral administrations (Srám *et al.* 1976).

No significant increase in the incidence of chromosomal aberrations was found in the bone marrow of CD1 mice in another study after oral administration of 50 or 200 mg/kg body weight (Rossi *et al.* 1983a). The authors attribute the negative result to the fact that epichlorohydrin was no longer detectable in the blood as early as 20 minutes after oral (in DMSO) or intraperitoneal (in water) administration.

Several authors obtained uniformly negative results in micronucleus tests with mice (Asita *et al.* 1992; Kirkhart 1981; Salamone *et al.* 1981; Tsuchimoto and Matter 1981).

Nor did epichlorohydrin induce any dominant lethal mutations (Epstein *et al.* 1972). The originally negative result was confirmed in detailed investigations (once intraperitoneally 5, 10 and 20 mg/kg body weight; once orally 20 and 40 mg/kg body weight; five times intraperitoneally 1 and 4 mg/kg body weight; five times orally 4 and 16 mg/kg body weight) (Srám *et al.* 1976).

## 2.7 Carcinogenicity

### 2.7.1 Human data

In a nested case-control study by Bond *et al.* (1986) among 19608 workers of a chemical production facility who were examined for possible health damage caused by carbon tetrachloride, a lowering of lung cancer mortality was found for the very small subcohort of persons ever exposed to epichlorohydrin (odds ratio 0.3; 95% CI 0.1–0.9; 5 cases).

Barbone *et al.* (1992, 1994) studied the frequency of lung cancer and CNS cancer in a nested case-control study based on a cohort previously examined by Delzell *et al.* (1989).



A positive association was found between potential exposure to epichlorohydrin and lung cancer after adjustment for smoking habits (odds ratio 1.7; 95% CI 0.7–4.1; 51 cases), but not in the calculation with regard to exposure period and cumulative dose. An association with potential exposure to epichlorohydrin was detected in 11 cases with CNS cancer (7 with brain tumours, 2 with meningiomas and 2 with benign tumours) and 44 controls matched for age (odds ratio 4.2; 95% CI 0.7–26). Associations with the exposure period ( $p = 0.11$ ) and cumulative exposure ( $p = 0.08$ ) were also observed. These results are not statistically significant. The small number of cases must be considered.

Dezell *et al.* (1989) reported an excess of lung cancer in a cohort study among 2642 male workers with at least six-month exposure to epichlorohydrin. At an expected level of 0.91 ( $p < 0.03$ ), 4 of 44 persons exposed in the production of the substance developed lung cancer.

Tsai *et al.* (1996) reported a cohort of 863 workers who had previously been examined by Enterline (1982) and Enterline *et al.* (1990). The rate of workers affected by lung cancer did not increase (SMR 0.7; 95% CI 0.5–1.1; 23 cases). Increased incidence rates of prostate cancer (SMR 2.3; 95% CI 1.0–4.5; 8 cases) and malignant melanomas (SMR 3.2; 95% CI 0.7–9.4; 3 cases) were found among workers whose initial exposure had taken place at least 20 years before. No relation between the frequency of developing cancer and the estimated exposure level was obtained in this study.

Olsen *et al.* (1994) described results of a retrospective cohort study on cancer mortality among 1064 male workers in the production areas for epoxy resins, glycerol and allyl chloride/epichlorohydrin. Exposures to epichlorohydrin in glycerol production (highest exposures) were between 1 ppm and 5 ppm before 1970 and below 1 ppm after 1970. A total of 66 cohort members died up to 1989, 10 of them from cancer (SMR 0.5; 95% CI 0.2–0.9).

### 2.7.2 Animal data

In a lung adenoma test with intraperitoneal administration of 20, 50 and 100 mg/kg body weight to an A/J strain of mice three times a week for 8 weeks, significantly more lung tumours were induced only in the males that had received the highest dose (Stoner *et al.* 1986).

In an initiation-promotion study, 2 mg epichlorohydrin in 0.1 ml acetone was applied once to the skin of 30 ICR/Ha Swiss mice. After 2 weeks, 2.5 µg phorbol myristate acetate in 0.1 ml acetone was applied three times a week for a period of 385 days. From the 92nd day, skin papillomas developed in 9 animals and a skin carcinoma in one animal. A skin papilloma was observed in 3 of the mice treated with phorbol myristate acetate alone after about 224 days, whereas the control group treated with acetone alone developed no tumours (Van Duuren *et al.* 1974). Another study carried out with epichlorohydrin as an initiator in 20 mice was negative (Van Duuren *et al.* 1972).

In a whole-body inhalation study carried out by Laskin *et al.* (1980), groups of 100 male Sprague-Dawley rats were subjected to lifetime exposure to 0, 10 and 30 ml epichlorohydrin/m<sup>3</sup> (purity 99%) for 5 hours daily on 5 days per week. Two further groups of 100 and 40 male rats were exposed to 100 ppm 6 hours daily for 30 days and then observed during their entire lifespan. One group of 100 male controls was sham-exposed and another group of 50 control animals remained untreated. No tumours developed after exposure to 10 ppm. Exposure to 30 ppm yielded a nasal papilloma in one rat after 40 days and a squamous cell carcinoma of the nasal cavity in a second rat after 752 days. Among the 140 rats that had been exposed to 100 ppm for 30 days, 15 rats developed squamous cell carcinomas and 2 rats developed nasal papillomas between days 330 and 933 of the study. One bronchial papilloma was observed on day 583 after the beginning of the study. Four of the exposed rats developed pituitary adenomas; a squamous cell carcinoma in the forestomach and further tumours were found in one animal. A total of 5 tumours occurred in the 150 control animals: 3 subcutaneous fibromas, 1 forestomach papilloma and 1 malignant lymphoma. The authors regarded the respiratory tract tumours as being related to exposure, unlike the other tumours.

Konishi *et al.* (1980) administered 0, 375, 750 and 1500 mg epichlorohydrin/l (purity not specified) to 6-week-old Wistar rats with the drinking water over a period of 81 weeks. The





animals were then sacrificed and the tissues examined histopathologically. Hyperplasias and forestomach tumours were found in the treated rats in relation to the dose in the order of the specified doses: hyperplasias: 0/10, 7/9, 9/10, 12/12; papillomas: 0/10, 0/9, 1/10, 7/12; carcinomas: 0/10, 0/9, 1/10, 2/12. No tumours were detected in other tissues.

Wester *et al.* (1985) administered daily doses of 0, 2 and 10 mg epichlorohydrin/kg body weight with a purity of 99.5% by gavage to groups of 50 newly weaned female and male Wistar rats daily on 5 days per week over a period of 2 years. Subsequently the animals was sacrificed. A dose-dependent increase of hyperplasias, papillomas and forestomach carcinomas was observed. In the order of the specified doses, the males showed 5/50, 24/49 and 6/49 hyperplasias, 1/50, 6/49 and 4/49 papillomas and 0/50, 6/49 and 35/49 carcinomas. The females revealed 3/47, 12/44 and 7/39 hyperplasias, 2/47, 3/44 and 0/39 papillomas and 0/47, 2/44 and 24/39 carcinomas.

Fifty mice that had been treated epicutaneously with epichlorohydrin (2 mg in 0.1 ml acetone, three times a week for 580 days) developed no tumours (Van Duuren *et al.* 1974). This observation is consistent with the findings of Weil *et al.* (1963), who observed no tumour formation after lifetime application of one brush filling each of undiluted epichlorohydrin to the shaved dorsal skin of 90-day-old CH3 mice three times a week.

After subcutaneous administration of 1 mg epichlorohydrin in 0.05 ml tricaprilin once a week for 580 days, 6/50 female IVR/HA Swiss mice developed local sarcomas and one developed an adenocarcinoma. The control incidence for local sarcomas was 1/50 (Van Duuren *et al.* 1974). Another, similar study yielded sarcomas in 2/50 mice (Van Duuren *et al.* 1972).

The intraperitoneal injection of 1 mg epichlorohydrin in 0.05 ml tricaprilin, once a week for 450 days, led to lung papillomas in 11 of 30 ICR/HA Swiss mice, whereas lung papillomas were observed in 10 of 30 control animals treated with tricaprilin and a local sarcoma was observed in one mouse (Van Duuren *et al.* 1974).

### 2.7.3 Mode of action and cancer risk assessment

Epichlorohydrin is reasonably anticipated to be a human carcinogen based on the experimental data (IARC 1999, NTP 2002). The primary experimental tumours are local. When administered by gavage, it induced forestomach tumours of rats. By inhalation (minimal effective concentration: 30 ppm), it induced tumours of the nasal cavity in rats. Subcutaneous injection produced local sarcomas in mice.

The local effect of epichlorohydrin on the rat nasal tissue has a parallel in the effect of the non-chlorinated compound, propylene oxide (for documentation, see SCOEL/SUM 161). Similar to propylene oxide, the induction of local cell proliferation appears to be a decisive factor (Girolamo *et al.* 2006). A particular impact of peak concentrations of epichlorohydrine for the local cancer risk is in-line with this view (Ginsberg *et al.* 1996). In vitro, the genotoxicity (cell transformation tests and DNA strand break induction) of both chemically related compounds has been compared, and epichlorohydrine turned out to be about 10-times more genotoxic than propylene oxide (Kolman and Dusinská 1995, Kolman *et al.* 1997).

Similar to propylene oxide, the protective effect of a rapid metabolic detoxification of epichlorohydrin is of relevance (Hindsø Landin *et al.* 1999).

By contrast to propylene oxide, epichlorohydrin is a bifunctional alkylating agent and induces DNA interstrand cross-links (Romao *et al.* 2007). Therefore, although there are similarities between epichlorohydrin and propylene oxide, differences in the modes of action ought to be considered.

The validity of the present database for the derivation of a quantitative assessment of human cancer risk has been a matter of debate. On the one hand, some authors consider the quantitative experimental data as not sufficient for such an assessment (Ginsberg *et al.* 1996, Kolman *et al.* 2002). On the other hand, the Dutch Expert Committee on Occupational Standards (DECOS) has used a linear extrapolation from the experimental data as a default method and estimated the additional lifetime cancer risk for epichlorohydrin to be  $4 \times 10^{-5}$  for 40 years of human occupational exposure to 0.19 mg/m<sup>3</sup>, and accordingly  $4 \times 10^{-3}$  for 40 years of occupational exposure to 19 mg/m<sup>3</sup> (DECOS 2000).



## 2.8 Reproductive toxicity

### 2.8.1. Human data

Two studies of possible fertility disorders after exposure to epichlorohydrin, and in some cases simultaneous exposure to allyl chloride and 1,3-dichloropropene, were negative (Milby and Whorton 1980; Venable *et al.* 1980).

### 4.9.2 Animal data

John *et al.* (1983a) exposed 30 male Sprague-Dawley rats and 10 New Zealand rabbits to concentrations of 0, 0.5, 25 and 50 ml epichlorohydrin/m<sup>3</sup> over 10 weeks for 6 hours daily on 5 days per week. The male rats (25) were mated with non-exposed female rats during and up to 10 weeks after exposure. The rate of fertilized females was significantly reduced only in the rats exposed to 50 ppm during the exposure phase (tested after 2, 4, 7 and 10 weeks), but not in the matings after the end of exposure (tested after 2, 5 and 10 weeks). The number of implantations was however significantly reduced during the exposure phase at 25 ppm. Histopathology or the weight of the reproductive organs revealed no changes compared with the control either during exposure or after the exposure period. The exposed rabbits were only mated in the tenth week of exposure and showed no reduced fertility.

Daily oral administration of 15 mg epichlorohydrin/kg body weight for 12 days led to sterility in male SD rats after one week. The animals were fertile again one week later (Hahn 1970). The histopathological examination of the testes, epididymides, prostate and seminal vesicles on day 12 of treatment revealed no differences from the control animals. This statement is based on an abstract without data and is therefore only of limited validity.

Cooper *et al.* (1974) observed sterility in male Sprague-Dawley rats lasting up to 10 weeks after five oral administrations of 50 mg/kg body weight daily and reduced fertility for the same period after a single administration of 100 mg/kg body weight (5 males per dose). The histopathological examination of the complex of testes, epididymides and *ductus deferens* revealed no changes up to 8 weeks after the single treatment. The validity of the study is restricted since the number of animals used was small and there was no control group.

In a study carried out by Cassidy *et al.* (1983) in Wistar rats, a significant increase in morphologically abnormal sperm head counts in sonicated testicular homogenates was observed in the group with higher exposure 11 days after the single oral administration of 25 and 50 mg/kg body weight. Total sperm counts were clearly reduced only in the group with lower exposure. The testis weight was unchanged in both dose groups. The examination of testicular sperm head anomalies 11 days after exposure is not an evaluated method.

Toth *et al.* (1989) treated male Long-Evans rats orally with 0, 12.5, 25 and 50 mg epichlorohydrin/kg body weight daily for 21 days. Following the last exposure, the males were mated with ovariectomized, hormone-treated females (1:1) for 3 hours to observe the mating behaviour and to obtain sperm samples for analysis. Two days later, the male rats treated with the highest dose were daily mated with one female in the pro-oestrus until all males had successfully copulated once within 5 days. After 48 hours, the male rats were sacrificed for histopathological examinations. Mating behaviour, the sperm count in ejaculates, the percentage of motile sperm or sperm morphology were not affected by the treatment with epichlorohydrin. Although all males treated with 50 mg/kg body weight and day had copulated (confirmed by the formation of a vaginal plug), none of the females was pregnant as opposed to 90% of the control group animals (examination of the implantations in the uteri 15 days after observation of the vaginal plug). The histopathological examination only showed a significant reduction of the sperm count in the *caudae epididymides* at the highest dose. Various motility parameters were however changed in relation to the dose (vigour and swimming pattern). The authors discussed this change as the cause of the lack of fertilization of ova in the highest dose group. It may





have been due to damage to the spermatozoa energy metabolism in the epididymis induced by the metabolite 3-chloro-1,2-propanediol.

After intraperitoneal treatment of rats with 3 (n = 3) and 6 (n = 7) mg epichlorohydrin/kg body weight and day for 4 days, sperm were obtained from the proximal region of the caudae epididymides and introduced into the uterus of stimulated female rats on day 5. On day 9, corpora lutea on the ovaries and implantations in the uteri were counted. These fertility parameters were reduced at both dose levels (Klinefelter *et al.* 1997).

Two examinations with the metabolite 3-chloro-1,2-propanediol provide information about the cause of the antifertile effect of epichlorohydrin.

Slott *et al.* (1997) treated groups of 9 male Syrian hamsters with 0, 33, 49, 66 and 83 mg 3-chloro-1,2-propanediol/kg body weight and day for 4 consecutive days, mated them on day 5 and counted the foetuses in the uteri of the fertilized females on the day before parturition. There was a dose-dependent decrease in the pregnancy rate of the sperm-positive females (100%, 78%, 67%, 22% and 0%). Epididymal sperm from the same males showed unaffected percentages of motile sperm, but sperm motility was reduced in relation to the dose. The sperm from treated males were also less likely to support *in vitro* fertilization (IVF). The authors concluded that 3-chloro-1,2-propanediol impairs sperm function.

A single oral administration of 5, 10, 25, 50 and 75 mg 3-chloro-1,2-propanediol/kg body weight reduced the following fertility parameters in SD rats: sperm ATP levels (3 hours and 5 days after treatment with 10 mg/kg body weight and higher), sperm motility (3 hours after treatment with 25 mg/kg body weight) and binding and penetration rates of zona pelucida-free oocytes *in vitro* from 10 mg/kg body weight without further increases at higher doses (Jelks *et al.* 2001). The authors concluded that altered ATP levels induced by 3-chloro-1,2-propanediol impair the fertilizing ability of sperm and thus confirm the assumptions of Toth *et al.* (1989).

No prenatal toxicity was found in an inhalation study with pregnant rats and rabbits at concentrations of 2.5 and 25 ppm although food consumption and weight gain of the rats were reduced at the high concentration (CMA 1979c; John *et al.* 1983b).

No teratogenic effects were observed in studies with rats and mice after oral administration of up to 160 mg/kg body weight, not even at maternally toxic doses and doses that led to reduced foetal weights (Marks *et al.* 1982).

## Recommendation

Epichlorohydrin is a directly acting genotoxic carcinogen in animal studies with a mainly local effect, with the target in the upper respiratory tract tissues after inhalation. Pituitary tumours were also induced experimentally. An epidemiological study showed possible associations between exposure to epichlorohydrin and the occurrence of CNS tumours. However, these data are not sufficient to derive a conclusive evaluation of the carcinogenicity for humans, nor can a safe concentration be specified for humans at present (2.7.3).

On the basis of the data on the genotoxicity of epichlorohydrin *in vivo*, particularly cytogenetic findings and findings on the development of epichlorohydrin-specific DNA adducts among persons exposed to epichlorohydrin, epichlorohydrin has been classified in germ cell mutagen.

In consequence of the clearcut direct genotoxicity, epichlorohydrin is categorised into the SCOEL carcinogen group A as a non-threshold carcinogen (Bolt and Huici-Montagud 2008). Accordingly, the derivation of a health-based OEL is not possible. An assessment of human cancer risk based on the available experimental data is accompanied with great uncertainties (2.7.3). The Dutch Expert Committee on Occupational Standards (DECOS) has applied a linear extrapolation from the experimental data as a default method and estimated the additional lifetime cancer risk for epichlorohydrin to be  $4 \times 10^{-5}$  for 40 years of human occupational exposure to  $0.19 \text{ mg/m}^3$ , and accordingly  $4 \times 10^{-3}$  for 40 years of occupational exposure to  $19 \text{ mg/m}^3$  (DECOS 2000).



Although analytical methods have been described, which may serve as a basis for biological monitoring (2.3.1), occupational field studies are lacking, so that a recommendation for a biological monitoring guidance value cannot be given. Several, although not always adequately documented, clinical findings on the sensitizing effect of epichlorohydrin on the skin are available. Animal studies provided evidence of skin sensitization.

Epichlorohydrin not only has local effects, but also shows systemic toxicity and is lethal after repeated epicutaneous application. However, here the corrosive effect may have destroyed the skin barrier. Absorption of diluted, no longer irritant solutions via intact skin cannot be ruled out. Therefore, a skin notation is recommended.

**In view of the above, SCOEL strongly recommends avoiding occupational exposure to epichlorohydrin.**



## References

- Asita AO, Hayashi M, Kodama Y, Matsuoka A, Suzuki T, Sofuni T (1992) Micronucleated reticulocyte induction by ethylating agents in mice. *Mutat Res* 271: 29–37
- Bader M, Rosenberger W, Gutzki FM, Tsikas D (2009) Quantification of N-(3-chloro-2-hydroxypropyl)valine in human haemoglobin as a biomarker of epichlorohydrin exposure by gas chromatography-tandem mass spectrometry with stable-isotope dilution. *J Chromatogr B Analyt Technol Biomed Life Sci* 877: 1402–1415
- Barbone F, Delzell E, Austin H, Cole P (1992) A case-control study of lung cancer at a dye and resin manufacturing plant. *Am J Ind Med* 22: 835–849
- Barbone F, Delzell E, Austin H, Cole P (1994) Exposure to epichlorohydrin and central nervous system neoplasms at a resin and dye manufacturing plant. *Arch Environ Health* 49: 355–358
- Basting I, Hoopmann M, Ehrenstein V, Suchenwirth R, Tödt H, Reichert J, Dressel H, Rosenberger A, Schmid M, Nowak D, Radon K (2006) Acute effects on the health of children after accidental exposure to epichlorohydrine. *Gesundheitswesen* 68: 309–315
- Beck MH, King CM (1983) Allergic contact dermatitis to epichlorohydrin in a solvent cement. *Contact Dermatitis* 9: 315
- Bolt HM, Huici-Montagud A (2008) Strategy of the Scientific Committee on Occupational Exposure Limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens. *Arch Toxicol* 82: 61–64
- Bond GG, Flores GH, Shellenberger RJ, Cartmill JB, Fishbeck WA, Cook RR (1986) Nested case-control study of lung cancer among chemical workers. *Am J Epidemiol* 124: 53–66
- BUA (Beratergremium für Altstoffe - Advisory Committee on Existing Chemicals of Environmental Relevance) (1992) Epichlorohydrin, BUA Stoffbericht 90, Hirzel Wissenschaftliche Verlagsgemeinschaft, Stuttgart
- Buckley LA, Jiang XZ, James RA, Morgan KT, Barrow CS (1984) Respiratory tract lesions induced by sensory irritants at the RD<sub>50</sub> concentration. *Toxicol Appl Pharmacol* 74: 417–429
- Cassidy SL, Dix KM, Jenkins T (1983) Evaluation of a testicular sperm head counting technique using rats exposed to dimethoxyethyl phthalate (DMEP), glycerol alpha-monochlorohydrin (GMCH), epichlorohydrin (ECH), formaldehyde (FA), or methyl methanesulfonate (MMS). *Arch Toxicol* 53:71–78
- Cheng T-J, Hwang S-J, Kuo H-W, Luo J-C, Chang MJW (1999) Exposure to epichlorohydrin and dimethylformamide, glutathione S-transferases and sister chromatid exchange frequencies in peripheral lymphocytes. *Arch Toxicol* 73: 282–287
- CMA (Chemical Manufacturers Association) (1979a) Pharmacokinetics of epichlorohydrin (EPI) administered to rats by gavage or inhalation. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI
- CMA (1979b) Epichlorohydrin – subchronic studies. I. A 90-day inhalation study in laboratory rodents. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI
- CMA (1979c) Epichlorohydrin – subchronic studies. IV. The effects of maternally inhaled epichlorohydrin on rat and rabbit embryonal and fetal development. Toxicology Research Laboratory Health and Environmental Sciences, Dow Chemical USA, Midland, MI
- Cooper ERA, Jones AR, Jackson H (1974) Effects of  $\alpha$ -chlorohydrin and related compounds on the reproductive organs and fertility of the male rat. *J Reprod Fertil* 38: 379–386
- Daniel FB, Robinson M, Olson GR, Page NP (1996) Toxicity studies of epichlorohydrin in Sprague-Dawley rats. *Drug Chem Toxicol* 19: 41–58
- DECOS [Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards] (2000) Epichlorohydrin (1-chloro-2,3-epoxypropane): health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands. Publication no. 2000/10 OSH
- De Flora S, Bannicelli C, Zanacchi P, Camoirano A, Petruzzelli S, Giuntini C (1984) Metabolic activation and deactivation of mutagens by preparations of human lung parenchyma and bronchial tree. *Mutat Res* 139: 9–14
- Delzell E, Macaluso M, Cole P (1989) A follow-up study of workers at a dye and resin manufacturing plant. *J Occup Med* 31: 273–278
- DFG [Deutsche Forschungsgemeinschaft] (2003) 1-Chlor-2,3-epoxypropan (Epichlorhydrin). In: *Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten*, ed. Greim H, 36. Lieferung, pp.1–21, Wiley-VCH, Weinheim
- DFG [Deutsche Forschungsgemeinschaft] (2009) Epichlorohydrine. In: *The MAK-Collection, Part 1*, Wiley-VCH, Weinheim, in press
- Enterline PE (1982) Importance of sequential exposure in the production of epichlorohydrin and isopropanol. *Ann N Y Acad Sci* 381: 344–349
- Enterline PE, Henderson V, Marsh G (1990) Mortality of workers potentially exposed to epichlorohydrin. *Br J Ind Med* 47: 269–276





- Epstein E (1974) Allergy to epichlorohydrin masquerading as trichloroethylene allergy. *Contact Dermatitis Newsletter* 16: 475
- Epstein SS, Arnold E, Andrea J, Bass W, Bishop Y (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol Appl Pharmacol* 23: 288–325
- Fakhouri G, Jones AR (1979) Epichlorohydrin: metabolism and toxicity in the rat. *Aust J Pharm Sci* 8: 11–14
- Fregert S, Gruvberger P (1970) Sensitization to epichlorohydrin and cross-sensitization to propane oxide. *Contact Dermatitis Newsletter* 8: 172
- Freuder E, Leake CD (1941) The toxicity of epichlorohydrin. *Univ Calif Berkeley Publ Pharmacol* 2: 69–78
- Gardner RJ, Burgess BA, Kennedy Jr GL (1985) Sensory irritation potential of selected nasal tumorigens in the rat. *Food Chem Toxicol* 23: 87–92
- Gingell R, Mitschke HR, Dzidic I, Beatty PW, Sawin VL, Page AC (1985) Disposition and metabolism of [<sup>2-<sup>14</sup>C</sup>]epichlorohydrin after oral administration to rats. *Drug Metab Dispos* 13: 333–341
- Ginsberg GL, Pepelko WE, Goble RL, Hattis DB (1996) Comparison of contact site cancer potency across dose routes: case study with epichlorohydrin. *Risk Anal* 16: 667–681
- Giri AK (1997) Genetic toxicology of epichlorohydrin: a review. *Mutat Res* 386: 25–38
- Girolamo F, Elia G, Errede M, Viginfino D, Cantatore S, Losusso L, Roncali L, Bertossi M, Ambrosi L (2006) In vivo assessment of epichlorohydrin effects: the chorioallantoic membrane model. *Med Sci Monit* 12: BR21–27
- Hahn JD (1970) Post-testicular antifertility effects of epichlorohydrin and 2,3-epoxypropanol. *Nature* 226: 87
- Hellmér L, Balcsföldi G (1992) An evaluation of the E. coli K-12 uvrB/recA DNA repair host mediated assay. II. In vivo results for 36 compounds tested in the mouse. *Mutat Res* 272: 161–173
- Hindsø Landin H, Osterman-Golkar S, Zorcec V, Törnqvist M (1996) Biomonitoring of epichlorohydrin by hemoglobin adducts. *Anal Biochem* 240: 1–6
- Hindsø Landin H, Grummt T, Laurent C, Tates A (1997) Monitoring of occupational exposure to epichlorohydrin by genetic effects and hemoglobin adducts. *Mutat Res* 381: 217–226
- Hindsø Landin H, Segerbäck D, Damberg C, Osterman-Golkar S (1999) Adducts with haemoglobin and with DNA in epichlorohydrin-exposed rats. *Chem Biol Interact* 117: 49–64
- Hine C, Rowe VK, White ER, Darmer Jr KI, Youngblood GT (1981) Epoxy compounds. In: Clayton GD, Clayton FE (Eds) *Patty's industrial hygiene and toxicology*, ed. 2A, Wiley-Interscience, New York, 2141–2257
- Holzer J, Voss B, Karroum S, Hildman H, Wilhelm M (2008) A comparative study of chemically induced DNA damage in isolated nasal mucosa cells of humans and rats assessed by the alkaline comet assay. *J Toxicol Environ Health A* 71: 936–946
- IARC (International Agency for Research on Cancer) (1999) IARC monographs on the evaluation of carcinogenicity of chemicals to man, ed. 71, IARC, Lyon, 603–628
- Ippen H, Mathies V (1970) Die „protrahierte Verätzung“. *Berufsdermatosen* 18: 144–165
- Jelks K, Berger T, Homer C, Miller MG (2001)  $\alpha$ -Chlorohydrin induced changes in sperm fertilizing ability in the rat: association with diminished sperm ATP-levels and motility. *Reprod Toxicol* 15: 11–20
- John JA, Quast JF, Murray FJ, Calhoun LG, Staples RE (1983a) Inhalation toxicity of epichlorohydrin: effects on fertility in rats and rabbits. *Toxicol Appl Pharmacol* 68: 415–423
- John JA, Gushow TS, Ayres JA, Hanley Jr TR, Quast JF, Rao KS (1983b) Teratologic evaluation of inhaled epichlorohydrin and allyl chloride in rats and rabbits. *Fundam Appl Toxicol* 3: 437–442
- Jolanki R (1991) Occupational skin diseases from epoxy compounds. *Acta Derm Venereol* 159, Suppl: 1–80
- van Joost T (1988) Occupational sensitization to epichlorohydrin and epoxy resin. *Contact Dermatitis* 19: 278–280
- van Joost T, Roesyanto ID, Satyawan I (1990) Occupational sensitization to epichlorohydrin (ECH) and bisphenol-A during the manufacture of epoxy resin. *Contact Dermatitis* 22: 125–126
- Kanerva L, Jolanki R, Alanko K, Estlander T (1999) Patch-test reactions to plastic and glue allergens. *Acta Derm Venereol* 79: 296–300
- Kirkhart B (1981) Micronucleus test on 21 compounds. In: de Serres FJ, Ashby J (Eds) *Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program, Progress in mutation research*, ed. 1, Elsevier, Amsterdam, 698–704
- Klinefelter GR, Laskey JW, Ferrell J, Suarez JD, Roberts NL (1997) Discriminant analysis indicates a single sperm protein (SP22) is predictive of fertility following exposure to epididymal toxicants. *J Androl* 18: 139–150
- Knaap AGAC, Voogd CE, Kramers PGN (1982) Comparison of the mutagenic potency of 2-chloroethanol, 2-bromoethanol, 1,2-epoxybutane, epichlorohydrin and glycidaldehyde in *Klebsiella pneumoniae*, *Drosophila melanogaster* and L5178Y mouse lymphoma cells. *Mutat Res* 101: 199–208



- Kolman A, Dusinská M (1995) Comparison of propylene oxide and epichlorohydrin effects in two transformation tests (C3H/1013:511/2 and SHE cells). *Toxicol Lett* 81: 213-221
- Kolman A, Spival I, Näslund M, Dusinská M, Cedervall B (1997) Propylene oxide and epichlorohydrin induce DNA strand breaks in human diploid fibroblasts. *Environ Mol Mutagen* 30: 40-46
- Kolman A, Chovanec M, Osterman-Golkar S (2002) Genotoxic effects of ethylene oxide, propylene oxide and epichlorohydrin in humans. Update review (1990-2001). *Mutat Res* 512: 173-194.
- Konishi Y, Kawabata A, Denda A, Ikeda T, Katada H, Maruyama H, Higashiguchi R (1980) Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. *Gann* 71: 922-923
- Kucerová M, Zhurkov VS, Políková Z, Ivanova JE (1977) Mutagenic effect of epichlorohydrin. II. Analysis of chromosomal aberrations in lymphocytes of persons occupationally exposed to epichlorohydrin. *Mutat Res* 48: 355-360
- Laskin S, Sellakumar AR, Kuschner M, Nelson N, La Mendola S, Rusch GM, Katz GV, Dulak NC, Albert RE (1980) Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. *J Natl Cancer Inst* 65: 751-757
- Lawrence WH, Malik M, Turner JE, Autian J (1972) Toxicity profile of epichlorohydrin. *J Pharm Sci* 61: 1712-1717
- Lefaux R (1966) *Chemie und Toxikologie der Kunststoffe*, Krauskopf-Verlag für Wirtschaft, Mainz
- Luo JC, Cheng TJ, Kuo HW, Chang MJ (2004) Decreased lung function associated with occupational exposure to epichlorohydrin and the modification effects of glutathione S-transferase polymorphisms. *J Occup Environ Med* 46: 280-286
- Marks TA, Gerling FS, Staples RE (1982) Teratogenic evaluation of epichlorohydrin in the mouse and rat and glycidol in the mouse. *J Toxicol Environ Health* 9: 87-96
- Milby TH, Whorton D (1980) Epidemiological assessment of occupationally related, chemically induced sperm count suppression. *J Occup Med* 22: 77-82
- NTP [National Toxicology Program] (2002) Epichlorohydrin. *Rep Carcinog* 10: 113-114.
- Olsen GW, Lacy SE, Chamberlin SR, Albert DL, Acreneaux TG, Bullard LF, Stafford BA, Boswell JM (1994) Retrospective cohort mortality study of workers with potential exposure to epichlorohydrin and allyl chloride. *Am J Ind Med* 25: 205-218
- Pallade S, Dorobantu M, Rotaru G, Gabrielescu E (1967) Étude expérimentale de l'intoxication par l'épichlorhydrine. *Arch Mal Prof Med Trav Secur Soc* 28: 505-516
- Picciano D (1979) Cytogenetic investigation of occupational exposure to epichlorohydrin. *Mutat Res* 66: 169-173
- Pina K, Osterman-Golkar S, Nogradi E, Segerbäck D (2000) <sup>32</sup>P-Post-labelling of 7-(3-chloro-2-hydroxypropyl)guanine in white blood cells of workers occupationally exposed to epichlorohydrin. *Carcinogenesis* 21: 275-280
- Pozzani UC, Carpenter CP (1960) The toxicity of epichlorohydrin, AIHA, Abstract, Industrial Health Conference, Rochester, New York
- Prens EP, de Jong G, van Joost T (1986) Sensitization to epichlorohydrin and epoxy system components. *Contact Dermatitis* 15: 85-90
- Prodi G, Arfellini G, Colacci A, Grilli S, Mazzullo M (1986) Interaction of halocompounds with nucleic acids. *Toxicol Pathol* 14: 438-444
- Quast JF, Henck JW, McKenna MJ (1979) A 90-day inhalation toxicity study of epichlorohydrin in laboratory rodents (Abstract). *Toxicol Appl Pharmacol* 48: A 43
- Rao KS, Betso JE, Olson RJ (1981) A collection of guinea pig sensitization test results grouped by chemical class. *Drug Chem Toxicol* 4: 331-351
- Rebandel P, Rudzki E (1990) Dermatitis caused by epichlorohydrin, oxprenolol hydrochloride and propranolol hydrochloride. *Contact Dermatitis* 23: 199
- Romano KP, Newman AG, Zahran RW, Millard JT (2007) DNA interstrand cross-linking by epichlorohydrin. *Chem Res Toxicol* 20: 832-838
- Rossi AM, Migliore L, Lascialfari D, Sbrana I, Loprieno N, Tortoreto M, Bidoli F, Pantarotto C (1983a) Genotoxicity, metabolism and blood kinetics of epichlorohydrin in mice. *Mutat Res* 118: 213-226
- Rossi AM, Migliore L, Barale R, Loprieno N (1983b) In vivo and in vitro mutagenicity studies of a possible carcinogen, trichloroethylene, and its two stabilizers, epichlorohydrin and 1,2-epoxybutane. *Teratogen Carcinogen Mutagen* 3: 75-87
- Salamone MF, Heddle JA, Katz M (1981) Mutagenic activity of 41 compounds in the in vivo micronucleus assay. In: de Serres FJ, Ashby J (Eds) *Evaluation of short-term tests for carcinogens*. Report of the International Collaborative Program, Progress in mutation research, ed. 1, Elsevier, Amsterdam, 686-697
- Schultz C (1964) Fettleber und chronisch-asthmaoide Bronchitis nach Inhalation eines Farblösungsmittels (Epichlorhydrin). *Dtsch Med Wochenschr* 89: 1342-1344
- Singh US, Secker-Samuelian K, Solomon JJ (1996) Reaction of epichlorohydrin with 2'-deoxynucleosides: characterization of adducts. *Chem Biol Interact* 99: 109-128
- Sloff VL, Jeffay SC, Dyer CJ, Barbee RR, Perreault SD (1997) Sperm motion predicts fertility in male hamsters treated with  $\alpha$ -chlorohydrin. *J Androl* 18: 708-716
- Srám RJ, Cerná M, Kucerová M (1976) The genetic risk of epichlorohydrin as related to the occupational exposure. *Biol Zentralbl* 95: 451-462





- Srám RJ, Zudová Z, Kuleshov NP (1980) Cytogenetic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. *Mutat Res* 70: 115–120
- Srám RJ, Tomatis L, Clemmesen J, Bridges BA (1981) An evaluation of the genetic toxicity of epichlorohydrin. A report of an expert group of the International Commission for Protection against Environmental Mutagens and Carcinogens. *Mutat Res* 87: 299–319
- Stoner GD, Conran PB, Greisiger EA, Stober J, Morgan M, Pereira MA (1986) Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice. *Toxicol Appl Pharmacol* 82: 19–31
- Thorgeirsson A, Freger S (1977) Allergenicity of epoxy resins in the guinea pig. *Acta Derm Venereol* 57: 252–256
- Topham JC (1980) Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens? *Mutat Res* 74: 379–387
- Toth GP, Zenick H, Smith MK (1989) Effects of epichlorohydrin on male and female reproduction in Long-Evans rats. *Fundam Appl Toxicol* 13: 16–25
- Tsai SP, Gilstrap EL, Ross CE (1996) Mortality study of employees with potential exposure to epichlorohydrin: a 10 year update. *Occup Environ Med* 53: 299–304
- Tsuchimoto T, Matter B E (1981) Activity of coded compounds in the micronucleus test. In: de Serres FJ, Ashby J (Eds) Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program, Progress in mutation research, ed. 1, Elsevier, Amsterdam, 705–711
- Van Duuren BL, Katz C, Goldschmidt BM, Frenkel K, Sivak A (1972) Carcinogenicity of haloethers. II. Structure-activity relationships of analogs of bis(chloromethyl)ether. *J Natl Cancer Inst* 48: 1431–1439
- Van Duuren BL, Goldschmidt BM, Katz C, Seidman I, Paul JS (1974) Carcinogenic activity of alkylating agents. *J Natl Cancer Inst* 53: 695–700
- Venable JR, McClimans CD, Flake RE, Dimick DB (1980) A fertility study of male employees engaged in the manufacture of glycerine. *J Occup Med* 22: 87–91
- Vogel E, Lee WR, Schalet A, Würgler F (1981) Mutagenicity of selected chemicals in *Drosophila* in comparative chemical genesis. *Environ Sci Res* 24: 175–256
- Weigel WW, Plotnik HB, Conner WL (1978) Tissue distribution and excretion of <sup>14</sup>C-epichlorohydrin in male and female rats. *Res Commun Chem Pathol Pharmacol* 20: 275–286
- Weil CS, Condra N, Haun C, Striegel JA (1963) Experimental carcinogenicity and acute toxicity of representative epoxides. *Am Ind Hyg Assoc J* 24: 305–325
- Wester PW, van der Heijden CA, Bisshop A, van Esch GJ (1985) Carcinogenicity study with epichlorohydrin (CEP) by gavage in rats. *Toxicology* 36: 325–339
- Würgler FE, Graf U (1981) Mutagenic activity of 10 coded compounds in the *Drosophila* sex-linked recessive lethal assay. In: de Serres FJ, Ashby J (Eds) Evaluation of short-term tests for carcinogens. Report of the International Collaborative Program, Progress in mutation research, ed. 1, Elsevier, Amsterdam, 666–672





[www.arbeidstilsynet.no](http://www.arbeidstilsynet.no)