Arbeidstilsynet

Høringsforslag

Grunnlag for fastsettelse av grenseverdi

Grunnlagsdokument for but-2-yn-1,4-diol

Kommisjonsdirektiv 2017/164/EU

Grunnlag for fastsettelse av grenseverdi.
Grunnlagsdokument for but-2-yn-1,4-diol.

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for but-2-yn-1,4-diol.

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

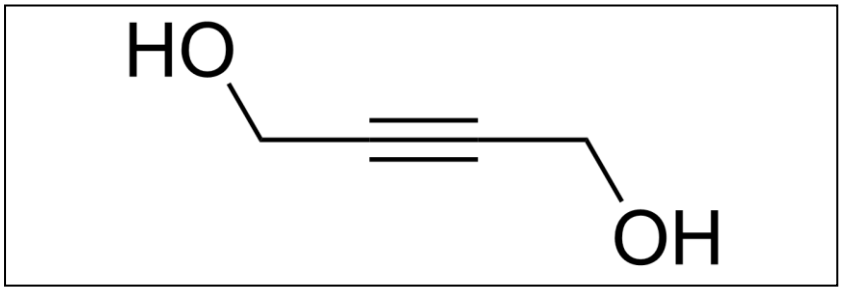
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for but-2-yn-1,4-diol. Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for but-2-yn-1,4-diol, og vurderinger og kommentarer fra Toksikologisk Ekspertgruppe for Administrative Normer (TEAN).

1. Stoffets identitet

Stoffet but-2-yn-1,4-diol og dets molekylformel, synonym av stoffets navn, stoffets identifikasjonsnummer i Chemical Abstract Service Registry number (CAS-nr.), European Inventory of Existing Commercial Chemical Substances (EINECS-nr. eller EC-nr.) og indekseringsnummer (Index-nr) er gitt i tabell 1. Strukturformel av but-2-yn-1,4-diol er vist i figur 1.

Tabell 1. Stoffets navn og identitet.

Kjemisk navn **Molekylformel**	**but-2-yn-1,4-diol** **$C_4H_6O_2$**
IUPAC navn	but-2-yn-1,4-diol
Synonymer	1,4-butyndiol; 2-butyn-1,4-diol; 2-butyndiol; 1,4-dihydroxy-2-butyn; butyndiol; bis(hydroxymetyl) acetylen
CAS-nr.	110-65-6
Index-nr.	603-076-00-9
EC-nr.	203-788-6



Figur 1. Strukturformel av but-2-yn-1,4-diol (https://en.wikipedia.org/wiki/1,4-Butynediol).

2. Fysikalske og kjemiske data

Stoffet but-2-yn-1,4-diol er en organisk forbindelse som er et alkyn og en diol. Det er et svakt gult/ fargeløst krystallinsk og hygroskopisk fast stoff som er svært løselig i vann og i polare organiske løsemidler. Det vises til tabell 2 for fysikalske og kjemiske data for but-2-yn-1,4-diol.

Tabell 2. Fysikalske og kjemiske data for but-2-yn-1,4-diol.

Molekylvekt (g/mol)	86,09
Fysisk tilstand (°C, 101,3 kPa)	Fast stoff
Smeltepunkt (°C)	50 - 58
Dekomponerer (°C)	>200 [1]
Kokepunkt (°C)	238
Selvantennelsestemperatur (°C)	335
Løselighet i vann (20 °C, g/l)	750
Damptrykk ved 20 °C (hPa)	0,0017
Damptetthet (air = 1) (g/cm^3)	1,1 (SCOEL: 1,05 – 1,17) [1]
Fordelingskoeffisient n-oktanol/vann (log K_{ow}, 25 °C)	-0,73
Omregningsfaktor (20 °C, 101 kPa)	1 ppm = 3,58 mg/m^3; 1 mg/m^3 = 0,280 ppm

[1]Data hentet fra SCOEL/SUM/159, mars 2011.

2.1 Forekomst og bruk

Stoffet but-2-yn-1,4-diol er et kommersielt viktig stoff og blir også brukt som et utgangsstoff for andre produkter, eksempelvis som mellomprodukt i syntese av butandiol og butendiol. Stoffet blir produsert og/eller importert i EØS-området i 100+ tonn hvert år, og stoffet blir også brukt i produksjon av metaller, metallprodukter og elektrisk, elektronisk og optisk utstyr. I tillegg blir stoffet brukt i en rekke produkter, blant annet i vask og rengjøringsmidler, i stoffer som korrosjonshemmer, brukt til overflatebehandling av metaller, og i galvanotekniske produkter som for eksempel i korrosjonshemmer til syrebad.

3. Grenseverdier

3.1 Nåværende grenseverdier

Norge har p.t. ingen grenseverdi for but-2-yn-1,4-diol.

3.2. Grenseverdier fra EU

Den europeiske vitenskapskomiteen, SCOEL foreslår for but-2-yn-1,4-diol i sitt kriteriedokument av mars 2011[1]:

IOELV (Indicative Occupational Exposure Limit Value) (8 timer): 0,5 mg/m^3

Verken korttidsverdi eller anmerkning er foreslått for but-2-yn-1,4-diol.

3.3. Grenseverdier fra andre land og organisasjoner

Ikke alle land og organisasjoner har i dag grenseverdier for stoffet but-2-yn-1,4-diol, og av de nordiske landene er det bare Finland som har en grenseverdi for stoffet. Foruten Finland i vår liste, har Nederland og Tyskland grenseverdier for but-2-yn-1,4-diol. Siden but-2-yn-1,4-diol er inntatt i Kommisjonsdirektivet 2017/164/EU, vil flere land fastsette en grenseverdi for stoffet. Organisasjonene ACGIH og NIOSH har heller ingen anbefalte grenseverdier for but-2-yn-1,4-diol. Grenseverdier for but-2-yn-1,4-diol fra andre land og organisasjoner er gitt i tabell 3 nedenfor.

Tabell 3. Grenseverdier for but-2-yn-1,4-diol fra andre land og organisasjoner. Land og organisasjoner som ikke har grenseverdier for but-2-yn-1,4-diol er markert med -.

Land Organisasjon	Grenseverdi (8 timer)	Korttidsverdi (15 min)	Anmerkning Kommentar
Sverige[1]	-	-	-
Danmark[2]	-	-	-
Finland[3]	0,14 ppm; 0,5 mg/m^3	-	-
Storbritannia[4]	-	-	-
Nederland[5]	0,1 ppm; 0,36 mg/m^3	0,1 ppm; 0,36 mg/m^3	H, hudopptak
ACGIH, USA[6]	-	-	-
NIOSH, USA[6]	-	-	-
Tyskland, MAK[6]	0,1 ppm; 0,36 mg/m^3	0,1 ppm; 0,36 mg/m^3	Gjelder korttidsverdi, 15 min: I (1)Overskridelsesfaktor C, takverdi H, hudopptak Hudsensibiliserende
Tyskland, Myndighetene[7]	0,1 ppm; 0,36 mg/m^3	0,1 ppm; 0,36 mg/m^3	Gjelder korttidsverdi, 15 min: 1(I) Overskridelsesfaktor Sh, hudsensibiliserende H, hudopptak Y, ikke fare for skade på foster dersom grenseverdi overholdes 11, sum damp og aerosol

[1] Arbetsmiljöverkets Hygieniska gränsvärden AFS 2015:7, https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf.
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[6] Guide to occupational exposure values compiled by ACGIH, 2017.
[8] 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

Stoffet but-2-yn-1,4-diol er klassifisert og merket i henhold til CLP Annex VI (Forordning EC No 1272/2008), og klassifisering og merking med koder i henhold til fareklasse, kategori og faresetninger er gitt i tabell 4 nedenfor.

Tabell 4. Fareklasser, farekategori med forkortelse, merkekoder og faresetninger for 1 but-2-yn-1,4-diol.

Fareklasse **Farekategori** **Forkortelse**	**Merkekode**	**Faresetning**
Etsende/irriterende for huden Kategori 1A, 1B, 1C Skin Corr. 1A, 1B, 1C	H 314	Gir alvorlige etseskader på hud og øyne
Akutt giftighet Kategori 3 Acute Tox. 3	H 331	Giftig ved innånding
Akutt giftighet Kategori 3 Acute Tox. 3	H 301	Giftig ved svelging
Akutt giftighet Kategori 4 Acute Tox. 4	H 312	Farlig ved hudkontakt
Spesifikk målorgantoksisitet – gjentatt eksponering Kategori 2 STOT RE 2 *	H 373	Kan forårsake organskader ved langvarig eller gjentatt eksponering
Sensibiliserende ved innånding eller hudkontakt Hudsensibilisering Kategori 1 Underkategori 1A, 1B Skin Sens. 1/1A/1B	H 317	Kan utløse en allergisk hudreaksjon

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 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 but-2-yn-1,4-diol.

4. Toksikologiske data og helseeffekter

4.1. Anbefaling fra SCOEL

EUs vitenskapskomite (SCOEL) har utarbeidet kriteriedokumentasjon for but-2-yn-1,4-diol datert mars 2011[1] hvor de anbefalte en grenseverdi for stoffet lik 0,5 mg/m^3, se Vedlegg 1.

SCOEL anbefalte ingen korttidsverdi for but-2-yn-1,4-diol da de rapporterer at det ikke finnes tilstrekkelig data for utleding av en korttidsverdi for stoffet.

Videre, SCOEL anbefalte heller ingen hudanmerking fordi systemisk toksisitet først forekommer ved eksponeringer ved mye høyere konsentrasjoner enn den foreslåtte 8-timers grenseverdien, samt at hudopptak anses for å være relativt lavt.

4.2. Kommentarer fra TEAN

SCOEL-dokumentet for but-2-yn-1,4-diol er datert mars 2011. I denne gjennomgangen er det i tillegg innhentet data fra MAK (2012)[2]. ACGIH oppgir ingen data for but-2-yn-1,4-diol. Det ble gjort litteratursøk i PubMed, Web of Knowledge and Google Scholar fra 2010 og fremover. RTECS (Registry of Toxic Effects of Chemical Substances) databasen ble også sjekket. Ingen nyere referanser av betydning for konklusjonene til SCOEL og MAK ble funnet.

Det er store mangler i kunnskapen om human toksisitet av but-2-yn-1,4-diol. Det er for eksempel ingen humane data for toksikokinetikk, effekter av akutte eller repeterte eksponeringer, irritative eller reproduksjonstoksiske effekter. Biomonitoreringsdata finnes ikke beskrevet. In vitro- og dyrestudier av mutagenisitet er negative. Ingen valide karsinogenesitetstester foreligger.

SCOEL angir, basert på inhalasjonsstudier i dyr, at kritisk effekt er irritasjon. Inhalasjons- og orale eksponeringsstudier i dyr støtter at systemiske effekter kun forekommer ved konsentrasjoner av but-2-yn-1,4-diol som ligger over de som forårsaker irritasjon. NOAEC på 0,5 mg/m^3 er beskrevet og blir benyttet av SCOEL til å utlede OEL. Fordi kritisk effekt er lokal irritasjon, benytter SCOEL ikke usikkerhetsfaktorer.

MAK (2012) vurderer som SCOEL at kritisk effekt av but-2-yn-1,4-dioler lokal irritasjon i øvre luftveier (NOAEC 0,5 mg/m^3), og de benytter begge samme nøkkelstudie. Ved å bruke «Bench Mark Dosing» (BMD) modellering, beregner MAK NAEC til 1,0 mg/m^3. Ettersom but-2-yn-1,4-diolforekommer som aerosol ved denne konsentrasjon, kan lokal eksponering ved aerosoldeponering i larynx og trakea derfor være høyere enn ved eksponering for damp, som gir en jevnere fordeling over utsatte vev. Med utgangspunkt i NAEC på 1 mg/m^3 benytter MAK (2012) "Preferred-Value Approach" til å fastsette en MAK-verdi (TLV) på 0,36 mg/m^3. I følge eksperimenter utført på vegne av MAK, forekommerbut-2-yn-1,4-diolsom damp ved konsentrasjoner lavere enn 1mg/m^3.

Det er god overensstemmelse mellom SCOEL (8-timers TWA 0,5 mg/m^3) og MAK (TLV 0,36 mg/m^3) sine vurderinger, og TEAN har ingen bemerkninger til de vurderinger som er gjort.
I følge SCOEL finnes det ikke tilstrekkelig data for utleding av korttidsverdi, men den kritiske effekten av but-2-yn-1,4-dioltilsier at det er behov for en korttidsverdi.

SCOEL anbefaler ingen "hud" anmerkning fordi systemisk toksisitet først forekommer ved eksponeringer for mye høyere konsentrasjoner enn foreslått 8-timers OEL, samt at hudopptak anses for å være relativt lavt. TEAN sier seg enig med SCOEL i deres vurdering av at det ikke er nødvendig med anmerkning for «hud». Det bemerkes dog at but-2-yn-1,4-diolhar sensibiliserende egenskap og at hudeksponering for høye konsentrasjoner har etsende eller irriterende effekt. Det kan derfor være behov for anmerking av sensibiliserende egenskap for hud ved direkte kontakt.

5. Bruk og eksponering

I Norge brukes but-2-yn-1,4-diol i en rekke produkter, blant annet i vaske- og rengjøringsmidler, i stoffer som korrosjonshemmer brukt til overflatebehandling av metaller, og i galvanotekniske produkter.

Mengden som anvendes er liten hvilket medfører at eksponeringen anses som lav. But-2-yn-1,4-diol har svært lavt damptrykk som også vil føre til mindre inhalasjon av stoffet og vil dermed redusere eksponeringen. Det antas derfor at eksponering for but-2-yn-1,4-diol vil være lavere enn konsentrasjonsnivået for anbefalt grenseverdi.

5.1. Opplysning fra Produktregistret

Data fra Produktregisteret er innhentet oktober 2017, og inneholder opplysninger om mengde og bruk av stoffet but-2-yn-1,4-diol i deklareringspliktige produkter. Produktregisterdata for but-2-yn-1,4-diol viser at stoffet blir brukt i totalt 15 produkter blant annet til overflatebehandling og bearbeiding av metaller, malerarbeid og til rengjøring. Flest produkter er rapportert for bruk i rengjøringsvirksomheter og til privat buk. Total netto mengde av produkter (unntatt til privat forbruk) som blir brukt er liten og utgjør ca. 0,04 tonn.

På grunn av sikkerhetsbestemmelsene i Produktregisteret kan vi ikke gi eksakte opplysninger ut over denne informasjon.

5.2. Eksponering og måledokumentasjon

I STAMIs eksponeringsdatabase EXPO er det ikke registrert eksponeringsmålinger for stoffet but-2-yn-1,4-diol.

5.2.1 Prøvetakings- og analysemetode av but-2-yn-1,4-diol

I tabell 5 er anbefalte metoder for prøvetaking og analyser av but-2-yn-1,4-diol presentert.

Tabell 5. Anbefalte metoder for prøvetaking og analyse av but-2-yn-1,4-diol.

Prøvetakingsmetode	Analysemetode	Referanse
Glassfiberfilter + kullrør	Desorpsjon m/DCM/MEOH,	Ingen god referanse er oppgitt
	GC-FID [1]	

[1]FID: Flame Ionisation Detector (Flammeionisasjonsdetektor)

6. Vurdering

Det finnes ikke tilstrekkelig kunnskap om human toksisitet av but-2-yn-1,4-diol. Det finnes ingen humane data for toksikokinetikk, effekter av akutte eller repeterte eksponeringer, irritative eller reproduksjonstoksiske effekter, og litteraturen rapporterer heller ingen biomonitoreringsdata. Det er også lite data om stoffets effekt på dyr.

Stoffet but-2-yn-1,4-diol er etsende og irriterer huden, øyne og luftveier. Kritisk effekt av eksponering for but-2-yn-1.4-diol er irritasjon i øvre luftveier. En rottestudie rapporterte en NOEAC for irritasjon i luftveier på 0,5 mg/m^3. For å unngå irritasjon i øvre luftveier anbefales at eksponeringen holdes så lav som mulig under 0,5 mg/m^3, som også svarer til SCOELs anbefalte grenseverdi.

Ingen tilgjengelige data støtter innføringen av en korttidsverdi. Likevel, but-2-yn-1.4-diol kan føre til kontaktallergi og er både i konsentrert form og fortynnet i vann etsende og irriterende for huden.

SCOEL anbefaler ingen anmerking for hud siden systemisk toksisitet først forekommer ved eksponeringer for mye høyere konsentrasjoner enn foreslått grenseverdi (8-timer), samt at hudopptak anses for å være relativt lavt. TEAN støtter vurdering gitt av SCOEL, og anmerkning H blir dermed ikke anbefalt.

Det er vitenskapelig dokumentert at stoffet but-2-yn-1.4-diol har sensibiliserende egenskaper og hudeksponering for høye konsentrasjoner har etsende eller irriterende effekt. Det kan derfor være behov for anmerking for allergifremkallende egenskap for hud ved direkte kontakt, og det anbefales derfor en anmerkning 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).

But-2-yn-1,4-diol har svært lavt damptrykk og av den grunn vil stoffet bli inhalert i mindre grad, og dermed vil eksponeringen bli redusert. Det antas derfor at eksponering for but-2-yn-1,4-diol vil være lavere enn konsentrasjonsnivået for anbefalt grenseverdi.

7. Konklusjon med forslag til ny grenseverdi

På bakgrunn av den foreliggende dokumentasjon og en avveiing mellom de toksikologiske dataene og tekniske og økonomiske hensyn, foreslås en grenseverdi (8 timer) på 0,5 mg/m^3 for but-2-yn-1,4-diol. Ingen tilgjengelige data støtter å innføre en korttidsverdi eller anmerkninger for but-2-yn-1,4-diol.

Anbefalt grenseverdi og anmerkning for but-2-yn-1,4-diol:

Grenseverdi (8-timer): 0,5 mg/m^3

Anmerkning: A (kan betraktes som allergifremkallende eller annen overfølsomhet) og E (EU har fastsatt grenseverdi for stoffet)

8. Nye grenseverdier

Dette kapitlet utarbeides etter at ASD har vedtatt ny grenseverdi.

Anbefalt grenseverdi og anmerkning for but-2-yn-1,4-diol:

Grenseverdi (8-timer): x ppm, y mg/m^3

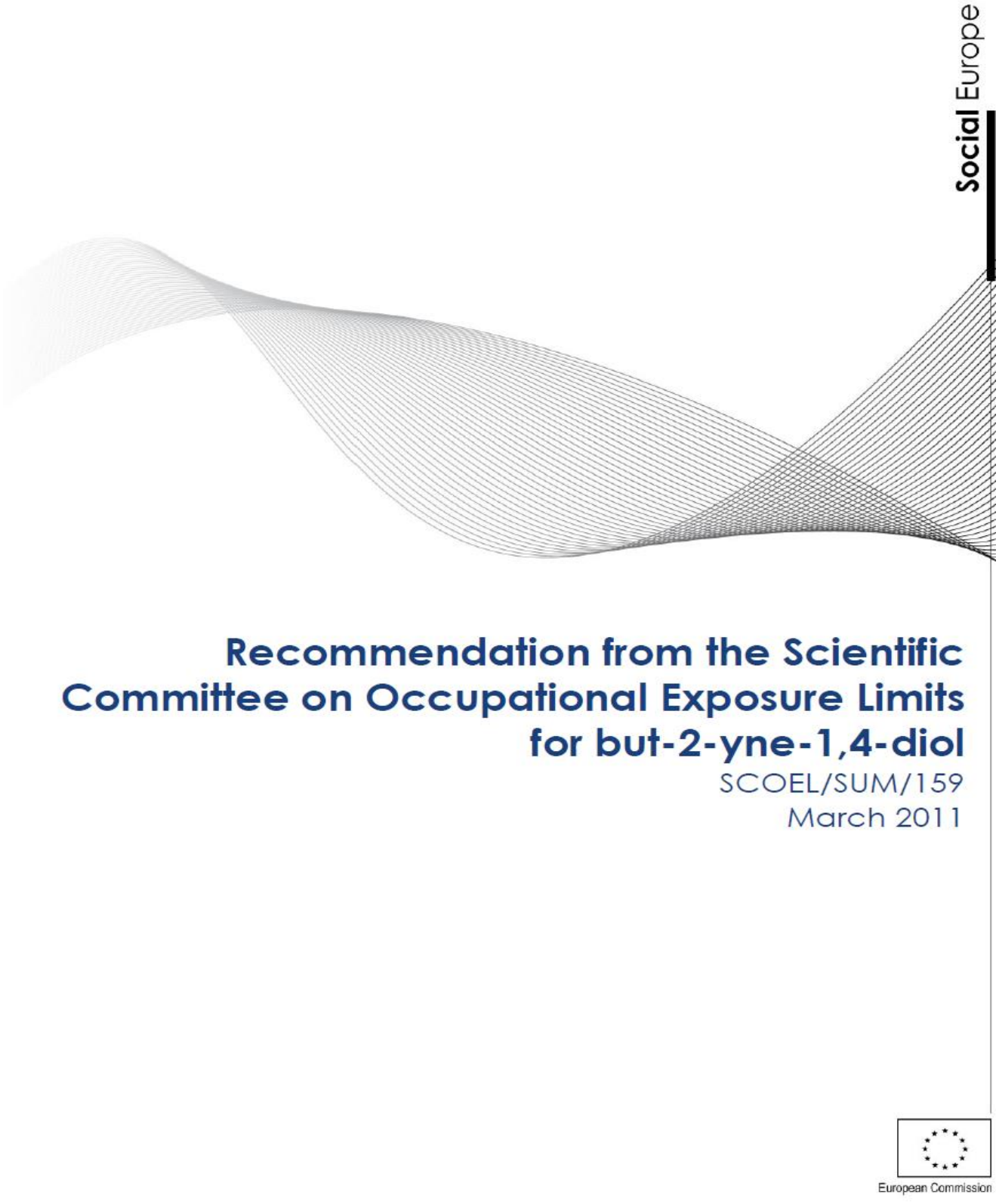
Anmerkning:

9. Referanser

1. Recommendation from the Scientific Committee on Occupational Exposure Limits for but-2-yne-1,4-diol, SCOEL/SUM/159, mars 2011.

2. MAK 2012, 2-Butin-1,4-diol (Butindiol) [MAK Value Documentation in German language, 2012]. doi: 10.1002/3527600418.mb11065d0052.

Vedlegg SCOEL



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Recommendation from the Scientific Committee on Occupational Exposure Limits for But-2-yne-1,4-diol

8 hour TWA:	0.5 mg/m³
STEL (15 min):	not assigned
Notation:	not assigned
BLV:	not assigned

Substance identification: But-2-yne-1,4-diol:

Synonyms: 1,4-Butynediol; 2-Butyne-1,4-diol; 2-Butynediol; 1,4-Dihydroxy-2-butyne; Bis(hydroxymethyl) acetylene

EC No.: 203-788-6

Annex I Index No.: 603-076-00-9

EU Classification:

Skin Corr. 1B	H314	Causes severe skin burns and eye damage
Acute Tox. 3 *	H331	Toxic if inhaled
Acute Tox. 3 *	H301	Toxic if swallowed
Acute Tox. 4 *	H312	Harmful in contact with skin
STOT RE 2 *	H373 **	May cause damage to organs through prolonged or repeated exposure
Skin Sens. 1	H317	May cause an allergic skin reaction

CAS No.: 110-65-6

MWt: 86.089

Conversion factor (20 °C, 101 kPa): 1 ppm = 3.58 mg/m³; 1 mg/m³ = 0.279 ppm

Structural formula:

HO-CH₂-C≡C-CH₂-OH

This evaluation is based on BG-Chemie (2005), ECB (2000), ECB (2005), Greim (2003), Greim (2006) and the references cited in these reviews.

Physico-chemical properties

But-2-yne-1,4-diol (butynediol) is a yellow scaly solid. The melting point of the substance is 50 - 58 °C and the boiling point is 238 °C. Violent decomposition occurs above 200°C. The vapour pressure, water solubility and log Pow are 0.0017 hPa, 750 g/l, and -0.73, respectively, at 20 °C. Butynediol has a density of 1.05 - 1.17 g/cm³ (Greim, 2006; BG-Chemie, 2005; ECB, 2005).

1. Occurrence/Use and occupational exposure

Butynediol is predominantly used as an intermediate in the synthesis of butanediol and butenediol. In minor amounts, it also serves as an intermediate for other chemicals (e.g. polyols, pharmaceuticals, herbicides, insecticides, flame retardants, plasticisers) and as an additive in galvanisation baths, cleaning agents, disinfectants and corrosion inhibitors (BG-Chemie, 2005; ECB, 2005).

2. Health significance

2.1 Toxicokinetics

2.1.1 Human data

No studies on toxicokinetics in humans are available.

2.1.2 Animal data

No quantitative data on the absorption by inhalation exposure are available.

After oral exposure of rats to 50 mg/kg butynediol, the absorption was at least 80%.

The absorption of butynediol (applied as 0.3 or 30% aqueous solutions) was minimal (<10%), regardless of the concentration of the solution (0.3 or 30%). Using a 30% ethanolic solution for the same procedure, an absorption of 7.5% was reported (RTI, 2002, cited by BG Chemie, 2005). Also the relatively low dermal LD50, as compared to the oral, LD50 (see sectiopn 3.2.2) suggest limited dermal absorption.

Experiments with intravenous injection in rats or mice showed that the half-life in blood is < 30 min. About 60% of the injected dose was excreted in bile (within 4 h in F344 rats or within 24 h in Sprague-Dawley rats) and was reabsorbed in the gut. The predominant metabolites in the bile were 4,4-bis(S-glutathionyl)-2-hydroxytetrahydrofurane and 3-(S-glutathionyl)-2(5H)furanone (RTI, 2002). In rats, butynediol is metabolised to toxic metabolites by hepatic alcohol dehydrogenase. Inhibition of this enzyme by Pyrazole reduced the toxicity after oral gavage (Greim, 2006; BG-Chemie, 2005).

After oral exposure of rats to radiolabelled butynediol, 54% of the administered dose was recovered in urine, 20% in faeces and 5 - 9% exhaled as CO_2. Following dermal exposure, approximately 20% of the absorbed activity was recovered in urine, 9% in faeces, 10% as exhaled CO_2 and 1% as exhaled volatile organics substances by 72 h after administration (RTI, 2002, citde by BG Chemie, 2005).

2.1.3. Biological monitoring

There are no data available. The critical effect of inhalation at workplace exposure of butynediol is irritation. This type of effect cannot be tested by biomonitoring.

2.2. Acute toxicity

2.2.1 Human data

Human data on effects of acute exposure are not available.

2.2.2 Animal data

The inhalation LC_{50} (4 h) was 690 mg/m³ in rats (aqueous solution aerosol). Most oral LD_{50} values in rats were about 100 mg/kg, with a range of 50 - 240 mg/kg. In other species the LD_{50} were similar. The dermal LD_{50} in rats was 424 mg/kg in males and 983 - 1240 mg/kg in females (administration as a paste in NaCl solution) (BG-Chemie, 2005; ECB, 2005). Dermal exposure of the pure compound was less toxic than administration of a 40% aqueous solution (Jedrychowski et al., 1992a). Symptoms at high doses were sedation, apathy, disturbances of balance, convulsions, tremor, accelerated respiration, bradycardia and diarrhoea. At necropsy, the animals revealed congestion of the internal organs, pulmonary oedema and haemorrhages as well as fatty infiltration of the liver (BG-Chemie, 2005; ECB, 2005)

2.3. Irritation

2.3.1 Human data

Human data on irritative effects are not available.

2.3.2 Animal data

Skin
Undiluted butynediol is irritating and corrosive to the skin of rabbits. After 4 h of dermal exposure to pure solid or solid moistened with water, the animals showed severe erythema and oedema within 24 h and exhibited crusts and necrosis within 6 days (Hüls AG, 1985a). Aqueous solutions of up to 20% were not irritating to rabbit skin, higher concentrations (> 30%) produced corrosion and irritation in the majority of the studies (Greim, 2006; BG-Chemie, 2005).

Eyes
Mice showed marked signs of eye irritation after repeated inhalation exposure to concentrations ranging from 90 to 120 mg/m³ (Stasenkova and Kochetkova, 1965a,b) (see section "repeated dose toxicity" for more details). Powdered butynediol is moderately irritating to the rabbit eye and may produce irreversible corneal opacity (Hüls AG, 1985b). Studies with solutions of about 30% produced slight irritation (Greim, 2006; BG-Chemie, 2005).

Respiratory tract
Irritation of the upper respiratory tract was observed in a rat study with repeated inhalation exposure to 5 mg/m³ and above (BASF AG, 1997, 1998). The NOAEC was 0.5 mg/m³. In a mouse inhalation study by Stasenkova and Kochetkova (1965a,b), the animals showed marked signs of irritation in the respiratory tract after exposure to concentrations ranging from 90 to 120 mg/m³ (see section "repeated dose toxicity" for more details).

2.4. Sensitization

2.4.1 Human data

There are several case reports describing contact allergies to butynediol. One woman developed dermatitis after use of a cleaning product, which contained 0.7% butynediol. Patch testing with a 0.01% aqueous solution of this substance gave a positive result (Baadsgard and Jörgensen, 1985). Two workers in the galvanic industry developed an itchy dermatitis. They had contact with butynediol during the handling of galvanisation solutions or cleaning products. Butynediol was identified as causative agent in both cases by patch testing (Blaschke et al., 2001; Malten, 1980). Six workers employed in butynediol

production developed allergic contact eczema, suspected to be evoked by butynediol. They were patch tested with a 0.5% solution of the pure material or a 1% solution of technical grade substance (containing formaldehyde). All of them reacted positively to butynediol, but not to formaldehyde (BASF AG, 2001).

2.4.2 Animal data

There are 2 Magnusson-Kligman tests according to OECD guideline 406. RCC (1990) used a 5% solution of butynediol in saline for intradermal induction and a 25% solution for topical induction. The animals were challenged with a 25% solution. Only 1 of 18 treated animals showed a positive response (RCC, 1990). In a study by Hüls AG (1985c), the intradermal induction was performed with a 0.5% solution in paraffin, the challenge with 25% aqueous solution. Five of 20 treated animals, but none of the control animals reacted positively. Another (insufficiently reported) study showed a negative result after intradermal and epicutaneous induction with 2% and 20% solutions, respectively. The challenge was undertaken with 5 or 25% solutions (Jedrychowski et al., 1992a). In a study by Haskell Laboratory (1966), guinea pigs were intradermally injected with a 10% aqueous solution of the substance, followed by two challenges with the same concentration. Five of 11 animals reacted clearly positively after the first challenge and 6 of 11 animals reacted positively after the second challenge (this study was not performed according to OECD guidelines).

In a ranking of a number of chemicals with respect to contact allergenic properties made by a group of thirty experts, butynediol was put in Category B, corresponding to "Solid-based indication for contact allergenic effects...less frequently proven contact allergenic effect in humans taking into account existing positive animal data" (Schlede et al., 2003).

2.5 Repeated dose toxicity

2.5.1 Human data

Human data on effects of repeated exposure are not available.

2.5.2 Animal data

Inhalation

BASF AG (1997) conducted a range-finding study according to OECD guideline 412. Five Wistar rats per sex and group were exposed by inhalation to 0, 25, 100 and 300 mg/m³ of liquid aerosols of aqueous butynediol solutions (6 h/d, 5 d). All exposed animals showed an increase of urobilinogen in urine (indicative of liver functional disturbance) and irritation in the upper respiratory tract. These consisted of laryngeal inflammation and metaplasia at 25 mg/m³ and above. Exposure to 100 mg/m³ and above resulted in hyperplasia of the larynx and lesions of the nose (inflammation, increased mucus formation and epithelial lesions in the olfactory epithelium). At the highest concentration, increased mortality occurred (one animal of each sex), as well as a slightly reduced body weight gain and clinical signs of toxicity (nasal crusts, accelerated respiration, piloerection and tremor). The urine of these animals was discoloured. There were functional and morphologic alterations of the liver (increased gamma GT, bilirubin and cholesterol serum levels, increased urobilinogen levels in urine as well as necrosis and dystrophy of the liver). Inflammation and/or epithelial changes in the nose and/or the larynx were evident in all animals. The animals that died prematurely showed severe damage of the liver, kidney, thymus, spleen and stomach. The LOAEC of this study is 25 mg/m³ (no NOAEC).

In a study by BASF AG (1998), performed according to OECD guidelines 412/413, Wistar rats (16 per sex and group), were exposed by inhalation to 0, 0.5, 5 and 25 mg/m³ of liquid aerosols of aqueous butynediol solutions for 6 h/d, 5 d/w (head-nose exposure). Half of the

animals were exposed for 2 weeks (10 exposures, 15 days), the other half for 4 weeks (20 exposures, 30 days). Systemic toxicity (including neurofunctional alterations on days 0, 8 or 18, and neuropathology) was examined after 10 or 20 exposures. Systemic effects were restricted to an increase in urobilinogen in urine in 2/5 males and 2/5 females at the highest concentration. As there were no accompanying signs of liver function disturbances or lesions, the authors regarded the concentration of 25 mg/m³ as the NOAEC for systemic toxicity. At 5 mg/m³ and above there were dose-dependent effects in the upper respiratory tract. Except tracheal inflammation in one female, there were no signs of irritation in the control animals. Minimal to slight focal laryngeal irritation (5 mg/m³: 1/5 of each sex, only after 20 exposures; 25 mg/m³: 4/5 males and females after 10 exposures, 2/5 males and females after 20 exposures) and squamous metaplasia in the larynx were observed (5 mg/m³: 4/5 males and 5/5 females after 10 exposures, 2/5 males and 5/5 females after 20 exposures; 25 mg/m³: 4/5 males and 5/5 females after 10 exposures, 4/5 males and 5/5 females after 20 exposures). Focal inflammation in the trachea occurred only at 25 mg/m³ after 20 exposures (2/5 animals of each sex). There was no increase in severity of the lesions at the longer exposure duration. The LOAEC for metaplasia and inflammation of this study is 5 mg/m³. The NOAEC for respiratory effects is 0.5 mg/m³.

In a mouse inhalation study by Stasenkova and Kochetkova (1965a,b) the animals (n = 20) were exposed for 1 month to air or a butynediol aerosol at concentrations ranging from 90 to 120 mg/m³ for 2 h/d on 6 d/w. There were marked signs of irritation of eyes and respiratory tract, a retardation of body weight gain and neurofunctional alterations. Two animals died during the study. This study is not appropriate for risk assessment due to insufficient data presentation.

Oral

In a study by BASF AG (1992) according to OECD guideline 407, Wistar rats were gavaged with nominal doses of 0, 5, 10 and 20 mg kg^{-1} d^{-1} butynediol (dissolved in water) on 5 consecutive days. The only effect seen in this study was a significant increase of cholesterol serum levels in high dose males. There were no alterations in neurofunctional tests (NOAEL 10 mg kg^{-1} d^{-1}).

Komsta et al. (1989) exposed Sprague-Dawley rats to 0, 1, 10 and 100 mg kg^{-1} d^{-1} butynediol (aqueous solution, by gavage) for 14 days. The animals of the highest dose showed clinical signs of toxicity, decreased body weight gain, increased liver weights, alterations in the serum concentrations of hepatic enzymes as well as significant increases of serum cholesterol and calcium. Female animals developed anaemia. No effects were seen in the mid and low dose groups (NOAEL 10 mg kg^{-1} d^{-1}).

In a 4-week study by Jedrychowski (1992b) butynediol was gavaged as an aqueous solution to Wistar rats (8 per sex and group) in daily doses of 0, 1, 10 and 50 mg kg^{-1} d^{-1} for 28 days. At 50 mg kg^{-1} d^{-1}, there was an increased mortality and a decreased body weight gain as well as the occurrence of anaemia and leukocytosis. The liver and kidney weights were increased at this dose, the liver weights also in females of the mid dose group. All animals of the 50 mg kg^{-1} d^{-1} group and some of the mid dose group had histopathological liver lesions. These findings were interpreted by the authors as signs of hepatic hyperplasia, but can also reflect cell degeneration (ECB, 2005). Lesions of the red pulp of the spleen were observed in 3/16 animals exposed to 10 mg kg^{-1} d^{-1} and in 5/10 animals examined in the high dose groups. No effects occurred at the low dose (LOAEL 10 mg kg^{-1} d^{-1}, NOAEL 1 mg kg^{-1} d^{-1}).

In a study by Knyshova (1968), male rats were exposed orally to butynediol at doses of 0, 0.04, 0.2 and 2 mg kg^{-1} d^{-1} for 6 months. Animals of the high dose group showed delayed

conditioned reflexes, reductions in cholinesterase activity, sulfhydryl enzyme activity and liver lesions. Other effects noted at this dose were the reduction of Nissl bodies and an increase of neuroglia content in the brain. Other organs showed hyperaemia. This study is not appropriate for risk assessment since the protocol does not conform to current guidelines and the data presentation is insufficient (Greim, 2006).

Dermal
No studies with repeated dermal exposure are available.

2.6. Mutagenicity

2.6.1. In vitro

Two studies (one with a preincubation protocol) investigating the mutagenic activity in bacteria are available. Butynediol was not mutagenic with and without metabolic activation in the Salmonella strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 (BASF, 1981; NTP, 1998). Negative results were also obtained in two in vitro tests on induction of chromosomal aberrations in V79 hamster cells without metabolic activation. In the presence of metabolic activation there was an equivocal result. Two out of three independent trials detected a slight increase in aberrations at toxic concentrations (CRR, 1989; 1991).

2.6.2. In vivo-human data

Human data on genotoxic effects are not available.

2.6.3. In vivo-animal data

A single intraperitoneal injection of 17.5 - 70 mg/kg did not induce micronuclei in the bone marrow of NMRI mice (RCC, 1998).

2.7. Carcinogenicity

2.7.1. Human data

Human data on carcinogenic effects are not available.

2.7.2. Animal data

No adequate studies on the carcinogenic effects in animals are available. In an older tumour initiation/promotion study with dermal exposure of mice, butynediol did not act as a tumour initiator (the promoter was croton oil). The duration of this experiment was short and the exposure to initiator and promoter was overlapping (Greim, 2006; BG-Chemie, 2005)

2.8. Reproductive toxicity

2.8.1. Human data

Human data on reproductive or developmental effects are not available.

2.8.2. Animal data

Fertility

In a one-generation study by BASF AG (1999) according to OECD guideline 415 and extended according to OECD guideline 416, Wistar rats (25 per sex and group) were exposed orally via drinking water at concentrations of 0, 10, 80 and 500 mg/l (about 1, 7.6 and 40 mg kg^{-1} d^{-1}) prior to mating (at least 76 days), during mating, gestation and lactation (until day 21). Then all F_0 animals and most of the pups were examined. One male and one female F_1 animal per litter were selected and a total of 25 animals of each sex were exposed to the same drinking water concentrations as their parents until sexual maturation and examined thereafter. Significant effects in the F_0 generation were seen at 80 mg/l (7.6 mg kg^{-1} d^{-1}) and above. At this dose, the water intake was reduced and the liver weights (only females) and kidney weights (both sexes) were increased. These effects were more marked at 500 mg/l drinking water, which also led to a retarded body weight gain and reduced adrenal and thymus weights in females. No effects on reproduction parameters or histopathological organ changes were evident (a slight, but significant reduction in sperm motility of F_0 males was within the range of historical control data). The only significant effect in the offspring, examined on postnatal day 21, was a reduced body weight gain in pups of the high dose group on postnatal day 7 and later, and corresponding changes in organ weights (brain, thymus, spleen). The offspring which was reared until sexual maturation remained unaffected at drinking water concentrations up to 80 mg/l. In the high dose group, there was a significant reduction of water uptake (both sexes), reduction of food intake and body weight gain (more marked in males). A slight but significant delay of vaginal opening in females and preputial separation in males at the high dose was attributed to the general retardation of development and not regarded as a specific delay of sexual maturation (ECB, 2005). The LOAEL and NOAEL for F_0 animals based on systemic toxicity is 7.6 mg kg^{-1} d^{-1} and 1 mg kg^{-1} d^{-1}, respectively. The LOAEL and NOAEL for developmental toxicity is 40 mg kg^{-1} d^{-1} and 7.6 mg kg^{-1} d^{-1}, respectively.

Developmental toxicity

Hellwig et al. (1997) examined developmental effects in Wistar rats (18 - 22 per group) after oral exposure to doses of 0, 10, 40 and 80 mg kg^{-1} d^{-1} butynediol on gestation days 6 - 15 (according to OECD guideline 414). At the high dose, there was evidence of maternal toxicity (reduced food intake, loss of body weight, one premature death and one animal with clinical signs of toxicity). The only effects seen in the foetuses were significant increases of the ratio of affected foetuses per litter with accessory 14^{th} rib and dilated renal pelvis and/or hydroureter in the 80 mg kg^{-1} d^{-1} group. Evaluation on the basis of foetal incidence or litter incidence revealed no significant differences. The concurrent controls had an uncommonly low incidence for these endpoints, compared to laboratory historical controls, and the observed effects are within the range of normal biological variation. Therefore the findings are not considered to be a substance-related effect (ECB, 2005). The LOAEL and NOAEL for maternal toxicity, is 80 mg kg^{-1} d^{-1} and 40 mg kg^{-1} d^{-1}, respectively. The NOAEL for developmental toxicity is 80 mg kg^{-1} d^{-1}.

2.9. Methods of exposure monitoring and analysis

For the purpose of measuring butynediol concentration in workplace air a method is used which allows the simultaneous determination of the total dust concentration (glass fibre filter) and of the concentration in the gas phase (activated charcoal). The filter and the activated charcoal are subsequently eluted with methylene chloride/methanol and determined by gas chromatography using a flame ionization detector (GC-FID). The detection limit is 0.035 mg/m3. Due to the measurement method and the sampling strategy applied, the measurement results are regarded as valid (ECB, 2005).

Recommendation

No adequate human data for deriving an OEL are available.

Based on animal data, no systemic effects (including neurotoxicity) are expected to occur at non-irritating concentrations, as there were no clear signs of systemic toxicity even at high concentrations (the only effect at 25 mg/m³ was increased urobilinogen in urine indicative of hepatic effects, but this was not accompanied by other liver effects). Higher exposure levels in a range-finding study produced marked toxicity in the liver, kidney, thymus, spleen and gastrointestinal tract. Subchronic or chronic animal inhalation studies are not available.

Mutagenicity tests in bacteria and one in vivo test (induction of micronuclei in mice) yielded negative results. The outcomes in mammalian cells in vitro concerning chromosomal aberrations are negative, showing positive results only at cytotoxic concentration. Carcinogenicity studies on butynediol are not available.

Animal inhalation and oral studies support that systemic effects occur only at higher exposures than those causing irritation. Thus, the NOAEL of 1 mg kg^{-1} d^{-1} (Jedrychowski et al., 1992b; BASF AG, 1999) corresponds to daily 8-h inhalation exposures at 7 mg/m³, assuming a daily inhaled volume of 10 m³, 100% uptake and a body weight of 70 kg. This concentration is above the LOAEC for irritation of 5 mg/m³ and more than tenfold higher than the NOAEC of 0.5 mg/m³ in the BASF (1998) study and the proposed OEL of 0.2 mg/m³.

Based on animal data, the critical effect of inhalation exposure to butynediol is irritation. The NOAEC of 0.5 mg/m³ established in the BASF (1998) rat inhalation study is used to derive an OEL. No uncertainty factor is considered necessary taking account of the nature of the effect (irritation) and that other effects are only seen at much higher exposure levels. The proposed 8-h OEL is therefore 0.5 mg/m³. No data are available to derive a short-term exposure level.

No "skin" notation is recommended, since systemic toxicity is expected only at exposure levels far higher than the recommended 8-h OEL. It should be noted, however, that butynediol is a skin sensitizer and that pure and moistened butynediol as well as concentrated aqueous solutions are corrosive or irritating to the skin.

A method based on sampling of dust on a glass fibre filter and vapour on activated charcoal followed by gas chromatography is available. The method measures the particle and vapour phases separately, the detection limit of 0.035 mg/m³ being well below the proposed OEL.

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