Arbeidstilsynet

Høringsutkast

Grunnlag for fastsettelse av grenseverdi

Grunnlagsdokument for svoveldioksid (SO_2)

Kommisjonsdirektiv 2017/164/EU

Tittel: Grunnlag for fastsettelse av grenseverdi. Grunnlagsdokument for svoveldioksid (SO_2).

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Denne rapporten omhandler det toksikologiske grunnlaget og vurderinger, samt tekniske og økonomiske hensyn for fastsettelse av grenseverdi for svoveldioksid (SO_2).

Innhold

Forord

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

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

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

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

Statens arbeidsmiljøinstitutt (STAMI) ved Toksikologisk ekspertgruppe for administrative normer (TEAN) bidrar med faglige vurderinger i dette arbeidet. TEAN vurderer og evaluerer de aktuelle SCOEL dokumentene, presiserer kritiske effekter og vurderer behov for korttidsverdier ut i fra den foreliggende dokumentasjonen. Videre søker og evaluerer TEAN nyere litteratur etter utgivelsen av dokumentet. TEAN bruker kriteriene gitt i SCOEL's metodedokument, "Methodology for the derivation of occupational exposure limits: Key documentation (version 7, June 2013)". Dette er inkludert i TEANs Metodedokument del B (Prosedyre for utarbeidelse av toksikologiske vurderinger for stoffer som skal implementeres i det norske regelverket for grenseverdier etter direktiv fra EU-kommisjonen) utarbeidet for denne revisjonen.

Informasjon om bruk og eksponering i Norge innhentes fra Produktregisteret, EXPO databasen ved STAMI og eventuelle tilgjengelige måledata fra virksomheter/næringer.
Beslutningsprosessen skjer gjennom drøftingsmøter der Arbeidstilsynet, Næringslivets hovedorganisasjon/Norsk Industri og Landsorganisasjonen i Norge deltar, samt orienteringsmøter og offentlig høring. Konklusjonene fra høringen med forskriftsendringer og nye grenseverdier forelegges Arbeids- og sosialdepartementet som tar den endelige beslutningen.

Innledning

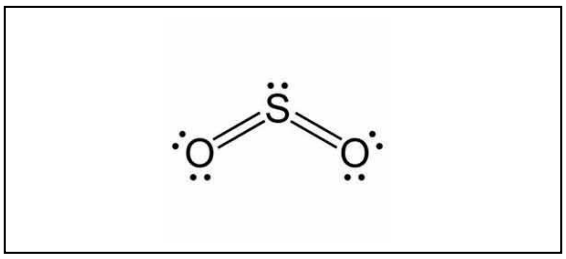
Dette grunnlagsdokumentet omhandler vurderingsgrunnlaget for fastsettelse av grenseverdi for svoveldioksid. Innholdet bygger spesielt på anbefalinger fra Scientific Committee on Occupational Exposure Limits (SCOEL) i EU for svoveldioksid (vedlegg 1), samt vurderinger og kommentarer fra Toksikologisk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

1. Stoffets identitet

Svoveldioksid og dets molekylformel, synonymer av stoffets navn, stoffets identifikasjonsnummer i Chemical Abstract Service (CAS-nr.), European Inventory of Existing Commercial Chemical Substances (EINECS-nr. og/eller EC-nr.) og Indeks-nr. der disse er kjent er gitt i tabell 1. Strukturformel av stoffet er vist i figur 1.

Tabell 1. Stoffets navn og identitet.

Navn **Molekylformel**	**Svoveldioksid** **SO_2**
Synonymer	-
CAS-nr.	7446-09-5
EC-nr.	231-195-2
Indeks-nr.	016-011-00-9



Figur 1. Strukturformel av svoveldioksid.

2. Fysikalske og kjemiske data

Svoveldioksid er en fargeløs, giftig, ikke brennbar gass med stikkende og irriterende lukt.

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

Tabell 2. Fysikalske og kjemiske data for svoveldioksid (SO_2).

Molekylvekt (g/mol)	64,06
Fysisk tilstand (20 °C, 101.3 kPa):	Gass, giftig
Smeltepunkt (°C):	-75,6 til -72 (Gjennomsnitt: 73,4)[1]
Kokepunkt (°C)	-10,0
Selvantennelsestemperatur (°C):	Ikke brennbar
Damptetthet (luft = 1, 0 °C):	2,26
Damptrykk (20 °C) (hPa)	3271
Løselighet i vann (20 °C)	11,28 g/100 ml
Løselig i andre løsemidler:	Alkohol, eddiksyre, svovelsyre, eter, kloroform og andre polare løsemidler
Omregningsfaktor (20 °C, 101 kPa)	1 ppm = 2,66 mg/m^3 1 mg/m^3 = 0,375 ppm

[1] https://comptox.epa.gov/dashboard/dsstoxdb/results?utf8=%E2%9C%93&search=7446-09-5

2.1. Forekomst og bruk

Svoveldioksid (SO_2) er en naturlig del av luften som følge av utslipp fra naturlige kilder og industriell virksomhet. Svoveldioksid dannes ved forbrenning av stoffer som inneholder svovel. De viktigste kildene til svoveldioksid i luft er forbrenning av kull og oljer som inneholder svovel, kjemisk- og metallurgisk industri, men også fra naturlige prosesser som vulkanutbrudd. Svoveldioksid brukes i stor utstrekning i treforedlingsindustrien og som en råvare i annen kjemisk industri.

3. Grenseverdier

3.1 Nåværende grenseverdi

Nåværende grenseverdi (8 timer) i Norge for svoveldioksid er: 0,8 ppm, 2 mg/m^3 med fotnote 12, fastsatt i 2007.

Fotnote 12: Enkelte bedrifter vil av teknisk-økonomiske årsaker ikke kunne overholde denne verdien. Det er disse bedriftenes ansvar å dokumentere et forsvarlig arbeidsmiljø. Det forutsettes at bedriften(e) har eller er tilsluttet bedriftshelsetjeneste, og at eksponerte arbeidstakere gjennomgår egnet helseundersøkelse.

3.2. Grenseverdi fra EU

Den europeiske vitenskapskomiteen, SCOEL foreslår:

IOELV (Indicative Occupational Exposure Limit Value) (8 timer): 0,5 ppm, 1,3 mg/m^3

STEL (Short Term Exposure Limit): 1 ppm, 2,7 mg/m^3 som korttidsverdi.

3.3 Grenseverdier fra andre land og organisasjoner

Nåværende grenseverdier for svoveldioksid fra andre land og organisasjoner er gitt i tabell 3 nedenfor.

Tabell 3. Grenseverdier for svoveldioksid fra andre land og organisasjoner. Land og organisasjoner som ikke har grenseverdier eller korttidsverdier for svoveldioksid er markert med -.

Land Organisasjon	Grenseverdi (8 timer)	Korttidsverdi (15 min)	Anmerkning Kommentar
Sverige[1]	2 ppm, 5 mg/m³	5 ppm, 13 mg/m³	1987
Danmark[2]	0,5 ppm, 1,3 mg/m³	-	1996
Finland[3]	0,5 ppm, 1,3 mg/m³	1 ppm; 2,7 mg/m³	2016
Storbritannia[4]	-	-	Storbritannia har ikke en fastsatt grenseverdi, men viser til: "Control of Substances Hazardous to Health (COSHH)"[8]
Nederland[5]	-	0,7 mg/m³	2008
ACGIH, USA[6]	-	0,25 ppm, 0,65 mg/m³	-
NIOSH, USA[6]	2 ppm, 5 mg/m³	5 ppm, 13 mg/m³	-
OSHA, USA[6]	3 ppm, 15 mg/m³	-	-
Tyskland, MAK[6]	1 ppm, 2,7 mg/m³	I(1) C 1 ppm, C 2,7 mg/m³	Gjelder korttidsverdi: I(1) - Overskridelsesfaktor C - toppeksponering/takverdi
Tyskland, Myndighetene[7]	1 ppm, 2,7 mg/m³	-	11/2011 1(I) - Overskridelsesfaktor Y - ikke fare for skade på foster dersom grenseverdi overholdes

[1] Arbetsmiljöverkets Hygieniska gränsvärden AFS 2015:7, https://www.av.se/globalassets/filer/publikationer/foreskrifter/hygieniska-gransvarden-afs-2015-7.pdf.
[2] At-vejledning, stoffer og materialer - C.0.1, 2007, https://arbejdstilsynet.dk/da/regler/at-vejledninger/g/c-0-1-graensevaerdi-for-stoffer-og-mat.
[3] Social og hälsovårdsministeriet, HTP-värden, Koncentrationer som befunnits skadliga, Helsingfors, 2016, http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/79110/STM_9_2016_HTP-varden_2016_Ruotsi_22122016_NETTI.pdf .
[4] EH40 andre utgave, 2013, http://www.hse.gov.uk/pubns/priced/eh40.pdf
[5] http://www.ser.nl/en/oel_database.aspx; http://www.ser.nl/en/grenswaarden/2%20butyne%201%204%20diol.aspx
[6] Guide to occupational exposure values compiled by ACGIH, 2017.
[7] Baua, TRGS 900, oppdatert 2016, https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/TRGS-900.pdf;jsessionid=439FFF321DF2323E60F868CD08E9CD3A.s1t2?__blob=publicationFile&v=2
[8] http://www.hse.gov.uk/pubns/chan34.htm

3.4 Stoffets klassifisering

Svoveldioksid er i henhold til CLP Annex VI, (Forordning EC No 1272/2008) tabell 3.1 (Liste over harmonisert klassifisering og merking av farlige kjemikalier) klassifisert og merket i ulike fareklasser, med faresetninger og koder, som gitt i tabell 4 nedenfor.

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

Fareklasse **Farekategori** **Forkortelse**	**Merkekode**	**Faresetning**
Gasser under trykk *Press. Gas*		
Etsende/irriterende for huden Kategori 1B *Skin Corr. 1B*	H314	Gir alvorlige etseskader på hud og øyne
Akutt giftighet Kategori 3 Acute Tox. 3	H331	Giftig ved innånding

[1] 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 fremmer ikke et forslag til biologisk grenseverdi for svoveldioksid.

4 Toksikologiske data og helseeffekter

4.1. Kommentarer fra TEAN

SCOELs kriteriedokument er fra 2009 med siste litteraturreferanse fra 2008. Det er ikke funnet nyere studier som er relevante for vår vurdering.

SCOEL har vurdert irritasjon i øvre luftveier og øyne, og redusert lungefunksjon, målt ved FEV1 eller luftveismotstand, som de vesentligste negative helseeffekter av SO_2. De fleste studier som har relevans for arbeidsmiljø er utført som provokasjonsstudier av unge, friske individer, eller individer med atopi eller astma. Et gjennomgående funn er at astmatikere er mer sårbare for effekter av SO_2 enn friske. Sårbarheten kan påvirkes av faktorer som tilleggs eksponeringer eller fysisk aktivitet. Opptaket av SO_2 øker ved fysisk aktivitet, men fysisk aktivitet kan også forverre bronkial irritasjon hos astmatikere.

Negative helseeffekter av SO_2, som nese- og halsirritasjon, redusert lungefunksjon og økt luftveismotstand er ofte observert ved akutte toppeksponeringer, og SCOEL er av den oppfatning at disse bør forebygges, og det anbefales derfor en STEL.

Ifølge SCOEL er det hos astmatikere observert negative helseeffekter ved 0.5 ppm, mens effekter hos friske vanligvis ikke oppstår ved nivåer under 1.0 ppm. SCOEL har som utgangspunkt at OEL-verdier skal settes for friske personer, og anbefaler derfor en OEL på 0.5 ppm, som vil beskytte ikke–astmatikere mot negative helseeffekter av SO_2. I tillegg setter SCOEL en STEL på 1.0 ppm. I og med at denne grenseverdien ikke beskytter alle astmatikere mot reaksjoner på SO_2, anbefaler SCOEL at astmatikere ikke blir eksponert for mer enn 0.2 ppm.

Det er i litteraturen ikke tilstrekkelig data til at man kan trekke konklusjoner vedrørende gentoksiske, reproduktive eller kreftfremkallende effekter av SO_2.

ACGIH (2008) har foreslått en lavere grenseverdi enn SCOEL, basert på en uttalt målsetning om å unngå negative helseeffekter hos astmatikere.

TEAN finner ingen grunn til å bestride SCOELs vurderinger av det vitenskapelige grunnlaget angående helseeffekter av SO_2. Det er imidlertid grunn til å gjøre oppmerksom på at SCOELs forslag til grenseverdi ikke tar sikte på å beskytte astmatikere mot uønskede helseeffekter av eksponering.

5. Bruk og eksponering

Svoveldioksid brukes i stor utstrekning i produksjon av papir og som en råvare i annen kjemisk industri. I Norge er industri og bergverk de største utslippskildene til svoveldioksid.

5.1. Opplysning fra Produktregistret

Data fra Produktregisteret er innhentet i oktober 2016.

Det er funnet opplysninger om mengde og bruk av svoveldioksid i 16 deklareringspliktige produkter i Norge. Total mengde av stoffet i disse produktene oppgis å være 35360 tonn.

På grunn av sikkerhetsbestemmelsene i Produktregisteret kan vi ikke gi eksakte opplysninger om i hvilke bransjer og i hvilket produkttyper svoveldioksid inngår.

5.2. Eksponering og måledokumentasjon

I arbeidsmiljøsammenheng forekommer svoveldioksid både som råvare og som en forurensning.

5.2.1. EXPO- data

Rapporterte målinger av svoveldioksid er hentet fra STAMIs eksponeringsdatabase EXPO.

Eksponeringsmålinger av svoveldioksid registrert i EXPO er utført over flere år. STAMI har siden 1984 kartlagt arbeidsatmosfæren på ulike arbeidsplasser der blant annet svoveldioksid kan være et

arbeidsmiljøproblem. Målinger av svoveldioksid for perioden 1984-2015 viser 755 prøver fra ulike bedrifter og næringer.

Grenseverdien for svoveldioksid ble revidert og ny grenseverdi fastsatt i 2007. Eksponeringsmålinger registrert i EXPO frem til 2007 ble da vurdert og var med å danne grunnlaget for den nye grenseverdien. Eksponeringsmålinger som fremstilles i denne vurderingen inneholder derfor målinger registrert etter den nye grenseverdien ble innført.

Det er registrert 14 målinger av svoveldioksid i perioden 2007 – 2010, hvorav 11 er personbårne prøver og 3 er stasjonære prøver. De personbårne prøvene er foretatt under produksjon av ferrolegeringer hvorav 8 av disse er målt under ovnstapping. Målingene viste toppverdier fra 3,2 ppm til 26,4 ppm, der den høyeste middelverdien lå på 0,26 ppm.

Ved 2 av de stasjonære prøvene ble det målt svoveldioksidverdier på henholdsvis 1,1 ppm og 5,1 ppm. Disse ble målt under produksjon av raffinerte petroleumsprodukter.

5.2.2. Prøvetakings- og analysemetode

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

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

Prøvetakingsmetode	Analysemetode	Referanse
Direktevisende gass-sensor	Elektrokjemisk sensor	
Direktevisende gass-sensor	FTIR spectrometri[1]	NIOSH 3800[2]
Filter (0.8 µm cellulose ester membran) + treated filter (cellulose + Na_2CO_3)	Ionekromatografi	NIOSH 6004[3]
Filter (5.0 mm PVC) + filter impregnert med KOH	Ionekromatografi	STAMI

[1] Fourier Transform Infrared Spectrometry
[2] NIOSH 3800 https://www.cdc.gov/niosh/docs/2003-154/pdfs/3800.pdf
[3] N 6004 henviser til metode i NIOSH Manual of Analytical Methods, 3rd ed., NIOSH, Cincinnati, Ohio, USA, 1984, med oppdateringer: http://www.cdc.gov/niosh/nmam/

6. Vurdering

Toksikologiske data for svoveldioksid (SO_2) er beskrevet i SCOEL-dokumentet i vedlegg 1, og kommentert av STAMI (TEAN) i kapittel 4.

Svoveldioksid er lettløselig i vann og danner svovelsyrling når den reagerer med vann. Ved eksponering for svoveldioksid absorberes den således lett i de øvre luftveiene. Den kritiske effekten av svoveldioksideksponering er irritasjon i øvre luftveier og øynene, samt redusert lungefunksjon og økt luftveismotstand.

Flere studier har vist at det er stor forskjell på effekt av eksponering for svoveldioksid mellom lungefriske personer og personer som har redusert lungefunksjon, som astmatikere. Astmatikere er spesielt følsomme og reagerer med irritasjonseffekter ved langt lavere verdier enn lungefriske. De

negative effektene på lungefunksjon i friske individer oppstår ved eksponering på 1 ppm eller høyere, mens hos astmatikere oppstår negative effekter allerede ved kortvarig eksponering på 0,5 ppm eller lavere.

Med utgangspunkt i at SCOEL setter grenseverdier (OEL) basert på friske personer, anbefaler de i sitt kriteriedokument en 8-timers grenseverdi på 0,5 ppm (1,3 mg/m^3). De kommenterer i tillegg at ved denne verdien vil de fleste være beskyttet, men ikke personer med bronkial astma eller kronisk bronkitt og anbefaler derfor at disse arbeidstakere ikke eksponeres for mer enn 0,2 ppm svoveldioksid.

For å forebygge negative helseeffekter som nese- og halsirritasjon, redusert lungefunksjon og økt luftveismotstand som følge av kortvarige toppeksponeringer, foreslår SCOEL en korttidsverdi på 1 ppm (2,7 mg/m^3).

Det er ikke funnet tilstrekkelig data som tilsier at svoveldioksid er sensibiliserende ved gjentatte eksponeringer, og ingen gode studier som indikerer at svoveldioksid har en kreftfremkallende effekt, er gentoksisk eller reproduksjonsskadelig.

Et lavt antall målinger er gjort av svoveldioksideksponering og registrert i EXPO etter at den gjeldende grenseverdien for svoveldioksid ble fastsatt i 2007. Men de personbårne målingene foretatt under produksjon av ferrolegeringer ved ovnstapping gir holdepunkter for at det kan være utfordrende for denne bransjen å overholde en enda lavere grenseverdi for svoveldioksid. Det er grunn til å tro at dette vil gjelde for flere næringer i Norge.

7. Konklusjon med forslag til ny grenseverdi

På bakgrunn av den foreliggende dokumentasjon og en avveiing mellom de toksikologiske dataene og eksponeringsdata forslås at dagens grenseverdi senkes, og at fotnote 12 bortfaller. I tillegg foreslås en korttidsverdi for stoffet, at anmerkningene S (korttidsverdi) og E (EU har fastsatt grenseverdi for stoffet) og en fotnote innføres.

Forslag til ny grenseverdi, korttidsverdi, anmerkning og fotnote:

Grenseverdi (8-timers TWA): 0,5 ppm, 1,3 mg/m^3

Korttidsverdi (15 min): 1,0 ppm, 2,7 mg/m^3

Anmerkning: S (korttidsverdi) og E (EU har fastsatt grenseverdi for stoffet)

Fotnote:
Enkelte bedrifter vil av teknisk-økonomiske årsaker ikke kunne overholde grenseverdiene. Det er disse bedriftenes ansvar å dokumentere et forsvarlig arbeidsmiljø. Det forutsettes at bedriften(e) har en plan for reduksjon av eksponering og at man kan vise lavere verdier over tid. Arbeidstilsynet, ansattrepresentanter og verneombud skal konsulteres og informeres om årlige planer og oppnådde resultater.

8. Ny grenseverdi

Dette kapitlet utarbeides etter at ASD har fastsatt den nye grenseverdien.

9. Referanser

1. ACGIH, Documentation of the TLVs and BEIs (2008). Sulfur dioxide

Vedlegg: SCOEL/SUM/27

Recommendation from the

Scientific Committee on Occupational Exposure Limits

for Sulphur Dioxide

8 hour TWA	:	0.5ppm (1.3 mg/m^3)
STEL (15 mins)	:	1.0 ppm (2.7. mg/m^3)
Additional classification	:	-
BLV	:	-

Substance identification:

Sulphur dioxide SO_2

Synonyms	:	Sulphurous oxide, sulphurous anhydride, sulphur oxide,
EINECS N°	:	231-195-2
EEC N°	:	016-011-00-9
EU Classification:		T- toxic
Risk phrases		R23 – Toxic by inhalation R34 - Causes burns
CAS		No. 7446-09-5
Molar mass	:	64.06 g/mol

Conversion factor (20°C, 101kPa) 1 ppm = 2.67 mg/m^3
1 mg/m^3 = 0.37 ppm

This evaluation is based on an earlier assessment of SCOEL (1998) further updated with assessments by DECOS (2003), WHO (2006), Brauer *et al.* (2002), ATSDR (1998), HSE (2002) and –U.S.EPA (2007), with the references cited in these reviews and aditional references from database search.

Physico-chemical properties

Sulphur dioxide is a colourless gas, with an irritating odour. It has a MPt of -72.7°C, a BPt of -10.02°C and a vapour pressure of 321 kPa at 20°C. Sulphur dioxide gas is 2.2 times denser than air

at 0°C. Its odour threshold is between 0.8 and 8 mg/ m^3 (0.3-3.0 ppm) (DECOS, 2003).
Sulphur dioxide is higly hydrophilic and dissolved easily in water. Sulfur dioxid is highly soluble in sulphuric acid, ethyl alcohols, acetic acid, chloroform, diethyl ether, and other polar solvents.

Sulphur dioxide gas is not combustible and ordinarily does not support combustion. The only exceptions are burning potassium or burning magnesium, which continue to burn in sulphur dioxide. In the presence of moisture, sulphur dioxide acts as a powerful reducing agent. The gas is very reactive: on contact with water it forms sulphurous acid. Certain metals and organic substances glow, burn or explode in an atmosphere of sulphur dioxide (von Burg, 1995).
Sulphur dioxide has pungent, irritating odour, similar to burning.sulfur. Sulphur dioxide (SO_2) is very soluble in water (11.28g/100 ml at 20°C). Rapidly converted to sulphurous acid (H_2SO3), which is a dibasic acid with pH less than 3. Sulphur dioxide is extremely stable in heat – up to 2000°C. Complex reactions of SO_2 occur in the atmosphere. (Brauer *et al.*, 2002) .

1. Occurrence/use and occupational exposure

Sulphur dioxide has been known to people for ages. Sulphur used to be burnt to produce sulphur dioxide, which was then used as a fungicide and insecticide. Priestley prepared sulphur dioxide in the year 1774 by heating concentrated sulphuric acid with mercury and called it "Vitriolic acid air". But it was Lavoisier, who proved that it was an oxide of sulphur.Sulphur dioxide is present in volcanic gases; in hot aqueous springs surrounding volcanic regions; in areas where sulphur is extracted by melting it, and in places where coal containing sulphur or sulphur compounds are burnt.

Sulphur dioxide is a normal component of air due to emissions from natural sources and industrial activities. Annualy, the equivalent of about 40-60 x106 tons is emitted into the atmoshere as an atmosheric polutant (Seiler *et al.*, 1988).

Over 65% of sulphur dioxide released to the air, or more than 13 million tons per year, comes from electric utilities, especially those that burn coal. Other sources of SO2 are industrial facilities that derive their products from raw materials like metallic ore, coal, and crude oil, or that burn coal or oil to produce process heat. Examples are petroleum refineries, cement manufacturing, and metal processing facilities. Also, road and non-road diesel equipment currently burn high sulfur fuel and release SO2 emissions to the air in large quantities (U.S. EPA, 2008).

Sulphur dioxide is used in the manufacture of sulphuric acid and other sulphur-containing chemicals, and as a bleaching or sterilising agent. It is also released into the environment from industrial processes such as ore smelting, coal and oil combustion, petroleum refining and water and sewage treatment. As of 2006, China is the world's largest sulfur dioxide polluter, with emissions estimated to be 25.49 million tons in 2005. This amount represents a 27% increase since 2000, and is roughly comparable with U.S. emissions in 1980. In much of western Europe and North Amerika countries concentrations of sulfur dioxide in urban areas continued to decline in recent years as a resultes of controls on emissions and changes in fuel use (WHO, 2000).

Highest occupational exposures are generally encountered during manufacture of cellulose pulp. The various uses of sulphur dioxide are: the manufacturing of sulphuric acid, sulphites, and hydrogen sulphite; in the sugar industry for refining and decolorizing sugar. Sulphur dioxide is used for refining kerosene, and other petroleum products. Sulphur dioxide is a reducing agent and is used for bleaching wool or straw and as a fumigant and food preservative. Large quantities of sulphur dioxide are used in the contact process for the manufacture of sulphuric acid. Sulphur dioxide is used as a disinfectant (IARC, 1992).

1.1 Exposure

Indoor air concentrations of SO_2 are generally lower than outdoor air concentrations, because absorption occures on walls, furniture,clothes and in ventilation systems (WHO, 1987).

Even though sulphur dioxide is widely used for a large number of industrial applications, there only have been few studies published on occupational exposure levels. Most of these studies are of limited use, because they are deficient in terms of current scientific criteria. In the pulp making and paper industry, mean concentrations of sulphur dioxide ranged from below detection level up to 68.1 mg/m^3, covering the period of 1954 to 1963. The variation is, for instance, explained by variations in the sampling time (mainly short-term measurements) and the type of operation. Short-term peak values of up to 266 mg/m^3 were measured in four Norwegian pulp making and paper plants (Skalpe,1964).
Covering the period of 1940-1986, mean levels of sulphur dioxide were lower than 2.6 mg/m3 in nickel, zinc, aluminium smelters and steel mills, but between 2.6 and 26 mg/m3 in copper smelters. Occasionally higher levels were measured.
Measurements of sulphur dioxide in other types of industry have revealed large variations. Most of these measurement stayed below 10 mg/m3: 7.7 mg/m3 (beverage industry); between less than 3 and 5 mg/m3 (sulphuric acid plants, long-term measurements); and, <2.6 mg/m3 (e.g. close to diesel engines, photographic laboratories, mineral fibre plant). Moreover, in all these industries peak exposure have been observed (Kangas *et* Rikkiydisteet ,1991; FIOH, 1990).

Benke et al. (1998) published a review on the exposure levels to several chemicals within the alumina and primary aluminium industry. In that review, the study by Chan-Yeung *et al.* (1989) was discussed. They reported a mean of 2.0 mg/m3 (n=121, TWA 8 hours) for measurements undertaken in 1980 compared to 2.1 mg/m3 (n=53) for the same smelter in 1986. Kongerud et Ramjør (1991) and Desjardins *et al.* (1994) measured lower levels: 0.42 mg/m3 (breathing zone samples, n=75, Norway) and 1.0 mg/m3 (0.4 ppm, Canada), respectively.

In 1999, Teschke *et al.* (1999) published the results of an international study on the occupational exposure to sulphur dioxide in the non-production departments of pulp paper and paper product mills. The data included exposure measurements of 246 chemical agents taken from the 1950s to the 1990s. For sulphur dioxide the following mean concentrations were measured (TWA > 1 hour): 19.0 mg/m3 (7.1 ppm, maintenance, construction, cleaning, n=40); 19.5 mg/m3 (7.3 ppm, storage, yard, loading, shipping, n=11); 1.9 mg/m3 (0.71 ppm, steam and power generation, n=45); and, 0.013 mg/m3 (0.005 ppm, effluent water treatment, n=39). However, most of the samples were below detection limit (limit not given).

1.2 Monitoring

Samples obtained from passive or active sampling are analysed by spectrophotometry or ion exchange chromatography.

The National Institute for Occupational Safety and Health (NIOSH,1994) recommended ion exchange chromatography method 6004 for determination of ambient levels of sulphur dioxide.This method is specific for sulphur dioxide and applicable for short-term sampling (: 0.5-20 mg/m3 per 100 L air sample).

2. Health Significance:

The main objective and the emphasis of this evaluation are to analyse the possible effects of the inhalatory exposure in the working settings in the concentration range relevant to working population.

2.1. Toxicokinetics

2.1.1. *Human Data*

2.1.2 *Animal Data*

- **Absorption:**

  As summarised by DECOS (2003) sulphur dioxide is a highly soluble in aqueous media. As a result, the substance is rapidly absorbed in the moist upper respiratory tract after inhalation, as was shown in both man and mammals (Speizer 1966, Balchum 1960).

  When rabbits were exposed to a concentration of 2.7 mg/m3, approximately 40% of the sulphur dioxide was absorbed by the nasopharyngeal mucosa. This increased to 95% when the exposure increased from 26.6 to 266 mg/m3 (Stranberg, 1964).

  Sulphur dioxide may reach the lower respiratory tract by oral inhalation and deep breathing, for instance during doing heavy work or exercise (DECOS, 2002).

  Penetration to the alveoli is greater when inhaled through the mouth than through the nose. During inhalation, it reacts with water to form sulphurous acid, which dissociates into sulphite and bisulphite ions. Suphite is converted to sulphate by action of suphite oxidase and individuals deficient in this enzyme constitute a higher risk group (Calbrese et al., 1981).

  In the moist mucous membranes, sulphur dioxide is rapidly hydrated to sulphurous acid(H2SO3).This sulphurous acid dissociates easily into sulphite (SO3-) and bisulphite (HSO3-) ions. Sulphite ions are then rapidly converted into sulphate, whereas bisulphite ions bind to to plasma and cellular proteins to form S-sulphonates (IARC, 1992).

- **Distribution:**

  In all species studied, the sulphur dioxide that is absorbed passes through the blood and lymph to all body tissues. When beagle dogs inhaled radio-labelled sulphur dioxide $^{35}SO_2$ after tracheotomy, most of the substance did concentrate in the trachea, bronchi, lungs and lymph nodes of the hilus, and in decreasing amounts in the kidneys, oesophagus, ovaries, stomach and other tissues. Only minimal amounts of ^{35}S were found in the liver, spleen and cardiac muscles (Balchum *et al.*, 1960).

  In the blood, a main part of sulphur dioxide is bound to serum proteins as S-sulphonates (Gunnison *et al.* Benton,1971 ; Menzel *et al*,1986). Free sulphur dioxide is transported almost totally as bisulphite.

- **Biotransformation :**

  Part of the inhaled sulphur dioxide is exhaled before the body absorbs it. Another part is eliminated by conversion into sulphurous acid on contact with moist upper respiratory tract (Balchum *et al.* ,1969; Frank *et al.*,1969). Bisulphite ions react (sulphonation or auto-oxidation) with biomolecules, such as cysteine containing proteins and DNA, to form S-

sulphonates. Formation of sulphonates prolongs the presence of sulphur dioxide in the body (Yokohama et al.,1971). Sulphite ions are rapidly metabolised to sulphate by sulphite oxidase, an enzyme with low activity in lung tissue. Sulphate, which is also an endogenous metabolite in mammals, is incorporated in the large sulphate pool of the body (IARC ,1992).

As summarised by Brauer *et al.* (2002) the ready solubility of sulphur dioxide in water forms the basis for its physiological and toxicological effects. Gasous SO_2 disolves in fluids found in the upper respiratory tract to form bisulfite, sulfite, and hydrogen ions that are quickly absorbed by the blood and distributed throughout the body. The efficiency of this processis affected by concentration of inhaled SO_2, where high concentration ($\geq$100 ppm) result in absorption of $\leq$ 90% of the pollutant , and low concentration ($\leq$ 2 ppm) result in 5 - 40% absorption. Inspiratory rate and route of inhalation further affect efficiency such that exercising individuals engaged in oronasal breathing absorb more SO_2 ($\geq$80%) than those at rest.

Once absorbed, sulfite ions in the blood can be oxidized to sulphates and excreated in the urine, or they can react with proteins to form S- sulphonate, which has been found at the elevated levels in the plasma and aorta of SO_2 exposed experimental animals.The biochemical significance of these findings is not yet understood, but they provide evidence for the possibility of toxicological effects in non-pulmonary target organs.

Once absorbed, bisulfite ions in the blood might be reponsible for inducing the bronchoconstriction generally associated with sulphur dioxide exposure. By disrupting the disulfide bonds present in tissue proreins, bisulfite may lead to the alteration of neurotransmitter receptors and the subsequent contraction of smooth muscle tissue in the lungs.

- **Elimination :**

  Circulating S-sulphonates slowly decompose into sulphur dioxide or sulphates. The sulphur dioxide is exhaled, whereas sulphates become part of the endogenous sulphate pool. These sulphates are slowly released via the blood into the urine (Calabrese *et al.*, l981).

2.1.3 *Biomonitoring*

No method has been published that allow for determination of biochemical or functional parameters useful for biological monitoring of occupational exposure Also S-sulphonate cannot be used for biological monitoring, because it is not a specific parameter for sulphur dioxide exposure.

2.2 Acute toxicity

2.2.1 *Human data*

Several reviews of the toxicology of sulphur dioxide have been published within the last decades.These reviews have generally been written with the aim of identifying appropriate levels for environmental ambient air quality standards and not for working air quality standards. . The

focus, therefore tends to be on the identification of dose- reponse relationshipfor effects in particular subgroups such as children, astmatics, those with chronic obstructive lung disease etc.. In general, the information gathered relates to the effect of peak pollution episodes rather than the long term consequences of exposure to SO_2. The usefulness of these reviews for the purpose of the OELs setting is limited because it provides only a brief overview of occupational studies.

Healthy adults

There are numerous studies since 1953 till recent years with healthy, non-smoking volunteers exposed to SO_2. under controlled condition to concentrations of as low as 0.53 mg/ m^3 to more than 60mg// m^3 SO_2. The exposures lasted from minutes up to several hours and were carried out with or without physical exercise. The main adverse effects observed were irritation of the upper respiratory tract and eyes, and decreased lung function, such as increased pulmonary airways resistance (DECOS, 2003).,
At very high concentrations (SCOEL, 1993), the absorption capacity of the upper respiratory airways may be exceeded, resulting in pathological changes that include; laryngotracheal and pulmonary oedema; and, symptoms may result in death.
Concerning the mechanism of bronchoconstriction, it is thought that sulphur dioxide stimulates irritant receptors, present in the epithelium of the upper airways (Costa *et* Schelegle, 1999). Stimulation of these receptors activates the nerve endings of involuntary muscles in the bronchi, resulting in bronchoconstriction. Atropine, an anticholinergic agent, can completely deactivate these nerve endings, resulting in relaxation of the involuntary muscles. When given to normal adults, who were exposed to sulphur dioxide, the bronchoconstriction was completely prevented (Nadel *et al*., 1965). However, when given to exposed asthmatics, atropine was only partly effective (Korpas *et* Timori , 1979).
The low concentrations of sulphur dioxide required to produce bronchoconstriction in sensitive asthmatics are likely too low to generate hydrogen ions in sufficient quantities to explain the airway effects of sulphur dioxide (Fine et al., 1987).
Ammonia can be present in high concentrations in the oral cavity and could play a role in neutralizing acidic ions. It is not clear whether the bronchoconstriction that occurs following oral ingestion of sulfite- containing liquids and foods in some asthmatics is mechanistically linked to sulphur dioxide induced bronchoconstriction (Frampton *et* Utell, 2007).
The difference in reaction between normal and asthmatic people is still not fully clarified. In general population, a clear positive association has been reported between those pathologies and day to day changes in hospitalisation rates and deaths (Anderson *et al*., 1997).

The critical effect of sulphur dioxide evaluated by SCOEL (1998) is irritation of the upper respiratory tract. In most epidemiological studies, the workers were exposed to complex mixtures of sulphur dioxide with particulate matters, other acid gases, metallic fumes or organic compounds. Workers exposed to approximately 4 ppm (11 mg/m^3) sulphur dioxide experienced tightness in the chest and reduced forced expiratory volume (FEV) (Archer *et al*, 1979).
Bedi *et al* (1984) reported that exposure of young volunteers to concentrations of 1 - 2 ppm (2.7 - 5.3 mg/m^3) for 2 hours resulted in a reduction in thoracic volume in non-smoking subjects.
Controlled exposure of healthy adults to 1 ppm (2.7 mg/m^3) sulphur dioxide with 1 mg/m^3 NaCl caused respiratory changes only in a group subjected to moderate exercise (Frank, 1980).
Exposure of 231 healthy subjects to 0.75 ppm (2 mg/m^3) sulphur dioxide, with and without

exercise, did not affect pulmonary function (Stacy *et al*, 1983).

However, electron microscopic examination of the nasal mucosa of 7 individuals exposed to 0.7 ppm (1.9 mg/m^3) sulphur dioxide for 2 hours revealed ciliary defects (Carson *et al.*, 1987).

Lawther *et al.* (1975) found that deep breathing of 1-ppm SO_2 by mouth resulted in an increase in specific airways resistance (sRaw) compared to breathing air alone.

Stacy *et al.* (1981) exposed 16 healthy males to 0.75-ppm SO_2 for 2 h with a 15-min period of exercise at the end of the first hour of exposure (ventilation ~ 60 L/min). A separate group of 15 healthy males were exposed to clean air for 2 h and served as the control for this study. In the SO_2-exposed group, airways resistance (Raw) decreased by 2 to 55% compared to baseline after the 15 min of exercise, but then returned to the baseline value by the end of the 2-h exposure. However, in the control group, Raw decreased throughout the 2-h exposure, resulting in statistically significant differences between the two groups in the change in Raw occurring between both baseline and post-exercise and between baseline and postexposure.

Islam *et al.*(1992) examined acute bronchoconstricting effects in twenty-suix young, non-smoking volunteers (17males/ 9females) exposed to 0.6-0.8 ppm SO_2. Specific airway resistance measurements were taken before, immediately,10 and 20 minutes after each eucapnic hyperventilation. Following hyperventilation with or without SO_2. all subjects showed variable degrees of bronchoconstriction. However, the authors found a strong increase of specific airway resistance with sulphur dioxide than without ($p<0.01$); the mean increase in specific airwy resistance was significntly higher in these responders 13 out 26 subjects) than in the non/ responders ($p<0.01$). All values tended to return to normal 20 minutes after the last exposure.

Kulle *et al.*(1984) exposed twenty young, non/smoking subjects (10 males /10 females) four hours to 1 ppm SO_2 in environmental chamber. The subjects performed light / to moderate exercise stints. No significant changes in pulmonary function or bronchial reactivity were observed in the individual exposure or 24 hours post exposure.

Similar results observed Schachter *et al.*(1984) in healthy subjects (4 males/6 females) exposed to 0, 0.25, 0.5,0.75 and 1 ppm. Subjects were exposed for 40 minutes in an environmental chamber. During the first 10 minutes of exposure , subjects perfermed exercise on a czcloergometer at level of 450 kpm/min on separate days , subjects were exposed to 0 and 1 ppm SO_2 in absence of exercise. No changes in pulmonary function were seen in healthz individuals on any day. The authors concluded that healthz individuals subjected to inhalation of up to 1 ppm demonstrated no significant pulmonary decrement at rest or during moderate exercise.

Case reports

In most epidemiological studies focused on workers, the workers were exposed to complex mixtures of sulphur dioxide with particulate matters and other acid gases.As it was evaluated by DECOS (2002) in none of the case studies reported below, the authors mentioned the levels to which the workers were accidentally exposed, although they surmised that these were high. Overall, acute poisoning from inhalation of very high concentrations of sulphur dioxide is characterised by intense irritation of the conjunctiva and upper respiratory tract mucosa with dyspnoea and cyanosis, followed rapidly by loss of consciousness. This may lead to death (Stellman *et* Mc Cann, 1998)

One 25-year-old previously healthy carpenter was exposed to sulphur dioxide at high concentrations for 15 to 20 minutes. An immediate episode of pulmonary oedema was followed by a silent interval with subsequent development of a severe, irreversible obstructive syndrome (Woodford et al., 1979).

Two maintenance workers were accidentally exposed to concentrated sulphur dioxide steam. Both subjects died of respiratory arrest within 5 minutes. Two other workers, who were near the exposure area, developed symptomatic severe airway obstruction and, asymptomatic mild obstructive and restrictive disease, respectively. A fifth subject continued to be asymptomatic with normal pulmonary function tests. The pulmonary function tests were performed on day 1, 50, 69 and 116 after the exposure (Chan-Yeung *et al*., 1979).

In 1983, a case report was published, in which lung function was followed for 4 years in seven Finnish men, who were exposed to sulphur dioxide in a pyrites dust explosion. The authors suggested that the bronchial hyperreactivity, such as observed in these men, may be a frequent sequel after exposure to high concentrations of sulphur dioxide and, that hyperreactivity may persist for several years (Harkonen *et al*., 1983).

In another case report, two non-smoking Canadian miners were followed over a two-year period, after being exposed to high concentrations of sulphur dioxide after a mine explosion (Rabinovitch, *et al.* 1989). The authors observed that: acute exposure to high levels of sulphur dioxide resulted in severe airway obstruction; these abnormalities are partially reversible; and, that most of the improvement occurred within 12 months after initial injury. These four case reports have been described briefly by Testud *et al.* (2000). In the same review, they reported also six cases of sulphur dioxide-induced respiratory symptoms. These cases were identified during a survey of wine cellars in the French Beaujolais district.

Asthmatic Individuals

Asthmatic subjects are a high risk group with respect to sulphur dioxide. Effects are exacerbated by increasing levels of exercise (SCOEL, 1998).

Bethel *et al.* (1985) reported that exposure of asthmatics to 0.25 ppm (0.67 mg/m^3) sulphur dioxide during heavy exercise resulted in mild bronchoconstriction, but that the effect was largely overshadowed by the effects of exercise alone.

Hackney *et al.* (1984) exposed 17 young asthmatic volunteers to 0.75 ppm (2.0 mg/m^3) for 3 hours with 10 minutes of heavy exercise initially, followed by rest. In general, it appeared that the bronchoconstriction induced by exercise during exposure was reversed immediately by rest, even though the sulphur dioxide was still present.

Development of tolerance has been observed in asthmatic subjects exposed repeatedly to the bronchoconstriction effects of 0.5 ppm (1.3 mg/m^3) sulphur dioxide for short periods (Sheppard *et al.*, 1983).

Exposure of 24 young adult asthmatics to 0, 0.25 and 0.5 ppm (0, 0.67 and 1.3 mg/m^3) sulphur dioxide for one hour with alternating 10 minute periods of moderate exercise and rest, at exposure intervals of one week, did not induce significant exposure related changes in pulmonary function (Linn *et al*., 1982).

Devalia *et al.* (1994) studied the effect of 6 hours exposure to 0.2 ppm (0.53 mg/m^3) sulphur dioxide on the airway response to inhaled house-dust-mite antigen in 10 volunteers with mild atopic asthma. No significant effects were observed in the lung function indices examined.

Overall, these studies indicate that asthmatics are unlikely to experience adverse effects at sulphur dioxide levels up to 0.75 ppm (2.0 mg/m^3) under normal working conditions.

Some of the studies on exposure to SO_2 in combination with execise involving asthmatic subjects have used change in airways resistance(sRaw) as the endpoint of interest while others have measured changes in FEV1 or both:

Linn *et al.* (1987) reported that following 1-h exposures to 0-, 0.2-, 0.4-, and 0.6-ppm SO2, the severity of respiratory symptoms (i.e., cough, chest tightness, throat irritation) increased relative air

exposures only in moderate/severe asthmatics who were exposed at the highest exposure concentration (0.6 ppm SO_2). It was also observed that these symptoms abated within <1 h after exposure.

Balmes *et al.* (1987) reported that 7/8 asthmatic adults developed respiratory symptoms including wheezing and chest tightness following 3-min exposures to 0.5-ppm SO_2 during eucapnic hyperpnea (minute ventilation = 60 L/min).

Gong *et al.* (1995) reported in a study with SO_2-sensitive asthmatics that respiratory symptoms (i.e., shortness of breath, wheeze, and chest tightness) increased with increasing SO_2 concentration (0-, 0.5-, and 1.0-ppm SO_2) following exposures of 10 min with varying levels of exercise. It was also observed that exposure to 0.5-ppm SO_2 during light exercise evoked a more severe symptomatic response than heavy exercise in clean air.

Tunnicliffe *et al.* (2003) found no association between respiratory symptoms (i.e., throat irritation, cough, wheeze) and 1-h exposures at rest to 0.2-ppm SO_2 in either asthmatics or healthy adults.

It has been demonstrated that asthmatic individuals exposed to <1-ppm SO_2 while performing moderate to heavy exercise for 5 min suffer significant bronchoconstriction or increases in sRaw (Bethel *et al.*, 1983; Linn et al., 1983, 1984).

Gong *et al.* (1995) was able to show an exposure-response relationship between SO_2 and respiratory effects by exposing 14 unmedicated, SO_2-sensitive asthmatics to 0-, 0.5-, and 1-ppm SO_2 under 3 different levels of exercise. It was shown that increasing SO_2 concentration had a greater effect on sRaw and FEV1 than increasing exercise level.

Tunnicliffe et al. (2003) evaluated the effects of a lower exposure concentration of SO_2 in resting healthy and asthmatic subjects. No significant changes in lung function as measured by FEV1, FVC, and maximal midexpiratory flow (MMEF) were observed following 1-h exposure to 0.2-ppm SO_2. The authors reported a small but statistically significant increase in respiratory rate in the asthmatic group after SO_2 exposure compared to placebo (958.9 breaths/h with SO_2 compared to 906.8 breaths/h with air). However, this effect was counterbalanced by a reduction in tidal volume, resulting in no net change in volume breathed during exposure.

One of the aims of the Linn *et al.* study (1987) study was to determine how the intensity of response varied with asthma severity or status. In this study, 24 normal, 21 atopic (but not asthmatic), 16 mild asthmatic, and 24 moderate/severe asthmatic subjects were exposed to 0-, 0.2-, 0.4-, and 0.6-ppm SO_2. The exposure protocol consisted of 1-h exposures that included three 10-min exercise periods (ventilation ~ 40 L/min). Physiological responses were measured at approximately 15- and 55-min of exposure. Pooling data from both the mild and moderate/severe asthmatic groups (n = 40) and using only measurements made at 15 min into the exposure, the group mean sRaw was doubled with 0.6-ppm SO_2 exposure.

In the project report (Hackney *et al.*, 1987) upon which the Linn et al. (1987) article was based, individual data were presented that showed that 15/40 moderate/severe asthma subjects (37.5%) had a doubling of the sRaw at concentrations of <0.6-ppm SO_2.

Linn *et al.* (1987) demonstrated that moderate and severe asthmatics had the most severe physiological and symptom responses. While the moderate/severe asthmatics were more responsive than mild asthmatics following exposure to clean air during exercise, their increases in response with increasing SO_2 concentrations were similar to the mild asthmatic group. Thus, it was concluded that SO_2 response was not strongly dependent on the clinical severity of asthma. The apparent lack of correlation between SO_2 response and asthma severity should be interpreted with caution, since the SO_2 response may have been attenuated by medication usage or its persistence.

Three of the moderate/severe asthmatics were unable to withhold medication usage during the exposure period. It was also suggested that individual SO_2 response could not be predicted by severity of asthma or asthma status, since a few of the atopic individuals who were not asthmatic nor had exercise-induced bronchoconstriction were reactive to SO_2. On the other extreme, a few of the asthmatics, including some in the moderate/severe group, did not react to 0.6-ppm SO_2. Nevertheless, the largest sRaw increases and most substantial decrements in FEV1 occurred in the moderate/severe asthmatic group

Horstman *et al.* (1986) exposed 27 asthmatic subjects for 10 min on different days to concentrations of SO_2 between 0- and 2-ppm SO_2 under exercising conditions (ventilation = 42 L/min). These authors reported that for 25% of the subjects, the concentration of SO_2 needed to produce a doubling of the specific airway resistance (SRaw) [designated as ($PC(SO_2)$)] was <0.5 ppm, and for about 20% of the subjects the $PC(SO_2)$ was >1.95 ppm, with a median $PC(SO_2)$ of 0.75 ppm. Though Hackney *et al.* (1987) demonstrated the distribution of bronchial sensitivity of asthmatics to SO_2, the authors cautioned against expressing SO_2 response in terms of $PC(SO_2)$.
Hackney *et al.* (1987) noted several limitations to using PC (SO_2) analysis for risk assessment purposes. First, the choice of a 100% increase in sRaw is arbitrary and may not necessarily have any health significance. For example, as noted by the authors, an increase in sRaw from 2 to 4 would meet the 100% criterion but may not be of clinical significance. However, an increase from 12 to 22, while not meeting the criterion, would be of clinical significance. Second, there may be loss of information from the rest of the exposure-response curve other than the chosen point. For example, two subjects may have similar values of PC (SO_2) but substantially different overall risk because of differences in threshold levels and slopes. Finally, PC (SO_2) based on the Hackney et al. (1987) study was not necessarily a stable and reproducible measurement. In some cases, the sRaw change exceeded 100% at low concentrations but not at high concentrations.
Two key studies have shown that a bronchoconstrictive response to SO_2 can occur in as little as 2 min in asthmatic subjects.
Horstman *et al.* (1988) exposed 12 SO_2-sensitive asthmatic subjects to 1.0-ppm SO_2 with exercise (ventilation = 40 L/min). Correcting for exercise-induced responses, sRaw was shown to increase by 121% after a 2-min exposure and by 307% after a 5-min exposure.

Balmes *et al.* (1987) exposed 8 asthmatic subjects to 0.5- and 1.0-ppm SO_2 during eucapnic hyperpnea (60 L/min) by mouthpiece on separate days for 1-, 3- and 5-min durations. The magnitude of bronchoconstriction increased progressively over the three time periods. At 0.5-ppm SO_2, sRaw increased by 34, 173, and 234% compared to baseline at 1, 3, and 5 min of exposure, respectively. For the 1.0-ppm SO_2 exposure, sRaw increased by 93, 395, and 580% compared to baseline at 1, 3, and 5 min of exposure, respectively.

The interaction of SO_2 with other common air pollutants or the sequential exposure of SO_2 after prior exposure to another pollutant can modify the SO_2-induced respiratory effects. However, only a few studies have looked at the interactive effects of coexisting ambient air pollutants :
Koenig et al. (1990) examined the effect of 15-min exposures to 0.1-ppm SO_2 in adolescent asthmatics engaged in moderate levels of exercise. Immediately preceding this exposure, subjects were exposed for 45 min to 0.12-ppm O3 during intermittent moderate exercise. In this study, subjects also underwent two additional exposure sequences with the same exercise regimen: 15-min exposure to 0.1-ppm SO_2 following a 45-min exposure to clean air, and 15-min exposure to 0.12-ppm O_3 following a 45-min exposure to 0.12-ppm O_3. The authors found that the change in FEV1 compared to baseline was significantly different following the O_3-SO_2 exposure (8%

decrease) when compared to the change following the air-SO_2 or O_3- O_3 exposures (decreases of 3 and 2%, respectively).
Jörres and Magnussen (1990) and Rubinstein et al. (1990) investigated the effects of a prior NO_2 exposure on SO_2-induced bronchoconstriction in asthmatic adults. While Jörres and Magnussen (1990) suggested that prior exposure to NO_2 increased the responsiveness to SO_2, Rubinstein et al. (1990) did not find that NO_2 exacerbated the effects of SO_2.

Individuals with Chronic Obstructive Pulmonary Disease (COPD)

Linn et al. (1985) examined the respiratory effects of SO_2 exposure on subjects with COPD. In this controlled laboratory study, 24 subjects with COPD were exposed for 1 h to 0-, 0.4-, and 0.8-ppm SO_2 with two 15-min periods of light exercise (ventilation = 18 L/min). In contrast to studies with asthmatics, most of the subjects in this study regularly used bronchodilatators and were permitted their use up to 4 h prior to the study. The authors reported no SO_2 effects on sRaw, spirometric measures, or arterial oxygen saturation. While it was concluded that older adults with COPD seem less reactive to SO_2 compared to heavily exercising young adult asthmatics, it was thought that this may be due to differences in medication usage as well as to the lower ventilation rate observed in subjects with COPD, which would itself result in a reduction in the pulmonary uptake of SO_2.

Summary of Human Studies on Lung Function in Adults :
In all reviews on SO_2 health effects it was established that subjects with asthma are more sensitive to the effects of SO_2 exposure than healthy individuals without asthma.
The evidence from the reviewed studies indicates increased respiratory symptoms with peak (5-15 min) SO_2 exposures above 0.5 ppm in asthmatic subjects.
Results from human clinical studies have consistently demonstrated decreases in lung function (e.g., decreased forced expiratory volume in 1 s [FEV1] and increased specific airways resistance [sRaw]) following peak exposures (5 to 15 min) to SO_2. These effects have clearly and consistently been shown among individuals with asthma, with asthmatics exhibiting significant decrements in lung function following 5- to 15-min exposures to SO_2 concentrations of as low as 0.5 ppm while performing moderate levels of exercise (e.g., Gong et al., 1995; Horstman et al., 1986; Linn et al., 1987; Sheppard et al., 1981).
The effect of peak SO_2 exposure on lung function has been shown to increase in magnitude with increasing SO_2 concentrations above 0.5 ppm. Studies have further observed significant decrements in lung function in some sensitive asthmatics following 5-15 min exposures to SO_2 concentrations of as low as 0.25 ppm while performing moderate levels of exercise (Horstman et al., 1986; Sheppard et al., 1981). Thus, the observations of increased bronchoconstriction and airway resistance in human clinical studies provide clear evidence for SO_2 effects with peak exposure.3

Airway Inflammation

Sandström *et al.* (1989) in a controlled-exposure, time-response study exposed 22 healthy male subjects for 20 min to 8-ppm SO_2 under light exercising conditions. Bronchoalveolar lavage was performed in all subjects at least 2 weeks prior to exposure, as well as at 4, 8, 24, and 72 h after exposure in 8/22 subjects. The authors found that as early as 4 h after exposure to SO_2, lysozyme-positive macrophages, lymphocytes, and mast cells were significantly increased compared to baseline. Twenty-four hours after exposure, these markers of inflammation, as well as the total alveolar macrophages (AM) and total cell number, were at peak levels. This study demonstrated

that SO_2-induced inflammation may extend beyond the short time period often associated with SO_2 effects.

Studies at levels of exposure relevant for ambient air pollution:
Tunnicliffe et al. (2003) measured levels of exhaled nitric oxide (eNO) in asthmatic and healthy adult subjects before and after 1-h exposure to 0.2-ppm SO_2 under resting conditions. While eNO concentrations were higher in the asthmatic versus healthy subjects, no significant difference was observed between pre- and postexposure in either group.
Adamkiewicz et al. (2004) examined exhaled nitric oxide (eNO) as a biological marker for inflammation in 29 older adults (median age 70.7 years). The mean 24-h average SO_2 concentration was 12.5 ppb (IQR 11.5). The authors reported that, while significant and robust associations were observed between increased daily levels of fine PM (PM2.5) and increased eNO, no associations were observed with any of the other pollutants examined, including SO_2, NO_2, and O3.

2.2.2. *Animal data on acute toxicity*

Animal toxicological studies

In the reviews on SO_2 it was reported bronchoconstriction (as indicated by increased pulmonary resistance) as the most sensitive indicator of lung function effects of acute SO_2 exposure based on the observations of increased pulmonary resistance in guinea pigs that were acutely exposed to 0.16-ppm SO_2. Some of the new animal toxicological studies are consistent with these observations:
increases in pulmonary resistance and decreased dynamic compliance were the most frequently observed effects in conscious guinea pigs exposed to 1-ppm SO_2 for 1 hour (Amdur *et al.*(1983) .
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Studies to understand the potential role of neuronal component in SO_2-induced pulmonary resistance used the anesthetics ketamine in guinea pigs exposed to 1-ppm SO_2 for 3 h/day for 6 days (Conner *et al.*, 1985), carbamate in rabbits exposed to 5-ppm SO_2 for 45 min (Barthélemy *et al.*, 1988), or surgical manipulation (bivagotomy).
These studies indicated that pulmonary resistance was increased in ethyl carbamate-anesthetized rabbits exposed to SO_2 but not in ketamine-anesthetized guinea pigs. Further, observations of the elimination of reflex bronchoconstrictor response by phenyldiguanide in rabbits exposed to 5-ppm SO_2, but not the lung resistance induced by histamine, suggested that SO_2-induced bronchoconstriction in rabbits is not mediated through the vagus nerve. Though these results provided some understanding on the mechanisms involved in the development of SO_2-induced bronchoconstriction, these studies were carried out using only one SO_2 exposure dose and precluded assessment of concentration-response relationships and identification of a no-effect level.
In summary, animal studies have shown that guinea pigs exposed to 0.16- to 1-ppm and rabbits exposed to 5-ppm SO_2 have increased pulmonary resistance that is not mediated through the vagus nerve.

Animal studies on inflammation:

Two recent studies that examined inflammatory responses in animals exposed to SO_2 report characteristic responses such as leukocyte influx and changes in enzyme levels or activities in the lung at high SO_2 concentrations.
Meng et al. (2005) observed elevated levels of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-. in lung tissue of mice exposed to SO_2 concentrations of 5.35 and 10.7 ppm. The levels of anti-inflammatory cytokine transforming growth factor were not affected at any exposure level.
Langley-Evans *et al*., (1996) in rats exposed to 5, 50, or 100 ppm of SO_2 for 5 h/day for 28 days, observed increased leukocyte numbers in bronchoalveolar lavage fluid at 100 ppm, but no such infiltration of leukocytes was observed in rats exposed to 5 or 50 ppm
In acute duration inhalation study with hamsters ($\leq$ 12/ group), there was a significant reduction in endocytosis by pulmonary macrophage (process used in defending lung against pathogens and foreign bodies) following to 50 ppm sulphur dioxide for 4 hours while exercising (Skornik *et* Brain, 1990).
Data from experiments in animals with acute or short-term exposure support the findings in humans, that sulphur dioxide irritates the (upper) respiratory tract and eyes and reduces respiratory defence mechanisms against bacterial infections. In addition, changes in enzyme activities in liver and blood were observed. However, the quality of the reporting of most of these studies was insufficient. Apart from that, most animals were exposed to very high levels (up to 267 mg/m^3 (subchronic) or >1,000 mg/m^3 (acute) (DECOS,2002)

In summary it could be concluded, that limited epidemiological, human clinical, and toxicological evidence does not indicate that exposure to low SO_2 concentration is associated with inflammation in the airways. The tests available have used high levels of exposure to SO_2.

2.2. 3. *Cardiovascular Effects*
Several recent epidemiological studies also have examined the association between air pollution and cardiovascular effects, including increased heart rate (HR), reduced heart rate variability (HRV), incidence of ventricular arrhythmias, changes in blood pressure, incidence of myocardial infarctions (MI), and ED visits and hospitalizations due to cardiovascular causes.

Heart Rate and Heart rate Variability

Brook et al. (2004) note that decreased HRV predicts an increased risk of cardiovascular morbidity and mortality in older adults and those with significant heart disease.
HRV is generally determined by analyses of time (e.g., standard deviation of normal R-R intervals and frequency domains (e.g., low frequency [LF] / high frequency [HF] ratio by power spectral analysis, reflecting autonomic balance) measured during 24 h of electrocardiography (ECG).
Sandström *et al.* (1988) exposed eight healthy, non-smoking individuals to clean filtered air or to 1, 5 and 10 mg/m^3 (0.4, 2 and 4 ppm) sulphur dioxide for 20 minutes. During the exposure the individuals exercised on a bicycle ergometer for 15 minutes. No differences in heart rate were observed at the different exposure, nor were there any significant changes in lung function. A few individuals complained about mild eye symptoms, mild breathlessness and cough. These complaints were not related to the exposed concentration. However, a concentration-related increase in nasal and throat irritation was observed.

Tunnicliffe *et al.*(2001) expose in a double-blind study, twelve normal and twelve mildly asthmatic adults, all nonsmokers to clean air or to a single dose of 0.53 mg/m^3 (200 ppb) sulphur dioxide for 1 hour during rest. No significant changes in lung function (e.g. FEV_1) or in maximum or minimum heart rates were found in any of the exposed subjects. However, spectral analysis of heart rate variability with sulphur dioxide exposure in normal subjects showed: higher values for total power (TP); high frequency power (HF); and, low frequency power (LF) compared to air ($p<0.05$ for TP) in normal subjects. In asthmatics, all three indices were lower, although not statistically significant. The authors also suggest that sulphur dioxide exposure can influence the autonomic nervous system, which may be important in understanding the mechanism involved in sulphur dioxide induced bronchoconstriction and of the cardiovascular effects of air pollution.

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In summary, it could be concluded that overall evidence that SO_2 affects cardiac autonomic control is weak and inconsistent.

Arrhytmia.

One toxicological study examined the effects of PM, ultrafine carbon, and SO_2 on spontaneous arrhythmia frequency in 18-month-old rats (Nadziejko et al., 2004). The rats were exposed to 1-ppm SO_2 for 4 h. No significant change in the frequency of spontaneous arrhythmias was found with SO_2 and ultrafine carbon exposure. However, rats exposed to concentrated ambient PM had a significantly greater increase in the frequency of delayed beats than rats exposed to air.

In summary, the limited toxicological evidence did not provide biological plausiblity of an effect of SO_2 on arrhythmias.

2. 3. Irritation and corosivity

The critical effect of sulphur dioxide evaluated by SCOEL (1998) is irritation of the upper respiratory tract. Irritative effectss observed in humans and in animals are included in the chapter 2.2.1. and 2.2.2.

Eyes

Liquid sulphur dioxide may cause frostbite or severe corneal damage by direct contact on the skin and eyes, respectively (von Burg, 1995).

2.4. Sensitisation

2.4.1. *Human data*

No human data has been presented, suggesting that sulphur dioxide may be a sensitising agent through immunologic mechanisms. However, in the literature, it has been suggested that air pollutants, such as sulphur dioxide, promote airway sensitisation by modulating the allergenicity of airborne allergens. In addition, it has been suggested that the sulphur dioxide-induced mucosal airway damage and impaired mucociliary clearance may facilitate the penetration and access of inhaled allergens to the cells of the immune system (D Amato,2002).

In a study of 10 mild asthmatics , prior inhalation of 0.2 ppm sulphur dioxide for 6 hours did not significantly affect the provocation dose of Dermatophagoides pteronyssinus allergen required to produce a 20% decrease in FVC1 (Devalia et al., 1996).

Increased prevalence of allergies was observed in 556 children (7-13 years) living near an aluminium smelter in Norway for seven years or more. The exposure to sulphur dioxide was on 0.008-0.009 ppm. However, there was no control for possible confounders such as fluoride or other air pollutants (Soyseth et al.,1996).

2.4.2. *Animal data on sensitisation*

A limited number of animal studies suggest acute SO_2-induced increases in airway obstruction and hypersensitivity in allergen-sensitized guinea pigs and sheep.
Increase sensitization to antigen was reported in a study of six guinea pigs exposed by inhalation to 5 ppm SO_2 for 8 hours/ day for 5 days, with intermittent inhalation of ovalbubin (Riedel et al., 1992).
Bronchial responses (pulmonary resistance or reduced dynamic compliance to agonists (i.e., histamine, methacholine (MCh), 5-hydroxytryptamine) are examined after exposure to evaluate toxic effects of pulmonary toxicants.
Exposure of rabbits to 5-ppm SO_2 for 2 h had no effect on airway responsiveness to histamine (Douglas *et al*., 1994).
Even at higher concentrations of 10-ppm SO_2 for 5 min, hyperresponsiveness and hyperreactivity effects to aerosolized MCh or 5-hydroxytryptamine were not observed in dogs (Lewis and Kirchner, 1984), but positive responses were observed at the higher concentration of 30 ppm.

The effect of SO_2 on antigen-induced sensitivity reactions was assessed in sheep. A 4-h exposure to 5-ppm SO_2 increased airway reactivity in response to carbachol in sheep that had been sensitized to Ascaris suum antigen 24-h postexposure, but increased sensitivity was not observed in nonsensitized sheep (Abraham *et al*., 1981).

Summary:
Limited epidemiological evidence suggests that exposure to SO_2 may lead to airways hyperresponsivness (AHR) in atopic individuals. Toxicological studies that observed increased airway obstruction and hypersensitivity in allergen-sensitized animals provide biological plausibility. The epidemiological evidence further indicates that atopic individuals may be at increased risk for SO_2-induced respiratory symptoms.

2.5.REPEATED DOSE TOXICITY

2..5.1. *Human data*

Epidemiological studies have associated chronic sulphur dioxide exposure with chronic coughing; bronchitis; increased susceptibility to airway infections; and, increased susceptibility to allergy by airborne allergens. However, because these studies included several confounding factors, they are considered insufficient for quantitative risk assessment.

Kehoe *et al.*(1932) conducted a study of workers exposed to sulphur dioxide in a refrigerant manufacturing plant. Prior to 1927 concentrations of SO_2 averaged between 80-100ppm. After the installation of the ventilation system, sulphur dioxide levels typically ranged between 5-35 ppm with occasional peaks as high as 50-75 ppm.The incidence of respiratory irritation and shortness of breath during heavy activity were significantly increased in 100 exposed workers.Chest X- rays revealed no differences between exposed and unexposed workers at the same plant.

A significant decrease in forced expiratory volume in 1 second (FEV1) was observed in 113 workers exposed to ≥1ppm sulphur dioxide for an unspecified time in copper smelter in Salt Lake City
(Smith *et.al.*,1977). Smoking status was assessed in the study. However,workers were also exposed to repirable dust.
A study conducted years later at the same copper smelter found no significant relationship between pulmonary function and exposure to ≥5 ppm sulphur dioxide in 430 workers (Lebowitz et al.,1979). Exposure duration ranged from 0 to >20 years and confounding factors such as age, smoking, and exposure to dust were corrected. The authors suggested that the previous findings of Smith et.al.(1977) may have resulted from limitations of the study,such as small sample size and inadequate correction for age.

In another study of 953 cooper smelters workers in Utah, a significantreduction in FVC and FEV1 was associated with long-term (>20 years) exposure to 0.4-3.0 ppm with increasing duration of exposure in both smokers and non-smokers but was not observed in controls. However,workers were also exposed to arsenic,copper, manganese, iron, and other metals. (Archer and Gillan,1978).
Workers(4,506 and 5,943) exposed to mean concentrations of approximately 0.84 – 1.2 ppm sulphur dioxide for an uspecified time period at two British steel plants did not experience an increase in repiratory symptoms or reductionin respiratoty performance (Lowe *et.al.*,1970). Confounding factors suc as smoking and occupational exposure to dust were controlled.

In a study of 56 workers exposed to 2-36 ppm sulphur dioxide in pulp mills for 1 month to 40 years,cough was reported by 56 % of workers, sputum production by 46% , and difficulty breathing by 22%. (Skalpe,1964). Symptoms were reported in higher percentages by workers ≤ 50 years –old.
Maximal expiratory flow rate was significantly reduce in workers ≤ 50 yers old. The author speculated the most likely reason for increased effects in the younger workers was that minor respiratory effects are more likely detected due to decreased prevalence of repiratory symptoms at a younger age. Occupational exposure to other chemicals was not reported but smoking status was controlled. Personal exposure levels were not measured in any of the studies but were estimated from area samples. The difference between workers under or over 50 years may be explained by a healthy worker effect that is not taken in account in the above studies.

2.5.2 *Animal studies*

Studies with chronic exposure of dogs suggest no increased sensitivity to agonists (i.e., histamine, methacholine (MCh), 5-hydroxytryptamine) at SO_2 concentrations of 15 ppm (Scanlon *et al.*, 1987).

Riedel *et al.* (1988) studied the effect of SO_2 exposure in ovalbumin-sensitized guinea pigs exposed to ambient air or to SO_2 at 0.1, 4.3, or 16.6 ppm for 8 h/day for 5 days. On bronchial provocation, they observed increased bronchial obstruction in animals exposed to 0.1-ppm SO_2 compared to air-exposed animals. In addition, increased amounts of anti-ovalbumin IgG antibodies were detected in bronchoalveolar lavage fluid of animals exposed to 4.3-ppm SO_2 and in the serum of animals exposed to 0.1-ppm SO_2.
Similar findings were observed in studies in which guinea pigs were exposed to ambient air or a single SO_2 concentration.

Airway obstruction induced by an ovalbumin challenge was higher in ovalbumin-sensitized guinea pigs exposed to 0.1-ppm SO_2 for 5 h/day for 5 days compared to sensitized guinea pigs that were not exposed to SO_2 (Park *et al*., 2001).
Study of Kitabatake *et al*.(, 1992, 1995) in guinea pigs sensitized with Candida albicans, exposure to 5-ppm SO_2 for 4 h/day on 5 days/week for 6 weeks resulted in an increased number of animals displaying prolonged expiration or inspiration after an inhalation challenge with C. albicans

The exposure levels in long-term animal studies were lower than in short-term animal studies (0.35 up to 133 mg/m^3). However, no concentration-response relationships could be established, because data were too limited to be useful for quantitative risk assessment (DECOS, 2003)

Wolf *et al.* (1989) evaluated mucociliary clearance in rats after exposure to SO_2. In this subchronic study, no effect on clearance of radiolabeled particles from the lung was observed in rats exposed to 5-ppm SO_2 for 2 h/day for 4 weeks.

There was only limited data available from animal toxicological studies on effects of SO_2 on immune and macrophage function. The studies reviewed there indicated no effect on susceptibility to bacterial infection with exposure to SO_2 at 5 ppm for 3 months and alterations in pulmonary immune system were reported with chronic exposure of mice to 2-ppm SO_2.
At high-dose exposures to 7- to 10-ppm SO_2 for 7 days, impairment of antiviral defenses was observed in mice (Clarke *et al*., 2000; Jakab *et al*., 1996).
Two recent studies using a 10-ppm SO_2 exposure regimen in mice found no effect on bactericidal activity toward Staphylococcus aureus following acute (4 h) exposure (Azoulay-Dupuis et al., 1982).
However, increased mortality rate and decreased survival time were observed in mice that were exposed to the same dose for 1 day or 1, 2, or 3 weeks and then challenged with an aerosol of Klebsiella pneumoniae (Clarke et al., 2000; Jakab et al., 1996). No effects on macrophage phagocytosis of red blood cells were observed in mice exposed to 10-ppm SO_2 for 4 h

2.6. GENOTOXICITY

2.6.1. *Human data*

Among the human studies there are many factors potentially contributing to differences among the control and the exposed group, which makes it difficult to specifically attribute a clastogenic effect to SO_2 (Nordenson *et al*., 1980; Meng and Zhang, 1990; Yadav and Kaukshik, 1996).
A single study with measured SO_2 mean values at "useful" ranges (only twice the TWA) was negative, but the number of workers was low (Sorsa *et al*, 1982).
As reviewed by HSE (2002), a few studies have been reported concerning the potential genotoxicity of SO_2 in workers, focussing on clastogenic effects in peripheral blood lymphocytes. Three such studies are cited in the corresponding IARC monograph (from a sulphuric acid factory in Chine, pulp mill in Sweden, Scandinavian light metal foundry (IARC,1992). An additional study of workers at an Indian fertilizer factory was published later (Yadav and Kaushik, 1996). These studies found increase in the frequency of chromosome aberrations, sister chromatid exchanges and micronucleated lymphocytes in exposed workers, but these studies reflect mixed exposures and there is not reliable information on exposures.
In summary no conlusions can be drawn concerning the role of SO_2 and therefore, genotoxicity of SO_2 is not relevant in the establishment of an occupational health-based limit valus

2.6.2 *Animal data*

In vivo – It was not possible to draw conclusions in animal studies (Renner and Wever, 1983 ; IARC, 1992).
In vitro - As reviewed by IARC (Monograph 54;1992), sulphur dioxide, its sulphite and bisulphite anions, induced gene mutations in several bacterial tests, lambda phage, yeast systems (Guerra et al., .1981) and in two studies in plant cells (Ma et al, 1973). However, these mutagenicity tests in bacteria have shown positive results only under certain conditions (Pagano and Zeiger, 1987), which are not relevant in exposed people (e.g. damage to DNA at non-physiological pH).

2.7. CARCINOGENICITY

2.7.1. *Human data*

Lee *et* Fraumeni (1969) performed a mortality study on 8,047 white males, who worked in copper smelters in the US The influence of sulphur dioxide exposure did not appear to be of importance. The authors recognised that it was impossible to separate completely arsenic exposure from that of sulphur dioxide exposure, because the workers were always exposed simultaneously to inorganic arsenic and sulphur dioxide. It has been suggested, that sulphur dioxide acts as a promoter of carcinogenesis, but this is not supported by epidemiological evidence (Enterline *et al*, 1987)|

In the year 1992 IARC concluded, that there is inadequate evidence for the carcinogenicity in humans of sulfur dioxide, sulfites, bisulfites and metabisulfites. There is limited evidence for the carcinogenicity in experimental animals of sulfur dioxide. There is inadequate evidence for the carcinogenicity in experimental animals of sulfites, bisulfites and metabisulfites Overall evaluation: Sulfur dioxide, sulfites, bisulfites and metabisulfites are not classifiable as to their carcinogenicity to humans (Group 3) (IARC, 1992).

The mortality of workers exposed to sulfur dioxide in the pulp and paper industry was studied by Lee (2002). The cohort included 57,613 worker employed for at least 1 year in the pulp and paper industry in 12 countries. From company questionnaires; 40,704 workers were classified as exposed to SO_2. The SMR analysis showed a moderate deficit of all causes of death [SMR = 0.89; 95% confidence interval (CI), 0.87-0.96] among exposed workers. Lung cancer mortality was marginally increased among exposed workers (SMR = 1.08; 95% CI, 0.98-1.18). After adjustment for occupational coexposures, the lung cancer risk was increased compared with unexposed workers (rate ratio = 1.49; 95% CI, 1.14-1.96). There was a suggestion of a positive relationship between weighted cumulative SO_2 exposure and lung cancer mortality (p-value of test for linear trend = 0.009 among all exposed workers; p = 0.3 among workers with high exposure). Neither duration of exposure nor time since first exposure was associated with lung cancer mortality. Mortality from non-Hodgkin lymphoma and from leukemia was increased among workers with high SO_2 exposure; a dose-response relationship with cumulative SO_2 exposure was suggested for non-Hodgkin lymphoma. For the other causes of death, there was no evidence of increased mortality associated with exposure to SO_2. Although residual confounding may have occurred, the results suggest that occupational exposure to SO_2 in the pulp and paper industry may be associated with an increased risk of lung cancer.

2.7.2. *Animal data*

Few animal studies have been directed towards the carcinogenicity of sulphur dioxide. Although tumour formation was observed, the studies showed considerable limitations, including: the use of animals with very high spontaneous tumour incidence; exposure to high levels of the substance; and, incomplete reporting on the tumour promoting activity of sulphur dioxide in combination with benzo[a] pyrene.

In summary all of the available epidemiological studies related to carcinogenity of SO_2 are limited by mixed exposures and lack of quantitative exposure information. There are not useful data concerning the carcinogenic potential of SO_2 from studies in animals. Given the uncertainties in the available data it is not possible to draw any firm conclusions about the carcinogenic potential of SO_2

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2.8. REPRODUCTIVE TOXICITY

2.8.1. *Human data*
No data available.

2.8.2. *Animal data*
Murray et al. studied the embryotoxic a teratogenetic effects of SO in New Zeland white rabbits (20 per group) and in virgin CF-1 mice (35-40 per group) exposed to 70 and 25 ppm SO_2. In both species the mild maternal mortality was observed, the few malformatios observed did not differ from controls and significant increase in the occurance of minor skeletal variants were observed (Murray, 1979).
Pertuzzi et al. in male and female CD-1 mice (40 per group) exposed to 0,5,12 and 30 ppm SO_2 starting in 9 days before the formation of breeding pairs and was ended at gestation day 12 – 14, for the total of 24 days, did not observed affection of reproductive performance and somatic and neurobehavioral development of offspring (Pertuzzi et al, 1996). In the same experimental design the group of reasearchers later studied in adulthood the behaviours of the CD-1 mice and these were not significantly modified (Fiore, 1998).

3. Recommendation

Several reviews of the toxicology of sulphur dioxide have been published within the last decades.These studies have generally been designed with the aim of identifying appropriate levels for environmental ambient air quality standards and not for working air quality standards. . The focus therefore tends to be on the identification of dose- reponse relationshipfor effects in particular subgroups such as children, astmatics, those with chronic obstructive lung disease etc. In general, the information gathered relates to the effect of peak pollution episodes rather than the long term consequences of exposure to SO_2. The usefulness of these outcomes for the purpose of the OELs setting is limited because of different target population and different conditions.

As concern information appropriate to adoption of the occupational exposure limits a number of studies have been carried out with healthy, non-smoking volunteers, who were exclusively exposed to sulphur dioxide at levels similar to working conditions. These volunteers were exposed to concentrations of SO_2 as low as 0.2 ppm up to more than 8.0 ppm. The exposures lasted from minutes up to several hours and were carried out with or without physical exercise (summarised in the tables attached). The main adverse effects observed were irritation of the upper respiratory tract and the eyes, and decreased lung function, such as increased pulmonary airway resistance. Data obtained from the clinical studies and from the epidemiological studies in general population

indicate that people with asthma or with other diseases concerning the respiratory tract, are more vulnerable to sulphur dioxide exposure than healthy people. Concerning asthma, this finding is supported by the animal data. However, numerous studies with asthmatics show that the level of susceptibility is strongly influenced by non-specific factors, such as physical activity and atmospheric conditions (dry, cold air). These factors alone may aggravate asthma. However, it is concerned that asthmatics are at higher risk when exposed to sulphur dioxide in combination with these non-specific asthma-aggravating factors.
In all reviews on SO_2 health effects it was established that subjects with asthma are more sensitive to the effects of SO_2 exposure than healthy individuals without asthma.
The evidence from the reviewed studies indicates increased respiratory symptoms with peak (5-15 min) SO_2 exposures above 0.5 ppm in asthmatic subjects.
The adverse effects on lung function in healthy people are associated with exposures in the region of 1 ppm (2.7 mg/m^3) or more (Bedi et al.,1984; Frank,1980; Lawther et al.,1975; Islam et al.,1992; kulle et al..1984; Schachter et al., 1984)
From the current data, the committee concludes that the acute effects of sulphur dioxide on the respiratory tract, such as nose and throat irritation, depressed lung function and increased airway resistance, should be prevented. In order to do this, the committee recommends adopting a STEL. The adoption of 8 hour TWA is forced by both, the human and animal data. These data support that chronic exposure to sulphur dioxide may lead to chronic irritation (bronchitis) and increased susceptibility to airway infections. SO_2-induced inflammation may extend beyond the short time period often associated with SO_2 effects.
Taken into account that OELs are recommended for healthy workers, an OEL for sulphur dioxide exposure is recommended as an 8-hour TWA of 0.5 ppm (1.3 mg/m^3) and a STEL (15 minutes) of 1.0 ppm (2.7 mg/m^3); the latter meant to limit peaks in exposure which could result in irritation. It shoud be noted that the proposed values should afford protection to most, but not all individuals suffering from bronchial asthma or chronic bronchitis. For asthmatics it is recommended to keep exposure below 0.2 ppm; there is indication, that asthmatics do not respond to levels below 0.2 ppm SO_2 (Tunnicliffe et al., 2003; Devalia et al., 1994).
No skin notation was considered to be necessary.
Concerning workers with a possible extra risk, the SCOEL likes to express its concern that asthmatics are at a higher risk when not only exposed to sulphur dioxide, but also to other (non-specific) factors which incite asthma.
Carcinogenicity and genotoxicity data are too limited to make a definite conclusion about the carcinogenic potential of sulphur dioxide in humans. Therefore, the committee recommends not classifying sulphur dioxide as a suspected carcinogen. In addition, the database is too restricted to allow any conclusion to be drawn on the adverse effects on fertility and development.
At the levels recommended, no measurement difficulties are foreseen.

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TABLE: KEY HUMAN HEALTH EFFECTS OF PEAK EXPOSURE IN HEALTHY ADULTS

SO_2 Concen-tration (ppm)	Exposure Duration	Observed Effects	Size of population	References
0.5	1 hour	No change in lung function, including specific airway resistance in healthy adults exposed (with exercise) .	24	Linn et al. (1987)
0.2	1hour	No changes in pulmonary functions and on heart rate at rest. Parameters of the spectral analysis of heart rate variability were increased ($p<0.05$ for total power)	12 nonsmokes	Tunnicliffe et al. (2001)
0.2		Some weak and inconsistent evidence to suggest that SO_2 exposure may lead to changes in heart rate variability.		Routledge et al. (2006)
≥ 1.0	**3 min – 1h**	**Among healthy adults, SO_2-attributed decrements in lung function generally occur at concentrations above 1 ppm during exercise and above 5 ppm at rest. Markers of airway inflammation are significantly elevated at 4 h postexposure, reaching peak levels 24 h postexposure.**		**Amdur et al. (1953); Kreisman et al. (1976); Lawther et al. (1955,1975); Sandström et al. (1989); Sim and Pattle (1957); Snell and Luchsinger (1969)**
0.75 ppm	2 hours	Exercise for 15 minuts after 1 hour exposure increased airways resistance temporarily by 2 - 55 %	16 expose/ 15 control	Stacey et al.(1981)
0.75 ppm	2 hours		231	Stacey et al (1983)
0.7 ppm	2 hours	Healthy adults with and without exercise - not affected pulmonary functions Ciliary defects detected by electron microscopic examination	7	Carson et al (1987)
1 ppm		Deep breathing by mouth increased specific airways resistance (sRaw)		Lawther et.al (1975)
1ppm	2 hours	Upper respiratory tract irritation in healthy adults performing moderate exercise (exposure to SO_2 and 1mg/m3 NaCl). The cause of effect is uncertain.		Frank (1980)
1-2 ppm	2 hours	Reduction in thoracic volume in non.smoking young volunteers		Bedi et al (1984)
4ppm		Tightness in the chest and reduced FEV in workers		Archer et al.(1979)
8 ppm	20 min	Induced airways inflammation beyond the short time period	22 healthy men	Sandstrom et al. (1989)

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TABLE: KEY HUMAN HEALTH EFFECTS OF PEAK EXPOSURE TO SULFUR DIOXIDE

SO_2 Concen-tration (ppm)	Exposure Duration	Observed Effects	Size of population	References
		ASTMATIC ADULTS:		
0.2-0.4	**1min – 6h**	**Significant reductions in FEV, and increases in specific Airways resistance (sRaw) observed among some asthmatic adults.**		**Bethel et.al. (1985); Horstman et al. (1986); Linn et al. (1982,1983,1987);); Schachter et al. (1984); Sheppard et al. (1981); Tunnicliffe et al. (2001,2003)**
0.2	1h	No association between respiratory symptoms, lung functions and 1 h exposure to SO_2 at rest in either asthmatics or healthy . No significant changes in max.or minimum heart rates. Higher total power in healthy.	12 asthmatics/ 12 healthy	Tunnicliffe et al. (2003)
0.2	6 hours	Airways response to inhaled house-dust-mite antigen at exposure to 0.2 ppm SO_2 . No changes in lung functions.	10 atopic asthmatic	Devalia et al. (1994)
0.25	1 h	During heavy exercise mild bronchoconstriction		Bethel et al. (1985)
0.25-0.5		Moderate exercise for 10 min, than rest and repeated in 1 week intervals did not induced changes in pulmonary functions	24 young astmatics	Linn et al.(1987)
0.4-0.6	**1 min – 2h**	**Decrements in lung function observed between 0.4 – and 0.6-ppm SO_2 in asthmatic adults and adolescents during exercise. Significant interindividual variability in response has been consistently demonstrated. Effects observed within 1-5 min of exposure are generally not enhanced by increasing exposure duration. Respiratory symptoms (e.g., wheezing and chest tightness) increase with increasing exposure concentrations above 0.4 ppm. No respiratory effects reported in healthy, non-asthmatic.**		**Balmes et al. (1987); Bedi et al. (1979); Gong et al. (1995); Horstman et al. (1986); Koenig et al.(1983); Linn et al. (1982,1983,1987); Magnussen et al. (1990); Schachter et al. (1984); Sheppard et al. (1981)**
0.5 ppm		Development of tolerance in asthmatic subjects exposed repeatedly to bronchoconstriction effects at 0.5 ppm SO_2		Shepard et al.(1983)
0.5			7/8	Balmes et al. (1987)

	3 min.	During eucapnic hyperpnoe respiratory symptoms – wheezing, chest tightness	asthmatic	
0.6-1.0	**1 min – 2h**	**Specific airway resistance shown to double following 10-min exposures to SO_2 concentrations between 0.25 and 0.75 ppm with moderate exercise in 50% of asthmatics tested. Some evidence of an increase in airway resistance in healthy, non-asthmatic subjects exposed to SO_2 , among asthmatics during exercise, even with continued SO_2 exposure.**		**Balmes et al. (1987); Gong et al. (1995); Hackney et al. (1984); Horstman et al. (1986,1988); Koenig et al. (1983); Linn et al. (1985, 1987); Schachter et al. (1984); Stacy et al. (1981)**
0.6	1 hour	Exposure to SO_2 and exercise increased severirty of respiratory symptoms in moderate/severe asthmatics. Abatemend within < 1 h.		Linn et al. (1987)
0.75	3 h	Bronchoconstriction induced by 10 min heavy exercise, than rest, bronchoconstriction reversed immediately by rest	17 young asthmatics	Hackney et al.(1984)
0-, 0.5-,1.0		SO_2 sensitive asthmatics respiratory symptoms increased with increased SO_2 concentration from 0-, O.5,- and 1 ppm SO_2 following 10 min exercise.		Gong et al. (1995)
< 0.6	1h	sRaw doubled in moderate/severe asthmatics	24 healthy, 21 atopic non asthmatics, 16 mild and 24 moderate/ severe	Linn et al. (1987), Hackney et al. (1987)
< 1 ppm	5 min	Moderate to heavy exercise in asthmatics is leading to significant bronchoconstriction or increase in sRaw		Linn et al. (1983)

TABLE: KEY HUMAN HEALTH EFFECTS OF REPEATED EXPOSURE TO SO_2

SO_2 Concentration (ppm)	Exposure Duration	Observed Effects	Size of population	References
O.7 (0 – 15)	≥2 years	No overall differences in pulmonary functions, more reported caugh and sputum production in exposed power station technicians, but not controlled for smoking.	38/34 controls	Froom et al (1998)
>1.0	years	Significant decrease in FEV1 in cooper smelters workers exposed to respirable dust and SO_2.	113	Smith et al (1977)
≥5	years	In the same cooper smelters workers no significant changes in pulmonary functions.	430	Lebowitz te al. (1987)
0.4- 3.0	>20 years	Significant reduction in FVC, FEV1 incooper workers smokers and in nonsmokers. Simultanous exposure to As, Cu, Mn, Fe and other metals.	953	Archer and Gillan (1978)
0.84- 1.2	years	British steel plants workers did not experienced increase in respiratory symptoms or reduction in lung functions. Confounding factors smoking, dust were controlled.	4,506 and 5,943	Lowe et al. (1970)
2- 36	1 month – 40 years	Cough in 56% , sputum production in 46% , difficulty breathing in 22 % of pulp mills workers. More in workers ≤ 50 years. Exposure estimated from the area samples	56	Skalpe et al. (1964)