Sulphur dioxide

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

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Mijnheer de staatssecretaris,

Bij brief van 3 december, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over zwaveldioxide. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport en de Minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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Sulphur dioxide

Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupatoinal Standards,
a committee of the Health Council of the Netherlands

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2003/08OSH, The Hague, 18 December 2003

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Samenvatting en advieswaarde

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden, aangeduid als maximaal aanvaarde concentraties (MAC-waarden).

In het voorliggende rapport bespreekt de commissie de gevolgen van blootstelling aan zwaveldioxide en presenteert zij een gezondheidskundige advieswaarde voor die stof. De conclusies van de commissie zijn gebaseerd op informatie afkomstig uit de rapporten geschreven door de Scientific Committee on Occupational Exposure Limits (SCOEL) van de Europese Gemeenschap (SCO93, SCO98) en op aanvullende wetenschappelijke publicaties die vóór mei 2002 zijn verschenen.

Fysische en chemische eigenschappen

Zwaveldioxide (SO_2; CAS nr. 7446-09-5) is een kleurloos gas met een sterk irriterende geur. De geurdrempel ligt tussen 0,8 en 8 mg/m^3. De molaire massa is 64,06 g/mol, het smeltpunt -72,7 °C en het kookpunt -10,0 °C. Zwaveldioxide is zeer goed oplosbaar in water.

Zwaveldioxide wordt gebruikt in de chemische industrie, bijvoorbeeld als antioxidant voor de productie van broom, als bleekmiddel bij het gieten van

magnesiumonderdelen, als katalysator voor furfuralharsen en in de productie van cellulosepulp en chemicaliën. Verder wordt zwaveldioxide gebruikt in de voedingsindustrie als conserveermiddel van groenten en fruit, als ontsmettingsmiddel in brouwerijen, en bij de productie van wijn- en voedingsmiddelen.

Monitoring

Zwaveldioxide kan zowel actief (pompsysteem) als passief (diffusie) worden bemonsterd. Beide bemonsteringen maken onder andere gebruik van zwaveldioxide absorberende vaste stoffen of vloeistoffen. Het Nederlands Normalisatie Instituut beveelt het gebruik van het 'voornorm' protocol (NVN2950) aan voor het monitoren van dampen en gassen in de werkomgeving. In het betreffende protocol wordt zwaveldioxide passief bemonsterd, waarna de uitslag direct weergegeven wordt op een display van een ‘pocket dosimeter’.

Het Amerikaanse National Institute for Occupational Safety and Health (NIOSH) beveelt voor kortdurende monsternames van zwaveldioxide een ionchromatografische analyse aan (Methode 6004; detectiegebied: 0,5-20 mg/m^3 per 100 L luchtmonster).

Grenswaarden

In Nederland geldt momenteel voor zwaveldioxide een wettelijke grenswaarde van 5 mg/m^3, gemiddeld over een achturige werkdag. In 1985 heeft de voorloper van de commissie, de Werkgroep van Deskundigen, een gezondheidskundige advieswaarde voorgesteld van 1,3 mg/m^3 (tijd gewogen gemiddelde (TGG) van 8 uur). In 1998 heeft de SCOEL ook een grenswaarde van 1,3 mg/m^3 geadviseerd, en een ‘short term exposure limit’ (STEL) van 2,7 mg/m^3 (TGG 15 min).

Kinetiek

Zwaveldioxide wordt voornamelijk via de slijmvliezen van de neus in het lichaam opgenomen. Opname via de longen is echter ook mogelijk en neemt toe bij inademing via de mond en bij diepe inademing, zoals gebeurt bij grote lichamelijke inspanning.

Omdat zwaveldioxide zeer goed wateroplosbaar is, zal het zodra het in contact komt met waterdamp die van nature aanwezig is in de ademhalingswegen worden omgevormd in zwaveligzuur. Dit zuur is instabiel en splitst zich snel in sulfiet- en bisulfietionen. De sulfietionen worden weer snel omgezet in het stabielere sulfaat. Deze sulfaten worden vervolgens opgenomen in het grote sulfaatdepot van het lichaam. De bisulfietionen op hun beurt binden zich aan lichaamseigen eiwitten tot zogenaamde S-

sulfonaten. In het bloed komt zwaveldioxide het meest voor in de vorm van deze S-sulfonaten.

Het zwaveldioxide verlaat het lichaam op verschillende manieren. Als sulfaat komt het langzaam vrij uit het sulfaatdepot, waarna het via de nieren wordt uitgescheiden. De S-sulfonaten vallen langzaam uiteen in sulfaten of in het 'oorspronkelijke' zwaveldioxide. Dit zwaveldioxide verlaat het lichaam via uitademing, de sulfaten volgen de route van de sulfaatdepots.

Effecten

Zwaveldioxide is irriterend voor neus, keel en ogen. Bij kortdurende hoge blootstelling kunnen bovendien klachten optreden als rhinitis, kortademigheid, benauwdheid op de borst en misselijkheid.

Epidemiologisch onderzoek bij chronisch blootgestelden bracht verschillende gezondheidsklachten naar voren, zoals bronchitis, verhoogde gevoeligheid voor luchtweginfecties en verhoogde kans op luchtwegallergieën. Deze epidemiologische gegevens bieden niettemin te weinig houvast om een gezondheidskundige advieswaarde te kunnen afleiden, omdat meerdere factoren een rol kunnen hebben gespeeld bij het ontstaan van deze klachten, zoals de mengselblootstelling. Ook is onvoldoende rekening gehouden met de persoonlijke levensstijl.

Naast deze epidemiologische onderzoeken is ook een aantal kwalitatief goede onderzoeken uitgevoerd met gezonde (niet rokende) vrijwilligers in een gecontroleerde omgeving. Daarbij ging het om acute of kortdurende blootstellingen gecombineerd met lichte lichamelijke activiteit, met blootstellingen variërend van 0,53 mg/m^3 tot ruim 20 mg/m^3, waarbij de effecten op de luchtwegen centraal stonden. De belangrijkste klachten die optraden waren irritatie aan de bovenste luchtwegen en ogen, en verminderde longfunctie. Deze klachten waren onmiskenbaar vanaf 2,7 mg/m^3, terwijl bij 2,0 mg/m^3 of lager geen noemenswaardige klachten zijn beschreven, met uitzondering van drie onderzoeken. In twee ervan, van dezelfde onderzoeksgroep, rapporteerden de onderzoekers een verminderde longfunctie bij 1,6-2,0 mg/m^3. De commissie laat deze onderzoeken echter buiten beschouwing, omdat de onderzoeksopzet te beperkt was. In een derde onderzoek met zeer lage blootstelling (0,5 mg/m^3) zijn milde effecten op de autonome hartfunctie beschreven, maar deze beschouwt de commissie niet als een nadelig effect. Ook dit onderzoek laat de commissie buiten beschouwing, omdat de gebruikte meetmethode zeer gevoelig was en de gemeten effecten niet leidden tot lichamelijke klachten of hartfunctieproblemen.

De commissie beschouwt daarom 2,0 mg/m^3 als de niet-waargenomen-nadelig-effect-concentratie (NOAEL) bij acute blootstelling. Deze NOAEL is gebaseerd op twee onafhankelijk van elkaar uitgevoerde onderzoeken, waarbij vrijwilligers gedurende 40

minuten of gedurende 4 uur werden blootgesteld aan zwaveldioxide, terwijl zij zich licht lichamelijk inspanden. Daarbij traden geen longfunctieveranderingen op.

Ten aanzien van mensen die mogelijk een extra risico lopen geven de gegevens afkomstig uit epidemiologisch onderzoek onder de algehele bevolking aan dat mensen met astma of andere aandoeningen aan de luchtwegen gevoeliger zijn voor zwaveldioxideblootstelling. Dit lijkt te worden ondersteund door laboratoriumonderzoek. Maar de commissie heeft ook vastgesteld dat de mate van gevoeligheid voor zwaveldioxide in astmatici sterk wordt beïnvloed door andere (niet-specifieke) factoren, zoals het doen van (zware) lichamelijke krachtsinspanning en klimatologische factoren (droge, koude lucht). Het is bekend dat al deze factoren op zichzelf astma bij astmatici kunnen oproepen of verergeren. Daarom kan de commissie niet concluderen of astmatici gevoeliger zijn voor blootstelling aan zwaveldioxide in afwezigheid van deze niet-specifieke factoren. Wel wil zij haar zorg uitdrukken voor de gecombineerde effecten van deze niet-specifieke factoren en zwaveldioxideblootstelling bij astmatici.

In dieren leidde korte en middellange blootstelling aan zwaveldioxide tot vergelijkbare effecten als bij de mens, zoals irritatie aan de bovenste luchtwegen en ogen. Daarnaast zijn verminderde afweer in de luchtwegen en afwijkingen in enzympatronen in bloed en lever vastgesteld. De dieren waren vaak echter aan zeer hoge concentraties blootgesteld (>267 mg/m^3 (middellange blootstelling) tot >1.000 mg/m^3 (korte blootstelling)). Bovendien vertoonden veel van deze onderzoeken ernstige tekortkomingen in onderzoeksopzet en verslaglegging.

Ook de dieronderzoeken naar de schadelijke effecten van zwaveldioxide na langdurige blootstelling acht de commissie niet geschikt. Hoewel in deze chronische onderzoeken lagere blootstellingen zijn gebruikt (0,35 tot 133 mg/m^3), zijn de gegevens te beperkt om een concentratie-effectrelatie te kunnen vaststellen en dus een gezondheidskundige advieswaarde te kunnen afleiden.

Een paar dieronderzoeken zijn uitgevoerd om te beoordelen of zwaveldioxide kanker-verwekkende of genotoxische eigenschappen bezit. Hoewel tumoren zijn gevonden na langdurige blootstelling, acht de commissie deze onderzoeken niet geschikt om daarover een uitspraak te kunnen doen; naast hoge blootstellingen blijken namelijk ook zeer gevoelige proefdieren te zijn gebruikt. Om vergelijkbare redenen kan de commissie geen uitspraak doen over de vraag of zwaveldioxide de tumorontwikkeling stimuleert.

Zwaveldioxide veroorzaakte DNA-schade in bacteriën, maar alleen onder condities die niet relevant zijn voor de mens. Daarnaast veroorzaakte het schade aan chromosomen in *in vitro* celsystemen en in levende muizen.

Het aantal dieronderzoeken naar de schadelijke gevolgen van zwaveldioxide op de vruchtbaarheid en op het nageslacht is zeer beperkt en levert onvoldoende bewijs dat, bij lage luchtconcentraties, zwaveldioxide reproductietoxisch is.

Evaluatie en advies

De commissie beschouwt de acuut optredende irritatie aan de luchtwegen en long-functieveranderingen als de meest gevoelige effecten na blootstelling aan zwaveldioxide. Daarom beveelt zij een gezondheidskundige advieswaarde voor kortdurende blootstelling aan (TGG 15 minuten). De humane gegevens afkomstig van vrijwilligersonderzoek zijn van voldoende kwaliteit om een dergelijke advieswaarde te kunnen afleiden.

Als uitgangspunt neemt de commissie de NOAEL van 2,0 mg/m^3, afkomstig van twee onafhankelijk van elkaar uitgevoerde onderzoeken. Ter compensatie voor mogelijke interindividuele verschillen corrigeert de commissie de NOAEL met een factor 3. Deze factor van 3 vindt de commissie noodzakelijk, omdat de NOAEL is gebaseerd op een beperkt aantal onderzoeken en een beperkt aantal vrijwilligers. Bovendien bestaan in de literatuur aanwijzingen dat gezonde vrijwilligers verschillend kunnen reageren bij bepaalde blootstellingen onder meer extreme omstandigheden. Deze correctie levert afgerond een gezondheidskundige advieswaarde op van 0,7 mg/m^3 voor kortdurende blootstelling (TGG 15 minuten).

Wegens een gebrek aan gegevens van voldoende kwaliteit en betrouwbaarheid kan de commissie geen gezondheidskundige advieswaarde adviseren, die zou kunnen beschermen tegen langdurige blootstelling.

De commissie is van mening dat mensen met astma in combinatie met andere astma-inducerende factoren eerder lichamelijke klachten kunnen krijgen.

De commissie is verder van mening dat zwaveldioxide onvoldoende is onderzocht op kankerverwekkende eigenschappen. Zij adviseert daarom de stof niet te classificeren.

Gezondheidskundige advieswaarde

De Commissie WGD van de Gezondheidsraad stelt bij beroepsmatige blootstelling aan zwaveldioxide een gezondheidskundige advieswaarde voor van 0,7 mg/m^3 (TGG 15 minuten).

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands sets Health-Based Recommended Occupational Exposure Limits (HBR-OEL) for chemical substances in air in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). They constitute the first step in a three-step procedure, which leads to legally binding occupational exposure limits.

In this report, the committee discusses the consequences of occupational exposure to sulphur dioxide and recommends a health-based occupational exposure limit. The committee's conclusions are made on the documents produced by the Scientific Committee on Occupational Exposure Limits of the European Commission (SCOEL; SCO93, SCO98) and on additional scientific papers published prior to May 2002.

Physical and chemical properties

Sulphur dioxide (SO_2; CAS no. 7446-09-5) is a colourless gas, with an irritating odour. Its odour threshold ranges between 0.8 and 8 mg/m^3. The molar mass of sulphur dioxide is 64.06 g/mol, its melting point -72.7 °C and its boiling point -10.0 °C. Sulphur dioxide is highly hydrophilic and dissolves easily in water.

Sulphur dioxide is used in the inorganic and petrochemical industries, such as in the production of cellulose pulp and chemicals. The substance has a lot of functions: as an

antioxidant in the bromine production; as a bleaching gas in casting magnesium parts and bleaching kaolin; as a rapid catalyst in furfural resins for manufacturing casting moulds; as a fruit and vegetable preservative in the food; and, as a disinfectant in the wine and brewery industry.

Monitoring

Various sampling and analysis techniques are available for determining ambient concentrations of sulphur dioxide in an occupational setting. Both passive and active samplers may be used. Samples obtained from passive sampling are analysed by spectrophotometry or ion exchange chromatography. The National Institute for Occupational Safety and Health (NIOSH) recommends the latter (Method 6004; detection range: 0.5-20.0 mg/m^3 per 100 L air sample).

Concerning personal exposure, direct reading pocket dosimeters may be used, as is described in a protocol, called 'Voornorm NVN 2950', from the Dutch Normalisation Institute.

Limit values

In 1985, the DECOS recommended an HBR-OEL for sulphur dioxide of 1.3 mg/m^3, as an 8-hour time weighted average (8-hour TWA). However, due to socio-economic constraints, the Netherlands has set a legal occupational exposure limit (OEL) of 5 mg/m^3 (8-hour TWA). In addition, the SCOEL has set a limit of 1.3 mg/m^3 (8-hour TWA) and of 2.7 mg/m^3 (15-minute TWA). Both in Germany and Denmark, OELs have been set at 1.3 mg/m^3, averaged over an 8-hour period of time; and, in the United Kingdom and Sweden of around 5 mg/m^3 (8-hour TWA) and 13 mg/m^3 (15-minute TWA, for Sweden a Ceiling). Finally, the American Conference of Governmental Industrial Hygienists has proposed a TLV of 5 mg/m^3 and a STEL of 13 mg/m^3.

Kinetics

Inhaled sulphur dioxide is mainly absorbed in the body through the epithelium of the upper respiratory tract (nose and throat). However, the substance may reach the lower respiratory tract (bronchi and alveoli in lungs) when it is deeply inhaled, as happens with doing heavy work or physical exercise.

Sulphur dioxide is a highly hydrophilic gas. Therefore, it reacts easily with water, which is present at the surface of the respiratory tract. When sulphur dioxide reacts with water sulphurous acid is formed. This sulphurous acid dissociates easily into sulphite and bisulphite ions. Sulphite ions are then rapidly converted into sulphate, whereas

bisulphite ions bind to proteins to form S-sulphonates. In the blood most of the sulphur dioxide is present as S-sulphonate and only a minor part as free sulphite/sulphate or bisulphite ions. Sulphates are quickly absorbed in the large endogenous sulphate pool of the body and then slowly released via the blood into the urine. Circulating S-sulphonates slowly decompose into sulphates or sulphur dioxides. The latter substance is exhaled.

Effects

In humans, sulphur dioxide is irritating to the eyes and the upper respiratory tract. Inhaling high concentrations may cause: rhinorrhae; coughing; shortness of breath; chest tightness; and, a choking sensation.

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.

A number of laboratory studies have been carried out with healthy, non-smoking volunteers, who were exclusively exposed to sulphur dioxide. These volunteers were exposed to concentrations of as low as 0.53 mg/m^3 to more than 60 mg/m^3. 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 the eyes, and decreased lung function, such as increased pulmonary airway resistance. These adverse effects were clearly present at exposure levels of 2.7 mg/m^3 or higher. None of these effects were observed at exposure levels below 2.0 mg/m^3, with the exception of three studies (two of the same research group): these three studies were, however, not considered for risk assessment, because of limitations in study design or the lack of toxicological relevance of the findings. In addition, at 2.0 mg/m^3, two independent studies were performed with volunteers, who were exposed for 40 minutes and 4 hours, respectively, with moderate physical exercise. In all these volunteers lung function remained normal. Based on these outcomes, the committee considers 2.0 mg/m^3 as the No Observed Adverse Effect Level (NOAEL) after short-term exposure.

Epidemiological data obtained from the 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 laboratory 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. Therefore, the committee cannot conclude whether or not asthmatics are more vulnerable to sulphur dioxide exposure in the absence of these non-specific stimuli. However, it is concerned that asthmatics are at higher risk when exposed to sulphur dioxide in combination with these non-specific asthma-aggravating factors.

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 committee noted that 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)).

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.

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 regard to genotoxicity, mutagenicity tests in bacteria scored positive in conditions not relevant for humans. Also, sulphur dioxide induced chromosomal aberrations *in vitro*, and micronuclei *in vitro* and *in vivo*.

In a limited number of experiments, the adverse effects of sulphur dioxide have been studied on reproduction. Litter of rabbits and mice were exposed to 187 and 67 mg/m^3, respectively. This resulted in minor skeletal variations and mild maternal toxicity. In another study, offspring of exposed mice (13.4 to 80 mg/m^3) showed no defects in reproductive performance, and in somatic and neurobehavioral development.

Evaluation

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 deriving a health-based occupational exposure limit for short-term exposure (Short-Term Exposure Limit (STEL); 15-min TWA).

From the human database a NOAEL of 2.0 mg/m^3 was derived (see previous paragraph). In addition, to the committee's opinion the NOAEL needs to be adjusted for inter-individual differences. This is needed, because the number of studies at the NOAEL and the number of participants in those studies were limited. Also, the committee is aware of the reporting of variable responses among healthy people at levels near the NOAEL. To compensate for these uncertainties, a factor of 3 was chosen. Consequently, the committee recommends a STEL for sulphur dioxide of 0.7 mg/m^3 (≈0.25 ppm).

Both epidemiological and animal data suggest that chronic exposure to sulphur dioxide may lead to chronic irritation (bronchitis) and increased susceptibility to airway infections. However, these data were not reliable or insufficient to assess concentration-response relationships. For this reason, the committee does not recommend an HBR-OEL (8-h TWA).

Concerning workers with a possible extra risk, the committee 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.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for sulphur dioxide of 0.7 mg/m^3 (≈0.25 ppm), as a 15-minute time weighted average concentration (STEL).

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (annex A). The purpose of the committee's evaluation is to set a health-based recommended exposure limit for the atmospheric concentration of the substance, provided the database allows the derivation of such a value.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister on the feasibility of using the health-based limit as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure, the Minister of Social Affairs and Employment sets the legally binding OEL.

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the committee, of the health hazard of sulphur dioxide. The members of the committee are listed in annex B. The first draft of this report was prepared by AAE Wibowo of the Coronel Institute,

Academic Medical Center of Amsterdam, for the Ministry of Social Affairs and Employment.

In 2002, the President of the Health Council released a draft of the report for public review. The individuals and organizations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

In 1998, the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission published a report on the health-risk assessment of sulphur dioxide (SCO98), of which a draft was published in 1993 (SCO93). The summary of the final report is included in the current document in annex D. The committee used data of this report for the present evaluation. In addition, more recent literature was retrieved from on-line databases: Toxline, Medline, Excerpta Medica and Chemical Abstracts. The final search has been carried out in May 2002. The searches were performed using sulphur dioxide and CAS no. 7446-09-5, as key words. In addition, in preparing the present report the following reviews have been consulted:

- Agency for Toxic Substances and Disease Registry, US Dept of Health and Human Services. Toxicological profile for sulphur dioxide. Contract no. 205-93-0606. Research Triangle Institute, Atlanta: 1998 (ATS98);
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- International Agency for Research on Cancer (IARC), WHO. Occupational exposures to mists and vapours from strong inorganic acids; and other industrial chemicals. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon, 1992; Volume 54 (ISBN 92 832 1254-1), pp 131-188;
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A list of abbreviations used in this report is given in annex G.

Chapter 2

Identity, properties and monitoring

2.1 Identity

CAS name	Sulphur dioxide
Synonyms	Sulphurous oxide, sulphurous anhydride, sulphur oxide, sulphurous acid anhydride, sulphur bioxide, bisulphite
CAS number	7446-09-5
EEC number	016-011-00-9
RTECS number	WS 4550000
EINECS number	231-195-2

2.2 Physical and chemical properties

Molecular formula	SO_2
Molecular weight	64.06 g/mol
Melting point	-72.7 °C
Boiling point	-10.02 °C
Relative density (water=1)	1.434 at –10 °C (liquid)
Vapour pressure (20 °C)	324.24 kPa (volatility high)
Solubility	Soluble in water (107 g/L at 20 °C). Highly soluble in sulphuric acid, ethyl and ethyl alcohols, acetic acid, chloroform, diethyl ether, and other polar solvents.
Odour threshold	0.8-8.0 mg/m^3 (0.3-3.0 ppm)
Conversion factors (20 °C, 101.3 kPa)	1 ppm = 2.67 mg/m^3 1 mg/m^3 = 0.37 ppm

At normal ambient temperatures, sulphur dioxide is a colourless gas, with a strong pungent (suffocating) odour. 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 (Bur95).

2.3 EU Classification and labelling (CKB99)

T symbol		Toxic
Risk phrases	R23	Toxic by inhalation;
	R34	Causes burns;
Safety phrases	1/2	Keep locked up and out of reach of children;
	9	Keep container in a well-ventilated place;
	26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice;
	36/37/39	Wear suitable protective clothing, gloves and eye/face protection
	45	In case of accident or if you feel unwell, seek medical advice; immediately (*show the label where possible*);

2.4 Validated analytical methods

2.4.1 Environmental monitoring

A variety of passive and active samplers may be used to provide data on ambient concentrations of sulphur dioxide (SCO93). Passive samplers contain sulphur dioxide diffusion tubes with solid or liquid absorbents. Samples obtained in this way are analysed by spectrophotometry or ion exchange chromatography.

The collecting medium for active sampling is typically a liquid bubbler, and less frequently solids, impregnated filters or plastic pouches. Samples are taken for a specified period and the volume of air is determined. The most used and reliable methods for analysing the collected liquid medium are: the acidimetric (total acidity) method (ISO1983); ion-exchange chromatography; the tetrachloromercurate method (ISO1990); and, the thorin method (ISO1980). The last two methods are less widely used because of the very hazardous reagents needed (WHO00, ATS98). The National Institute for Occupational Safety and Health (NIOSH) recommends method 6004 (ion exchange chromatography) for determination of ambient levels of sulphur dioxide (NIO94). This method is specific for sulphur dioxide and applicable for short-term sampling (range: 0.5-20 mg/m^3 per 100 L air sample).

Concerning personal exposures, direct reading pocket dosimeters may be used, as is described in a protocol, called ‘Voornorm NVN 2950’, from the Dutch Normalisation Institute (NNI90).

2.4.2 *Biological monitoring*

No method is established for assessing a biological index of exposure.

Chapter 3

Sources

3.1 Natural occurrence

Gaseous sulphur dioxide is emitted mostly by volcanic activity and being a combustion product, it may be released into the atmosphere by natural fires.

3.2 Man-made sources

3.2.1 Production

Sulphur dioxide is produced by: combustion of sulphur; roasting of sulphide ores (iron pyrites); and by calcination of natural sulphates. The gas thus obtained is purified, liquefied, and stored in special containers or converted to sulphuric acid in suitable industrial facilities.

Sulphur dioxide is generally available as a compressed gas (Bur95), in industrial or commercial grade (99.98% pure), with a moisture content set at 100 ppm max. There is also a refrigeration grade with a maximum water content set at 50 ppm.

The committee did not find information on the production of sulphur dioxide in the European Union countries. In the USA, in 1990, sulphur dioxide was produced at a level of 290 thousand tonnes (IAR92).

3.2.2 *Use*

Sulphur dioxide has various commercial uses. The dominant uses of sulphur dioxide are as a captive intermediate in the production of sulphuric acid and in the pulp and paper industry for sulphite pulping. Other uses are found within (SCO93, IAR92, Bur95):

- the chemical industry: intermediate production of bleaches; reducing agent;
- the food processing, beverage industry and agriculture: fumigant; preservative; bleach and steeping agent for grain; disinfectant; antioxidant;
- the oil refining industry: elimination oxygen in petroleum of deep deposits; extraction solvent; co-catalyst;
- the mineral industry: flotation depressants for disulphide ores; reduction of ferric to ferrous ions;
- the bromine industry: antioxidant;
- the water treatment: reduction of residual chlorine after chlorination; antioxidant.

No quantitative data is available on the use of sulphur dioxide in the Netherlands or other European countries.

Chapter 4

Exposure

4.1 General population

In Europe, emission of sulphur dioxide from industry and energy producing plants has been considerably decreased over the last two decades. In the Netherlands, the total annual emission of sulphur dioxide in the atmosphere decreased from 487 thousand tonnes in 1980 to 91 thousand tonnes in 2000. Of the latter, 55% is emitted by industry, 26% by automobiles and 15% by power plants (RIV01).

As a result of the reduced production and emission, the ambient air concentration of sulphur dioxide has also considerably decreased: in Europe with 40% over the last two decades. In the Netherlands in 1997, ambient air concentrations of sulphur dioxide averaged 6, 9 and 10 $\mu g/m^3$, measured over one year in the countryside, streets and cities, respectively; with 24-hour peaks of 100, 90 and 60 $\mu g/m^3$ and one-hour peaks of 270, 210 and 210 $\mu g/m^3$, respectively (RIV00).

Indoor concentrations of sulphur dioxide are generally lower than outdoor concentrations, because sulphur dioxide absorption occurs on walls, furniture, clothes and in ventilation systems (WHO87).

4.2 Working population

Sulphur dioxide may be present in industrial environments, arising from processes in which the gas is handled or evolved, and from combustion sources. The number of workers worldwide exposed to sulphur dioxide has been estimated to be several

millions. For instance, in the USA, NIOSH estimated that about 500,000 workers were exposed in 1974; the corresponding figure in Finland was 10,000 in 1991 (IAR92). No data is available on the number of occupationally exposed workers in the Netherlands.

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. The main limitations relate to: sizeable fluctuations in concentration levels in the workplace; variations in exposure duration; the quality of the monitoring techniques which has varied over the years; concurrent exposure to other gaseous chemicals or particulates; and, absence of source specification of sulphur dioxide release (IAR92, SCO93).

IARC (IAR92) and the SCOEL (SCO93) reviewed papers on exposure levels of sulphur dioxide in the workplace. These papers were published before 1991. Below, a summary of their findings is given.

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 (Ska64).

Covering the period of 1940-1986, mean levels of sulphur dioxide were lower than 2.6 mg/m^3 in nickel, zinc, aluminium smelters and steel mills, but between 2.6 and 26 mg/m^3 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/m^3: 7.7 mg/m^3 (beverage industry); between less than 3 and 5 mg/m^3 (sulphuric acid plants, long-term measurements); and, <2.6 mg/m^3 (*e.g.* close to diesel engines, photographic laboratories, mineral fibre plant). Moreover, in all these industries peak exposure have been observed. More detailed information on exposure levels can be found in the publications of Kangas (Kan91) and FIOH (FIO90).

More recently, Benke *et al*. (Ben98) 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*. (Cha89) was discussed. They reported a mean of 2.0 mg/m^3 (n=121, TWA 8 hours) for measurements undertaken in 1980 compared to 2.1 mg/m^3 (n=53) for the same smelter in 1986. However, Kongerud and Ramjør (Kon91) and Desjardins *et al*. (Des94) measured lower levels: 0.42 mg/m^3 (breathing zone samples, n=75, Norway) and 1.0 mg/m^3 (0.4 ppm, Canada), respectively.

In 1999, Teschke *et al*. (Tes99) 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/m^3 (7.1 ppm, maintenance, construction, cleaning, n=40); 19.5 mg/m^3 (7.3 ppm, storage, yard, loading, shipping, n=11); 1.9 mg/m^3 (0.71 ppm, steam and power generation, n=45); and, 0.013 mg/m^3 (0.005 ppm, effluent water treatment, n=39). However, most of the samples were below detection limit (limit not given). Hence, no further measurements was undertaken for sulphur dioxide.

Chapter 5

Kinetics

5.1 Absorption

Sulphur dioxide is a highly water-soluble gas. As a result, the substance is rapidly absorbed in the moist upper respiratory tract after inhalation, as was shown in both man and mammals (Spe66a/b, Bal60). Sulphur dioxide may reach the lower respiratory tract by oral inhalation and deep breathing, for instance during doing heavy work or exercise. When rabbits were exposed to a concentration of 2.7 mg/m^3, 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/m^3 (Str64).

In the moist mucous membranes, sulphur dioxide is rapidly hydrated to sulphurous acid (H_2SO_3). This sulphurous acid dissociates easily into sulphite (SO_3^{2-}) and bisulphite (HSO_3^-) ions. Sulphite ions are then rapidly converted into sulphate, whereas bisulphite ions bind to proteins to form S-sulphonates (IAR92).

5.2 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 after tracheotomy, most of the substance concentrated 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 were found in the liver, spleen and cardiac muscles (Bal60).

In the blood, a main part of sulphur dioxide is bound to serum proteins as S-sulphonates (Gun71, Men86). Free sulphur dioxide is transported almost totally as bisulphite.

5.3 Biotransformation

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 (IAR92).

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 (Yok71).

5.4 Elimination

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 (Bal69, Fra69).

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 (Cal81).

5.5 Possibilities for biological monitoring

Given the toxicokinetic characteristics of sulphur dioxide described previously, 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.

5.6 Summary and evaluation

Sulphur dioxide is highly soluble in aqueous media. On contact with the moisture of the nasal mucosa, sulphur dioxide is rapidly hydrated to sulphurous acid, which quickly dissociates into sulphite and bisulphite ions. Once absorbed, sulphite is oxidised into sulphate, and bisulphite is covalently bound to plasma and cellular proteins to form S-sulphonates. Sulphates become part of the large sulphate pool within the body, from which it is slowly released and primarily excreted from the body in the urine. Circulating S-sulphonates decompose into sulphur dioxide, which is then exhaled, or into sulphate.

Chapter 6

Effects

Numerous studies have been published on the adverse effects of sulphur dioxide inhalation. In addition, the committee derived data for this report primarily from the SCOEL documents (published in 1993 and 1997), supplemented with recent publications. Furthermore, the committee restricted its assessment to low exposure concentration data.

6.1 Observations in humans

6.1.1 Irritation and sensitisation

Irritation

Sulphur dioxide is irritating to the eyes and upper respiratory tract, such as the nose and throat (SCO93, Dou87). Inhalation of sulphur dioxide at a concentration of 10.7 mg/m^3 (6 ppm) or higher, caused instantaneous mucous membrane irritation. This is accompanied with symptoms, including: ocular irritation and lacrimation; rhinorrhae; coughing; shortness of breath; chest tightness or discomfort; and, a choking sensation (Sul92). At very high concentrations (SCO93, no levels reported), the absorption capacity of the upper respiratory airways may be exceeded, resulting in pathological changes that include: laryngotracheal and pulmonary oedema; and, symptoms, such as bronchoconstriction. These pathological changes and symptoms may result in death. In fact, in the general population, a clear positive association has been reported between

those pathologies and day-to-day changes in hospitalisation rates and deaths (And97). The day-to-day changes are the result of the daily variations in the outdoor concentration of sulphur dioxide.

Concerning the mechanism of bronchoconstriction, it is thought that sulphur dioxide stimulates irritant receptors, present in the epithelium of the upper airways (Cos99). Stimulation of these receptors activates the nerve endings of involuntary muscles in the bronchi, resulting in bronchoconstriction. Atropine, a sympathetic cholinergic blocking 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 (Nad65). However, when given to exposed asthmatics, atropine was only partial effective (Kor79). The difference in reaction between normal and asthmatic people is still not clarified.

Liquid sulphur dioxide may cause frostbite or severe corneal damage by direct contact on the skin and eyes, respectively (Bur95).

Sensitisation

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'Am02a and D'Am02b).

6.1.2 Toxicity due to acute and short-term exposure

Healthy subjects

A summary of the most relevant studies with healthy persons is given in Annex F.

In a double-blind study, twelve normal and twelve mildly asthmatic adults, all non-smokers, were exposed 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. Therefore, they cannot exclude the possibility that asthmatic subjects with a heart disease may develop serious health problems (Tun01).

The committee noted that spectral analysis of heart rate variability is an extremely sensitive parameter, which currently is hard to extrapolate to chronic effects observed in humans. Moreover, the effects of sulphur dioxide on heart rate variability in healthy subjects were more positive than negative, while for asthmatic subjects they were uncertain. The committee, therefore, believes that this study is of little relevance for risk assessment.

Weir *et al*. (Wei72, abstract only) reported on four groups of three healthy males, who were continuously exposed in randomised sequence for 120-hour periods to 0, 0.8, 2.7 and 8.0 mg/m^3 (0, 0.3, 1.0 and 3.0 ppm) sulphur dioxide. No dose-related changes were observed concerning subjective complaints, clinical evaluation and most pulmonary function measurements. The only significant but minimal effect observed by the authors was decreased airway conductance and compliance at 8 mg/m^3, which returned to normal after stopping the exposure.

Sandström *et al*. (San88) 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 was 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.

Islam *et al*. (Isl92) examined the acute bronchomotoric effects of a low concentration of sulphur dioxide in twenty-six young, non-smoking volunteers (9 females, 17 males; age range: 15-26 years). Half of them performed eucapnic hyperventilation with dry filtered air via a mouthpiece for 5 minutes. This procedure was repeated thirty minutes later, but this time with 1.6-2.0 mg/m^3 sulphur dioxide (exact concentration not given). The other half of the volunteers did the same, but in reverse order (first sulphur dioxide exposure and then filtered air). Specific airway resistance measurements were taken before, immediately, 10 and 20 minutes after each eucapnic hyperventilation. Following hyperventilation with or without sulphur dioxide, all subjects showed variable degrees of bronchoconstriction. However, the authors found a stronger increase of specific airway resistance with sulphur dioxide than without (p<0.01). Also, the authors considered 13 out of the 26 subjects as responders (3

females, 10 males), because they showed a more than 100% increase in specific airway resistance (sRaw). The mean increase in specific airway resistance was significantly higher in these responders than in the non-responders ($p<0.001$). All values tended to return to normal 20 minutes after the last exposure.

Two years later, the same group of investigators reported on a second study with comparable results (Isl94). In the second study, 37 healthy non-smoking volunteers were exposed to 1.9 mg/m^3 for 5 minutes during eucapnic hyperventilation. Three minutes after ending the exposure the specific airway resistance was significantly increased. After stopping the exposure, values returned to normal between 20 and 40 minutes. Of the 37 subjects, 14 were considered responders (increase of sRaw ≥ 100%). In addition, the authors found an age dependent airway responsiveness to sulphur dioxide exposure, suggesting that airway responsiveness to sulphur dioxide is more frequent among volunteers below than above 30 years of age.

The committee noted that in both studies by Islam *et al*., none of the volunteers were exposed to sulphur dioxide while breathing normally.

In another study, healthy, non-smoking, Caucasian, male volunteers (n=11) were exposed to a single concentration of 2.0 mg/m^3 (0.75 ppm) sulphur dioxide for 4 hours while doing two 15-min exercise sessions on a treadmill (at 2 and 4 hours into exposure). Just prior to exposure (air control) 2 and 4 hours into the exposure, and 24 hours after exposure, pulmonary function was tested by spirometry. The investigators did not find any significant change in lung function, such as in airway resistance, lung volume and airflow measurement responses were observed (Sta83).

Carson *et al*. (Car87), exposed seven healthy volunteers to 2.0 mg/m^3 (0.75 ppm) sulphur dioxide for two hours. As a result of this exposure, four volunteers showed damage to the nasal epithelium. This damage was characterised as compounded cilia. Compounded cilia are fused cilia or cilia melted together, which may occur following viral infections or exposure to toxic substances. According to the authors, their results suggest that sulphur dioxide may be a causative agent in ciliary compounding in the upper respiratory tract.

The committee, however, considers these findings inconclusive, because after exposure nasal samples were taken on the contralateral nasal turbinate instead on the inferior nasal turbinate, as was done before exposure.

Fifteen healthy male subjects, four of whom were smokers, were exposed to 2.7 mg/m^3 (1 ppm) sulphur dioxide on day one; 13.4 mg/m^3 (5 ppm) on day two; and, 66.8 mg/m^3 (25 ppm) on day three, for 6 hours per day on three consecutive days (And74). Exposure to sulphur dioxide caused a dose-dependent and significant increase in nasal airflow resistance and a fall in forced expiratory volume. Even the lowest concentration caused a significant effect ($p<0.05$) compared to clean air exposure. The authors, furthermore, observed that the volunteers, when they were exposed to the

lowest concentration showed more pronounced airway resistance in the first three hours of exposure than in the last four to six exposure hours.

The committee noted that in the study no distinction was made between smokers and non-smokers.

Lawther *et al*. (Law75) conducted a series of experiments with 12 or 13 healthy persons, who were free from respiratory symptoms. They were exposed to filtered air or to 2.7 and 8.0 mg/m^3 (1 and 3 ppm) sulphur dioxide with or without forced deep breathing. Deep breathing was needed to increase penetration of sulphur dioxide into the lung. Some exposures were done in an exposure chamber, whereas other exposures were done by deep breaths from a bag containing sulphur dioxide or air. Exposure to 2.7 mg/m^3 sulphur dioxide for one hour caused no significant changes in lung function and airway resistance, with normal breathing. However, deep breathing increased airway resistance and this increased even more in volunteers exposed to 8.0 mg/m^3 with deep breathing. Apart from that, the authors observed a wide range of sensitivities to sulphur dioxide among the subjects. Also, they reported that the changes in airway resistance were short-lived.

Frank (Fra80) published a study, in which healthy volunteers (n=7; controls, n=6) were exposed to a mixture of 2.7 mg/m^3 sulphur dioxide plus 1 mg/m^3 NaCl for two hours, while doing moderate exercise (walking on an inclined treadmill at a speed increasing the minute ventilation five to six fold). In the exposed volunteers, the observed a significant increase in pulmonary flow resistance compared to the control subjects breathing clean air. Furthermore, half of the exposed subjects experienced shortness of breath and wheezing.

Kulle *et al*. (Kul84) performed a study with normal, healthy, non-smoking volunteers (n=10/sex) to evaluate the effects of sulphur dioxide on pulmonary function and non specific bronchial reactivity to methacholine. The subjects were exposed to 2.7 mg/m^3 (1 ppm) sulphur dioxide for 4 hours. The day before and the day after sulphur dioxide exposure all subjects breathed clean filtered air for 4 hours (control days). During the exposure and control days, all subjects performed physical exercise on a bicycle ergometer, two times for 15 minutes. Pulmonary function was assessed both before and after exposure. Challenges with methacholine were performed immediately after the end of each exposure. No significant changes in pulmonary function and bronchial reactivity to methacholine were observed. During exposure to sulphur dioxide, four subjects complained about upper respiratory irritation and one about eye irritation during exposure to sulphur dioxide. In a comparable study performed by the same authors, the lung function parameters $FEF_{25-27\%}$ and FEV_1/FVC were decreased 17 minutes after the start of the exposure. Also nose and throat irritation worsened. However, these changes in lung function parameters and complaints about irritation were completely gone the day after exposure (Kul86).

Young non-smoking adults (n=9) were exposed to a concentration of sulphur dioxide of 2.7 or 5.3 mg/m^3 for two hours without physical exercise, or during three 30-min sessions of physical exercise (Bed84). Of the several lung function parameters measured (thoracic gas volume, maximal voluntary ventilation, functional residual capacity), only the specific airway resistance was significantly increased from 1.77 to 1.95 cm H_2O/sec or from 1.73 to 1.88 cm H_2O/sec when exposed to 2.7 or 5.3 mg/m^3, respectively. In a subsequent study, however, no changes in airway resistance was found in volunteers (n=14) exposed to 5.3 mg/m^3 for 30 minutes while doing physical exercise (Bed89).

In two other studies, performed by the group of Sandström (San89a and b), volunteers (n=12/group) were exposed to 10 or 20 mg/m^3 (4 and 8 ppm) sulphur dioxide for 20 minutes. Before and 24 hours after the exposure, the number of alveolar macrophages were measured. A significant (p<0.01) increase in total number (0.8×10^7/L) and percentage (14%) of lysozyme positive macrophages were observed in the low-dose group compared to the values before exposure (0.4×10^7/L and 5%). Even larger increases were observed in subjects exposed to 20 mg/m^3; this was accompanied with an increase in macrophages and lymphocytes. All values returned to normal within 72 hours after exposure.

Asthmatic subjects

Several laboratory studies have been published on exposure effects of sulphur dioxide in asthmatic persons. The most relevant publications are discussed below.

In 1984, the interaction between low ambient temperature and lung function were studied in asthmatic persons. Eight asthmatics were exposed for successive 3-min periods with doubling concentrations of sulphur dioxide of 0.3, 0.7, 1.3, 2.7 and 5.3 mg/m^3, on three separate days (She84). The concentration of sulphur dioxide inducing a '100% increase of specific airway resistance' increased immediately with increasing ambient temperature: 1.36±0.53 mg/m^3, cold dry air (-20°C, 0% humidity); 1.60±1.07 mg/m^3, dry warm air (22°C, 0% humidity); and, 2.32±1.09 mg/m^3, warm humid air (22°C, 70% humidity). In these ambient conditions, breathing clean air did not change specific airway resistance values.

Linn *et al*. (Lin84a) investigated the relation between low ambient temperature (5°C), relative humidity (50% or 85%) and sulphur dioxide exposure (0.5, 1.1 or 1.6 mg/m^3). Eight asthmatic persons were exposed for 5 min, while heavy exercising. All persons showed slight exacerbated bronchial constriction, and this was independent on the relative humidity and exposure level. The authors ascribed the observed effects totally to sulphur dioxide exposure (Lin84a).

The group of Linn *et al.* (Lin87) published another study, in which healthy volunteers (n=24), atopics (n=21, not asthmatic), volunteers with minimal or mild asthma (n=16) and volunteers with moderate or severe asthma (n=24) participated. They were exposed to clean air or to concentrations of sulphur dioxide of 0.5, 1.1 and 1.6 mg/m^3 for 1 hour, while doing three 10-min periods of exercises. Normal subjects and most atopics showed little response. However, a few atopics and a lot of asthmatics developed bronchoconstriction and respiratory symptoms. The authors could not relate these effects reliably by clinical status, by responsiveness to sulphur dioxide or by exercising.

Ten volunteers with mild atopic asthma were exposed to 0.53 mg/m^3 (200 ppb) sulphur dioxide or air for 6 hours (Dev94). Ten minutes after the exposure, they were challenged with pre-determined concentrations of extracts of house dust mite (*Dermatophagoides pteronyssinus)*. Sulphur dioxide did not alter the airway response (FEV_1, FVC, and cumulative breath units of *D. pteronyssinus* allergen required to produce a 20% fall in FEV_1 ($PD_{20}FEV_1$)).

Schachter *et al*. (Sch84) examined the acute respiratory effects of sulphur dioxide in ten asthmatic and ten healthy subjects. These subjects were exposed in a double-blind random sequence to clean air, 0.7, 1.3, 2.0 and 2.7 mg/m^3 (0.25, 0.50, 0.75 and 1.0 ppm) sulphur dioxide for 40 minutes, including moderate exercise on a cycloergometer in the first 10 minutes of exposure. On a separate day, subjects were exposed to clean air and 2.7 mg/m^3 sulphur dioxide in the absence of exercise. No changes in pulmonary function tests, including airway resistance tests, were observed in healthy subjects on any day, or in asthmatic subjects at rest. However, when the same asthmatic subjects performed moderate exercise, consistent decrements in most lung functions occurred in the groups exposed to 2.0 and 2.7 mg/m^3 sulphur dioxide. At 0.7 and 1.3 mg/m^3, statistically significant changes in lung function parameters were confined to small drops in flow rates at low lung volumes.

In another study, non-smoking males (n=28), having mild asthma and being hyperresponsive to methacholine, were exposed to clean air, 0.7, 1.3 or 2.7 mg/m^3 (0.25, 0.5 and 1 ppm) sulphur dioxide with natural breathing for 75 minutes. Each exposure included three 10-min periods of moderate treadmill exercise. In subjects exposed to 1.3 and 2.7 mg/m^3, the specific airway resistance increased twofold and threefold, respectively, compared to the pre-exposure levels (clean air). In the first exercise period the increase of the specific airway resistance was higher than in the two following periods, suggesting adaptation. No significant increase was observed at 0.7 mg/m^3 compared to clean air exposure (Rog85).

A comparable study was reported by Witek and Schachter (Wit85). Asthmatic persons were exposed in double blind random order to clean air, 0.7, 1.3, 2.0 and 2.7 mg/m^3

(0.25, 0.5, 0.75 and 1 ppm) for 5 to 10 minutes. They were then asked to perform moderate exercise for 10 minutes, which was followed by a second exposure of 30 minutes. Pulmonary function was measured prior to and at several time intervals after the second exposure. On the next day, methacholine inhalation challenges were performed using progressive concentrations of up to 25 mg/mL. Lung function was assessed before and after challenges with methacholine. A significant correlation existed between the concentration of sulphur dioxide and the concentration of methacholine required to produce bronchoconstriction ($r=0.86$; $p<0.05$): the higher the response to sulphur dioxide, the higher the response to metacholine. The authors concluded that individuals with greater non-specific sensitivity might be more vulnerable to bronchospasm from elevated sulphur dioxide concentrations than normal individuals.

Young volunteers (n=24), suffering from chronic obstructive pulmonary diseases, including: chronic bronchitis; pulmonary emphysema; asthma; and, chronic bronchitiectasis, were exposed to clean air, 1.1 or 2.1 mg/m^3 sulphur dioxide for one hour, while doing two 15-min periods of mild or strenuous exercises. No statistically significant changes in physiology or symptoms could be attributed to sulphur dioxide exposure (Lin85).

Bethel *et al*. (Bet83) exposed ten persons suffering from mild asthma to 1.3 mg/m^3 sulphur dioxide for 5 minutes, while performing moderate exercise. As a result, their specific airway resistance increased from 2.24 (clean air control) to 13.55 cm H_2Oxsec ($p<0.005$). In a subsequent study with similar experimental conditions (n=9 subjects, exercising more vigorously), bronchoconstriction was also induced at 0.7 mg/m^3 (specific airway resistance from 5.23 to 12.54 cm H_2Oxsec). However, the authors found out that these inductions did not differ from the results obtained when the same persons were exposed to filtered air only (specific airway resistance from 6.71 to 13.59 cm H_2Oxsec). Therefore, they concluded that the effect of sulphur dioxide exposure on bronchoconstriction is small and largely overshadowed by the bronchoconstrictor effect of doing exercise alone (Bet85).

Asthmatic subjects (n=14) were exposed to purified air or to 1.6 mg/m^3 sulphur dioxide for 6 hours on two successive days (Lin84b). Both at the beginning (early) and 5 hours (late) after starting the exposure, the subjects exercised heavily for 5 minutes. During or immediately following early or late exercise, bronchoconstriction and lower respiratory symptoms were observed in both groups. However, the effects in the group exposed to sulphur dioxide were more marked than in the group exposure to clean air. On the second day, the symptoms were less severe than on the first day. In addition, no meaningful differences in response between early and late exercise periods on either day were observed.

Eleven volunteers with asthma were exposed to filtered air or to 2.0 mg/m^3 (0.75 ppm) sulphur dioxide for 10 minutes, while exercising. Sulphur dioxide increased

significantly the specific airway resistance and lowered, also significantly, the FEV_1 compared to air exposure. Furthermore, the total symptom score was increased (symptoms scored amongst others cough, sputum, dyspnoea, wheeze, chest tightness, and throat and eye irritation). However, the authors did not mention whether or not these parameters were significantly changed. No differences were found between air- and sulphur dioxide-exposed subjects regarding total cell counts from sputum. However, the percentage of eosinophils was significantly increased in sulphur dioxide-exposed individuals compared to clean air-exposed individuals (Gon01).

Ten asthmatic volunteers were exposed to clean air or to sulphur dioxide at a concentration of 2.7 mg/m^3 (26°C, 70% relative humidity) for 1 hour, while performing 3 sets of 10-min exercises. Their specific airway resistance increased rapidly after the start of the exposure, which persisted during the 30 minutes of exposure: from 5.4 (before exposure), 14.7 (after first exercise), 12.8 (after second exercise) to 11.1 cm H_2O/sec (after third exercise). All sulphur dioxide responses were significantly higher than the clean air responses (Keh87).

6.1.3 Case reports

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 (Ste98).

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 (Woo79).

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 (Cha79).

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 (Har83).

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 (Rab89). 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*. (Tes00). In the same review, they reported also on six cases of sulphur dioxide-induced respiratory symptoms. These cases were identified during a survey of wine cellars in the French Beaujolais district.

6.1.4 Epidemiological studies

General effects

Stjernberg *et al*. (Stj84) performed a longitudinal study in employees of a sulphite pulp factory combined with a paper mill. Of the 41 workers exposed to sulphur dioxide (concentrations not measured) in 1966, three suffered from chronic bronchitis, whereas 13 of them suffered from it in the1980 re-examination. For comparison, of the 10 control workers, who were not directly exposed to irritating gases, only two had developed chronic bronchitis in 1980.

Mortality and cancer

Lee and Fraumeni (Lee69) performed a mortality study on 8,047 white males, who worked in copper smelters in the US. The smelter workers were simultaneously exposed to inorganic arsenic and sulphur dioxide. Depending on the work area, they were categorised according to three qualitative exposure doses: light, medium and heavy. No quantitative exposure data were presented. The excess of respiratory cancer showed a gradient in proportion to the degree of exposure to arsenic and accompanied by high or moderate exposure to sulphur dioxide. The authors suggested that sulphur dioxide might have enhanced the carcinogenic effect of arsenic.

The committee noted that the authors could not make a distinction between arsenic and sulphur dioxide exposure. Also, in this study, smoking habits were not taken into account.

Years later, a new study was performed on 1,800 men, who worked in the same factory. However, now they were classified in 4 exposure categories, with respect to

arsenic and three exposure sulphur dioxide exposure categories: low, medium and high (Wel82). A clear dose-response relationship was demonstrated between arsenic exposure and respiratory cancer. 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.

Enterline *et al*. (Ent87), investigated the mortality of 6,078 male copper smelter workers, who were employed for at least three years between 1949 and 1980. They found a dose-dependent relationship between lung cancer and exposure to arsenic and sulphur dioxide. However, when smoking habits were taken into account, they found that only smoking and arsenic enhanced significantly the mortality figures of cancer.

A historical study on 400 male workers exposed to sulphur dioxide, while employed in a sulphuric acid plant in Sweden between 1961 and 1985, showed an increased mortality. The increase was mainly explained by an increase of bladder cancer. No relation could be assessed between increased mortality and the presence of non-malignant or malignant respiratory diseases. The median of the yearly time weighted averages was 9.1 (range 2.4-124) mg/m^3 at stationary sampling and 3.6 (1.1-23) mg/m^3 in the respiratory zone. Considerably higher peak levels were recorded occasionally (Eng88).

Abbey *et al*. (Abb99) studied the number of deaths in a cohort of 6,338 non-smoking California Seventh-day Adventists from 1977 through 1992. The purpose of this investigation was to study the relationship between long-term ambient concentrations of air pollutants, such as sulphur dioxide, and mortality. Estimates of monthly ambient concentrations of sulphur dioxide and other pollutants were formed for the period 1966-1992 using fixed monitor stations. The average ambient sulphur dioxide concentration between 1973 through 1992 was estimated to be 15 ± 7.5 $\mu g/m^3$ (5.62 ± 2.81 ppb). The authors identified 1,628 study subjects who died, of which 30 died of lung cancer. Sulphur dioxide was significantly associated with increased risk of lung cancer mortality in both sexes (RR males, 1.99 (95% CI, 1.24-3.20); RR females, 3.01 (95% CI, 1.88-4.84)). This effect remained stable in two-pollutant models with other pollutants. The association did not appear to be due to confounding by any of a large number of measured risk factors (*e.g*. time spent indoors, time trends, smoking in the past, food consumption) in this cohort. No associations were found for other death causes, such as cardiopulmonary mortality. The authors realised that differences could be due to measurement error and that some of the observed effects could be the result of unknown correlation among pollutants and other confounding factors.

Overall, the committee noted that, due to limitations in study design, from none of these epidemiological studies concentration-response relationships could be assessed. Additionally, of particular concern is the presence of confounding factors, such as co-

exposure, and the absence of information on smoking habits and other lifestyle factors. Also, the possible occurrence of adaptation to the irritant effect of sulphur dioxide is not well taken into account.

6.1.5 Other relevant studies

Genotoxicity

Chromosome breakages have been observed in lymphocyte cultures of healthy non-smoking human subjects exposed to various pollutants, such as sulphur dioxide, arsenic and lead (Bec86).

In workers (n=40) chronically exposed to sulphur dioxide, the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral blood lymphocytes were significantly increased compared to non-exposed workers. No significant differences were found between smokers and non-smokers (Men90).

Yadav and Kaushik (Yad96) investigated the genotoxic effects of sulphur dioxide exposure on workers of a fertiliser factory. From a total of 84 individuals, of which 42 were exposed to an average of 41.7 mg/m^3 sulphur dioxide in the ambient air, blood samples were taken and analysed. The frequency of sister chromatid exchanges and chromosomal aberrations increased significantly compared to non-exposed individuals. In addition, these frequencies increased significantly with the duration of exposure.

Although the committee takes these observations as serious, the previous two studies have some limitations. For instance, the job history was not given. For this reason, the committee considers these human genotoxicity data to be insufficient to suggest that sulphur dioxide is genotoxic in humans.

6.2 Animal experiments

6.2.1 Irritation and sensitisation

In animals sulphur dioxide is a respiratory irritant. As in humans, most of it is absorbed in the upper respiratory tract, whereas very little reaches the lungs. Detailed data on the irritant effects of sulphur dioxide are given in paragraph 6.2.3.

Riedel *et al*. (Rie88) described the effects of sulphur dioxide exposure on local bronchial sensitisation to inhaled ovalbumin antigens. Perlbright-White female guinea pigs were exposed to ambient air or to sulphur dioxide at concentrations of 0.3, 11.5 or 44.3 mg/m^3 (0.1, 4.3 or 16.6 ppm, respectively) for 8 hours per day on 5 consecutive days. On days 3, 4 and 5, the exposure was followed by nebulized ovalbumin inhalation for 45

minutes. One week after ending the last exposure, specific bronchial provocation with inhaled ovalbumin, followed by plethysmographic measurements of airway obstruction was performed every two days during a period of two weeks. Bronchial reactions to inhaled ovalbumin was demonstrated in 1/14 (control), 4/6 (0.3 mg/m^3), and all of the animals in the high-dose groups (11.5 and 44.3 mg/m^3, n=5 and 6 animals, respectively). In all sulphur dioxide-exposed groups, the degree of bronchial obstruction was significantly higher than in the control group (p<0.05). Also, the level of ovalbumin-specific antibodies in serum and bronchoalveolar fluid was significantly increased compared to the control group (p<0.05). The authors concluded that exposure to sulphur dioxide at concentrations of 0.3 and 11.5 mg/m^3 can facilitate local allergic sensitisation of ovalbumin in the guinea pig.

6.2.2 *Toxicity due to acute exposure*

The SCOEL (SCO93) reviewed numerous publications on the acute exposure of sulphur dioxide, but stated that none of them were performed according to the codes of good laboratory practice. Below are described additional studies, which are not evaluated by SCOEL.

Adult, male, Hartley guinea pigs (n=4/group) were exposed to clean air or to 1,070 mg/m^3 (400 ppm) sulphur dioxide for three hours. In the sulphur dioxide-exposed animals no damage was found in the epithelial lining or ciliated cells, although granulocyte invasion was observed in the tracheal basal membrane. Sulphur dioxide exposure significantly lowered the airway mucociliary transport velocity, a parameter for mucociliary clearance: 2.9±0.7 mm/min compared to 5.9±0.1 mm/min (control values). Even 24 hours after exposure, mucociliary transport velocity was still low (2.8±0.9 mm/min) (Kim99).

Common ground squirrels (n=5/group), which were exposed to 1,350 mg/m^3 sulphur dioxide for 4 minutes, developed lung oedema. In addition, the pulmonary surface tension, which represents the amount of cardiac lipids, and protein content of cellular membranes were significantly reduced compared to controls (Ran79).

Min *et al*. (Min94) investigated histopathologic changes in the olfactory epithelium after sulphur dioxide exposure. Female ICR mice (n=4/group) were exposed to a single dose of 53 mg/m^3 (20 ppm) sulphur dioxide for 30, 60 or 120 minutes. The mice were sacrificed immediately, 24, 48 or 72 hours following exposure. Parameters measured included: inflammatory cell infiltration; oedema; desquamation of the epithelium in the nasal cavity; and, atrophy (loss of cilia). Injuries to the olfactory epithelium became more severe when the exposure lasted longer and were most evident at 24 hours.

6.2.3 *Toxicity due to short-term exposure*

SCOEL (SCO93) described several short-term studies on various animal species. With a few exceptions, the study results described in the original papers were of limited use, because of inadequate reporting. In addition, the experimental designs did not always meet the internationally accepted standards.

Effects on the respiratory tract

The committee noted that several studies have been carried out to investigate the pathogenesis of bronchitis. In these studies, bronchitis was induced after short-term exposure by sulphur dioxide.

Tusl *et al*. (Tus83) continuously exposed mixed breed or Wistar male rats (n=not given) to 0.05, 0.5, 1.0 and 5.0 mg/m^3 sulphur dioxide for 2, 4 or 6 weeks. The observations included: reduced number, viability and adhesion capacity of isolated alveolar macrophages; changed activities of cytoplasmic lactate dehydrogenase, lysosomal galactosidase, glucosidase and acid phosphatase. The committee noted that the results were not adequately described.

Male Dunkin-Hartley guinea pigs were exposed to air (n=7) or to 0.27 mg/m^3 (0.1 ppm) sulphur dioxide (n=12) for 5 hours per day on 5 consecutive days. Other guinea pigs were also simultaneously exposed to ovalbumin aerosols. One week after the last exposure, all animals underwent bronchial challenge with 1% ovalbumin aerosols. Twenty-four hours after this challenge, bronchoalveolar lavage and histopathologic examinations were performed. None of the parameters tested, that is: airway resistance; infiltration of inflammatory cells; and, the histopathology of bronchial and lung tissue, were significantly changed after sulphur dioxide-exposure compared to animals exposed to clean air (Par01).

Ferin and Leach (Fer73) investigated the effects of exposure to sulphur dioxide on lung clearance of inert particles (TiO_2) in Long-Evans male rats. Lung clearance is part of the defensive mechanisms of the respiratory tract. The animals (n=9-10/group) were exposed to clean air or to 0.27, 2.7 and 53.4 mg/m^3 (0.1, 1.0 and 20 ppm) sulphur dioxide for 7 hours/day, 5 days/week for 10 to 25 days. The day following the last exposure, all the animals were exposed to TiO_2 aerosols (15 mg/m^3) for 7 hours. Finally, the animals were sacrificed at several time points (1 to 136 days) after TiO_2 exposure. The clearance of particles in the groups of animals exposed to the lowest dose of sulphur dioxide, as determined at day 25 after TiO_2 exposure, did not differ from the control groups (25 exposure days) or was even higher (10 and 23 exposure days). When exposed to 2.7 mg/m^3 with 10 to 20 exposure days, the clearance was at control level or

even higher. However, with 25 exposure days, the clearance of particles was statistically significantly depressed. A small but significant depression in clearance was already observed in animals exposed to 53.4 mg/m^3 sulphur dioxide with 10 exposure days.

More recently, a dose-dependent hypersecretion of the trachea was reported in male Sprague-Dawley rats (n=not given) continuously exposed to sulphur dioxide at concentrations of 13.4, 26.7, 53.4, 106.8 or 213.6 mg/m^3 for 3 to 25 days (Wag97).

Effects on other organs

Lovati *et al*. (Lov96) reported changes in fat and carbohydrate metabolism in male Sprague-Dawley CD rats (n=9/subgroup), which suffered from hypercholesterolemia and diabetes. The animals were continuously exposed to 13.4 or 26.7 mg/m^3 sulphur dioxide for 14 days. Also they were fed standard or cholesterol enriched diets. Rats showed a significant dose-dependent increase in serum triglycerides, but reduced HDL cholesterol levels compared to controls. In contrast, diabetic animals exposed to 26.7 mg/m^3 showed a fall in serum and liver triglycerides and an increase of plasma HDL cholesterol. The type of diet did not influence these results.

Male Wistar rats (n=4/group; n=8 controls) were exposed to 13.3, 133 or 267 mg/m^3 (5, 50 or 100 ppm, respectively) sulphur dioxide for 5 hours a day for 7 to 28 days. Significant evidence of lung inflammation (increase in number of neutrophil recovered by bronchoalveolar lavage) was only observed in rats exposed to 267 mg/m^3. At 13.3 mg/m^3, glutathione (GSH) pools in the lungs, the heart and the kidneys were depleted. Also, at the same exposure concentration, GSH-related enzyme activities in the lungs were lowered compared to those in control animals. However, animals exposed to 133 mg/m^3 maintained their tissue GSH status, although activities of several GSH-related enzymes were altered in the lung tissue (Lan96).

A study has been published in which male Swiss-Albino rats (n=16; n controls=14) were exposed daily to 26.6 mg/m^3 sulphur dioxide for 60 days (1 hour a day). Sulphur dioxide enhanced lipid peroxidation and influenced the activities of other antioxidant enzymes in erythrocytes. Also, GSH-related enzyme activities were altered (Güm98). Two years later, the same authors published a study in which Swiss male albino rats (total n=78), divided into three age groups (3, 12 and 24 months), were exposed daily to filtered air or to 26.6 mg/m^3 (10 ppm) air for six weeks (1 hour a day). At the end of the exposure period, animals were deprived of food for 24 hours, before blood samples were taken for analyses. Exposure to sulphur dioxide resulted in significantly lowered blood plasma levels of the antioxidants vitamin C and ceruloplasmin in all age groups, except for vitamin C levels in the 3-month old animals, compared to their corresponding controls (Güm00). In addition, under the same experimental conditions, exposure to sulphur dioxide significantly increased antioxidant enzyme activities, and decreased

glutathione peroxidase activity in the brains of all age groups. Catalase activity was not altered (Yar99).

Male Dahl rats (n=10/group), resistant (DR) or susceptible (DS) to salt-induced hypertension, were exposed to 133 mg/m^3 (50 ppm) sulphur dioxide for 31 weeks (6 h/day, 5 days/week). Subgroups of rats were maintained on either high or low salt diets. Only the blood pressure in the DS rats on a high salt-diet increased significantly compared to their air-exposed counterparts. All exposure-related differences in blood pressure disappeared after terminating the sulphur dioxide exposure. Based on these results and the fact that the authors exposed the animals at relatively high levels of sulphur dioxide (100 times ambient levels), they postulated that the influence of ambient levels of sulphur dioxide on hypertension was very low (Dre83).

Haider (Hai85) reported that the lipid profiles in brains of guinea pigs were altered, after the animals were exposed to 266 mg/m^3 sulphur dioxide for 21 days (1h/day). A few years later, the same authors published a study in which the animals, exposed to the same sulphur dioxide levels, also showed altered lipid profiles in other organs, such as in the liver, the heart, the lungs and the kidneys (Hai85).

6.2.4 *Toxicity due to long-term exposure and carcinogenicity*

General effects

Alarie *et al*. (Ala70) exposed Hartley albino guinea pigs (n=50/sex/exposure group) to clean air or to 0.35, 2.7 or 15.3 mg/m^3 sulphur dioxide for 3 months or one year (22 h/day, 7 days/week). Biological measurements included: body weight; pulmonary function tests; haematology; clinical biochemical determinations; and, histopathologic examinations. No significant differences were observed in any of the measured parameters compared to the control group after 3 months of exposure or after one year. However, the animals exposed to 15.3 mg/m^3 sulphur dioxide showed a lower incidence and severity of spontaneous disease normally present in those animals after one year. Furthermore, microscopic examinations of the liver in animals of the highest-dose group revealed an increase in the size of the hepatocytes, which was accompanied by cytoplasmatic vacuolisation.

The committee has serious doubt about the meaning of these findings in the liver. Hence, it considers this study of little relevance.

Hirsch *et al*. (Hir75) investigated the effects of sulphur dioxide on mucociliary activity. Purebred beagle dogs (n=8; n=3 controls) were exposed to clean air or to 2.7 mg/m^3 (1 ppm) sulphur dioxide by a facemask for one year (1.5 hr/day, 2 times/day, 5 days/week). As a result of the sulphur dioxide exposure, the frequency distribution curve of individual disc velocities significantly changed within a single animal. This

indicated impairment of mucociliary activity of the trachea. However, between exposed animals and controls, no significant differences in lung function or mucociliary activity were observed.

The committee noted that mucociliary impairment did not differ between the animals, but only within a single animal. In addition, the statistical power of the study is very small. The results warrant, however, further research, because mucociliary impairment may increase the susceptibility to bacterial or viral airway infections.

Lewis *et al*. (Lew73) exposed female beagle dogs (n=4/group) to 13.4 mg/m^3 sulphur dioxide on daily base for 20 months (21 h/day). No significant histological changes were observed in the lungs and the kidneys. The only significant finding was the increased mean nitrogen washouts of the lungs (p<0.01).

The committee considers these findings inconclusive, because a low number of animals were used, the description of the publication was limited, and no further details were given.

Cynomolgus monkeys (5 males and 4 females) were exposed to 13.7 mg/m^3 (5 ppm) sulphur dioxide for 78 weeks (24 h/day, daily with two interruptions/day). No harmful effects to lung mechanics, blood pressure, histology of the lung and other organs, blood count and, routine clinical blood chemistry was observed (Ala75).

The committee is uncertain about the validity of the results, because the description of the publication was limited and no further details were given.

Scanlon *et al*. (Sca87) exposed adult mongrel dogs to 40 and 133 mg/m^3 (15 and 50 ppm) sulphur dioxide through cuffed tracheostomy tubes for 2 hours per day, 4 or 5 days per week for 5 months (low exposure) or 10-11 months (high exposure). Before they were killed, the dogs were allowed to recover for 3-4 months (low exposure) or for 7-9 months (high exposure). The dogs (n=4) exposed to 133 mg/m^3 sulphur dioxide showed hypersecretion of mucous cells and respiratory airway obstruction. Closer histopathologic examinations revealed epithelial hypertrophy and increased size of mucosal glands. No inflammation or changes in response to histamine was observed. The observed effects were minimal in dogs (n=3) exposed to 40 mg/m^3 sulphur dioxide and absent in air-exposed control dogs (n not given).

The committee noted that the dogs were only exposed to high concentrations of sulphur dioxide and that the results did not demonstrate a concentration-response relationship.

Carcinogenesis

So far, only one animal study has been published on the carcinogenicity of sulphur dioxide. In this study, male and female LX mice (n = 35 males + 30 females; controls n = 41 males + 39 females), highly susceptible to the induction of lung adenomas in

response to urethane, were exposed to 1,300 mg/m^3 (500 ppm) sulphur dioxide for 10 months (300 days; 5 min/day, 5 days/week) (Pea67, IARC92). The time of tumour appearance was shorter in exposed mice than in non-exposed mice. The percentage of mice over 300 days old with lung tumours are shown in Table 6.1:

Table 6.1 Tumour development after sulphur dioxide exposure in LX mice (Pea67, IARC92).

sulphur dioxide exposure (mg/m^3)		no lung lesion	primary carcinoma	adenoma	hyperplasia
0	male (n=35)	69%	6%	31%	9%
	female (n=30)	77%	not given	17%	10%
1,300	male (n=28)	46%	7%	54%	18%
	female (n=30)	53%	18%	43%	10%

The committee noted limitations in study design, such as the use of highly susceptible animals, high exposure levels and the absence of statistical analysis. Therefore, the committee believes that no firm conclusion can be made from this study.

In the literature, it has been suggested that sulphur dioxide may have a tumour enhancing effect when animals are exposed concomitantly with known carcinogenic agents, such as benzo(a)pyrene. As a possible mechanism, the irritant effect of sulphur dioxide is mentioned. Irritation can retard the pulmonary clearance of carcinogenic agents and increase the retention time.

Regarding the tumour promoting potential, both the SCOEL (SCO93) and IARC (IAR92) evaluated the studies by Laskin *et al*. (1976) and by Gunnison *et al*. (1988). Laskin *et al*. reported the presence of squamous bronchial cell carcinoma in rats exposed to sulphur dioxide in combination with benzo(a)pyrene in conditions, in which the two substances separately did not induce bronchial cell carcinoma. The Working group of IARC noted the incomplete reporting of the experiment and the absence of survival data. In addition, Gunnison *et al*. concluded that the high incidence of tumours in the group of rats given benzo(a)pyrene alone precluded detection of an enhancing effect of sulphur dioxide on the incidence of benzo(a)pyrene-induced lung tumours.

The committee noted the incompleteness of the previous studies. For this reason, the committee cannot make a final conclusion As for whether or not sulphur dioxide may enhance or promote tumour development.

6.2.5 *Genotoxicity*

Mutagenicity

Sulphur dioxide and its sulphite and bisulphite anions, induced gene mutations in several bacterial (TA98, TA98NR and YA98DNP$_6$ strains, *Escherichia coli*), lambda phage and yeast (*Sacharomyces cerevisiae*) systems (Pag87, IARC92, SCO93, Wol86). However, not all data presented in the literature were positive. For instance, in a *Salmonella typhimurium* (TA98) mutagenesis test system, sulphite was neither toxic nor mutagenic to the bacteria under the experimental conditions (Ree87), whereas sulphite enhanced the mutagenicity of a benzo(a)pyrene derivate.

In vitro mammalian cell systems

In vitro studies on a variety of cellular models, such as hamster foetal pulmonary cells and rat hepatocytes, have shown that sulphur dioxide reduces the proportion of single-chain DNA breakages. On the other hand, it did not amplify DNA in Chinese hamster cell line CO 60, whereas the known nitrosamine carcinogens did (Poo88a/b).

In vivo tests

Recently, Meng *et al.* (Men02) published the results of a study on the clastogenic and genotoxic effects of sulphur dioxide. Male and female Kunming mice (n=10/sex/group) were exposed to filtered air or to 14, 28, 56 or 84 mg/m^3 sulphur dioxide for 4 hours a day for seven consecutive days. A full day after the end of the experimental period the animals were killed. In both male and female mice, the frequencies of the micronuclei in the polychromatic erythrocytes from the bone marrow increased significantly with increasing concentrations of sulphur dioxide. The authors concluded that sulphur dioxide has clastogenic and genotoxic properties.

Miscellaneous

Sulphur dioxide induced chromosomal aberrations in *Tradescantia paludosa* and *Vicia faba*, and micronuclei in *Tradescantia paludosa* (IARC92).

Mallon and Rossman (Mal83) observed that when bisulphite (100 mM) was added to a reaction mixture of activated thymus DNA, it inhibited almost totally the incorporation of nucleotides. Based on these findings, the authors suggested that binding

of bisulphite to DNA polymerase enzymes reduces its activity and enhances the mutagenic capacity of bisulphite.

6.2.6 *Reproductive toxicity*

Murray *et al*. (Mur79) studied the embryotoxic and teratogenic effects of sulphur dioxide in New Zealand white rabbits (n=20/group) and in virgin CF-1 mice (n=35-40/ group). The rabbits and mice were exposed to 187 and 67 mg/m^3 (70 and 25 ppm) sulphur dioxide, respectively, between GD 6-18 (rabbits) and GD 6-15 (mice). In both species, inhaled sulphur dioxide produced mild maternal toxicity. The few malformations that were observed in the sulphur dioxide-exposed litter did not differ from controls. However, in both species a significant increase in the occurrence of minor skeletal variants were observed (Mur79).

Petruzzi *et al*. (Pet96) exposed male and female CD-1 mice (n total=40/sex) to 0, 13.4, 32.0 or 80.1 mg/m^3 (0, 5, 12 en 30 ppm) sulphur dioxide. The exposure was started 9 days before the formation of breeding pairs and was ended at gestation day 12-14, for a total of 24 days. The exposure was near continuous, covering about 80% of the total time indicated. The adult mice showed acute transient behavioural effects, such as increased rearing and social interactions. Grooming was dose-dependently decreased. However, reproductive performance and postnatal somatic and neurobehavioral development of offspring was not affected.

Later, the same research group used the same experimental design to study the offspring's social and/or agonistic behaviour in adulthood (Fio98). At adulthood, following a 4-week isolation period, the animals underwent an aggressive encounter with non-exposed CD-1 male opponents of the same age, body weight and isolation conditions. The levels of several responses such as rattling, freezing and defensive postures were reduced by sulphur dioxide exposure, whereas offensive and attack behaviours were not significantly modified.

6.3 Other relevant studies

No other relevant studies are known.

6.4 Summary and evaluation

General toxicity

Human data

Sulphur dioxide irritates the eyes and the upper respiratory tract. Inhalation of high concentrations may cause: rhinorrhae; coughing; shortness of breath; chest tightness; and, choking sensation.

Based on epidemiologic data, investigators have reported an association between sulphur dioxide exposure and complaints, such as chronic coughing and bronchitis. Also, data obtained from the general population suggest that chronic exposure may facilitate airway infections or airway allergy to airborne allergens. However, evidence of these associations is weak, because part of these studies showed limitations in study design and a lot of confounding factors were not taken into account. These confounding factors concern lack of information on combined exposure with other toxic substances, smoking habits and other personal lifestyle factors. For these reasons, the committee considers these data inadequate for the quantitative risk assessment.

A number of laboratory studies have been performed in healthy, non-smoking volunteers to investigate the toxic effects of sulphur dioxide on the upper and lower respiratory tract. The exposures ranged from 0.53 to more than 60 mg/m^3 sulphur dioxide and lasted from a few minutes up to a few hours, with or without physical exercise. The main adverse effects that have been observed were: irritation of the upper respiratory tract and the eyes; and decreased lung function, such as increased pulmonary airway resistance. These adverse effects were clearly present when the volunteers were exposed to a concentration of 2.7 mg/m^3 or higher, but not at and below 2.0 mg/m^3. Three studies, which concern increased airway resistance or mild effects on the autonomic heart function near or below 2.0 mg/m^3, are not considered for risk assessment, because of limitations in study design or the little relevance of the findings. At 2.0 mg/m^3 two studies, independently carried out from each other, showed no changes in lung function test in volunteers exposed to sulphur dioxide for 40 minutes or 4 hours, with moderate physical exercise.

Epidemiological data obtained from the general population indicate that people with asthma or with other diseases concerning the respiratory tract are likely more vulnerable to sulphur dioxide exposure than healthy people. Accordingly, the committee has found laboratory data suggesting that asthmatics are more vulnerable, even at low exposure levels. However, numerous studies with asthmatics showed that the level of

susceptibility is strongly influenced by a variety of non-exposure factors, such as by the presence of heart diseases or other lung diseases, (forced) physical activity and, even by atmospheric conditions (dry, cold air). All these factors alone may aggravate asthma. Therefore, the committee cannot conclude whether or not asthmatics are more vulnerable to sulphur dioxide exposure in the absence of these non-specific stimuli than healthy workers. However, the committee likes to express its concern that asthmatics are at extra risk when not only exposed to sulphur dioxide, but also to these non-specific asthma-aggravating factors.

Animal data

Data from experiments in animals with acute or short-term exposure support the findings in humans, in that sulphur dioxide causes irritation to the (upper) respiratory tract and eyes. Also reported are: reduced respiratory defence mechanisms against bacterial infections; changes in lipid metabolism; and, changes in enzyme activities in liver and blood. However, the main drawback of these animal studies is the poor reporting and the very high exposure levels used (up to 267 mg/m^3 (subchronic) or >1,000 mg/m^3 (acute)). Hence, no concentration-response relationships could be established. Also, no concentration-response relationships could be established from long-term exposure. Although in these long-term studies, the exposure levels were lower (0.35 up to 133 mg/m^3), data were too limited to be useful for the quantitative risk assessment.

Carcinogenicity and genotoxicity

In a few epidemiological studies, sulphur dioxide was suspected to cause lung or stomach cancer. However, the committee considers these studies of limited use, because most workers were simultaneously exposed to various other toxic substances, such as gases, particulate compounds and metallic fumes. In addition, not always personal lifestyle factors were taken into account, such as smoking habits.

Sulphur dioxide showed to be a weak carcinogen in one mouse inhalation study. In addition, sulphur dioxide was tested as a tumour promotor when administered with benzo(a)pyrene. However, the committee believes that no firm conclusion can be made from these studies, because of the very limited study design.

Mutagenicity tests in bacteria showed positive results, but only in conditions not relevant to humans. Sulphur dioxide induced chromosomal aberrations *in vitro*, and micronuclei *in vivo* and *in vitro*.

Reproduction toxicity

In a limited number of experiments, the potential hazard of sulphur dioxide has been studied on reproduction. In litter of rabbits and mice exposed to 187 and 67 mg/m^3, respectively, minor skeletal variations were observed. This was accompanied by mild maternal toxicity. In another study, offspring of exposed mice (13.4 to 80 mg/m^3) showed no defects in reproductive performance, somatic and neurobehavioral development.

Chapter 7

Existing guidelines, standards and evaluation

7.1 General population

The Regional Office for Europe of the World Health Organisation recommended a guideline for sulphur dioxide of 0.5 mg/m^3 (0.2 ppm; 10-minute exposure limit) not to be exceeded. From this guideline, a one-hour exposure limit of 0.35 mg/m^3 (0.13 ppm) can be estimated (WHO00).

7.2 Working population

The Netherlands
In 1985, the committee published a criteria document on sulphur dioxide and recommended a health-based occupational exposure limit of 1.3 mg/m^3 (0.5 ppm, 8 h TWA) (WGD85). In 1985 the committee concluded in its criteria document that:

The critical organ is the respiratory tract, and in practice inhalation is also the sole route of exposure.

The following effects were shown in human subjects after short-term exposure. The mean NOAEL on various lung function parameters in young healthy volunteers was higher than 1.3 mg/m^3 SO_2 after 2 hours of exposure. However, specific groups of hyper-reactive subjects were not taken into consideration in these experiments. The mean minimal observed adverse effect level was estimated at a level between 2 and 3 mg/m^3 after exposure during 2 hours in young healthy volunteers exercising alternate physical activities. Exposure to 2.6 mg/m^3 SO_2 during 1 to 6 hours induced a decrease of the nasal mucous flow rate and the forced expiratory flow of the lungs (FEF25-75%) of volunteers, which were dose and time dependent.

Experimental studies on volunteers exposed to SO_2 have shown that about 10 to 20% of the so-called healthy subjects reacted stronger to irritants than the rest, even when asthmatics with symptoms were excluded.

Epidemiological studies were less useful for determining an occupational exposure limit since in most cases the population was exposed to a mixture of contaminants.

There was a report of an increased risk of chromosomal aberrations in humans, due to exposure to SO_2. However, the results were insufficiently confirmed. The possibility of a co-carcinogenic activity of SO_2 has been suggested, which needed corroboration. There was no information of effects on the reproduction due to SO_2.

Due to socio-economic constraints, however, the legally-binding Maximal Accepted Concentration (MAC) has been set at 5 mg/m^3 (2 ppm) sulphur dioxide (8-h,TWA) (SZW02).

The following evaluations were given:

European Commission
The SCOEL of the European Commission published its final document on sulphur dioxide in December 1998 (SCO98). They recommended an occupational exposure limit of 1.3 mg/m^3 sulphur dioxide (8-h TWA) and a STEL of 2.7 mg/m^3 SO_2. It was based on a LOAEL of 2.7 mg/m^3 sulphur dioxide, at which functional changes were found in healthy adult volunteers, and studies in asthmatics showing no appreciable effects at exposures from 0.7 to 2.0 mg/m^3 sulphur dioxide.

Sweden
In 1985, the Swedish National Board of Occupational Safety and Health published a consensus report on sulphur dioxide (Lun85). They based their OEL on a study describing direct irritation of the nose and throat, and a gradual increase of pulmonary resistance in subjects exposed to sulphur dioxide. The critical effect was pulmonary resistance, although this effect was reversible in experimental animals exposed to low levels. The current occupational exposure limits for sulphur dioxide in Sweden are 5 mg/m^3 (8-h, TWA), and 13 mg/m^3 (Ceiling) (SNB00).

The USA - ACGIH
The American Conference of Governmental Industrial Hygienist revised the TLV for sulphur dioxide in 1992. They recommended a TLV of 5.2 mg/m^3 (2 ppm) sulphur dioxide (8-h, TWA) and a STEL of 13.4 mg/m^3 (5 ppm) (ACG02), because sulphur dioxide was classified as a ‘mild’ respiratory irritant, and inhalation of 13.4 mg/m^3 sulphur dioxide or more induced bronchoconstriction in humans. It was estimated that a

worker inhaling 10.7 mg/m^3 sulphur dioxide for 8 hours and performing light work would absorb approximately 140 mg sulphur dioxide.

IARC
In 1992, the IARC (IARC92) published an evaluation on the carcinogenic risks of sulphur dioxide, sulphites and bisulphites (see also annex E for a summary). The IARC concluded that 'there is limited evidence of the carcinogenicity in experimental animals of sulphur dioxide. Because there is, moreover, inadequate evidence of the carcinogenicity in humans, IARC concluded that sulphur dioxide, sulphites and bisulphites are not classifiable As for their carcinogenicity to humans (Group 3)'.

The occupational exposure limits of sulphur dioxide in other countries are presented in Table 7.1.

Table 7.1 Current occupational exposure limits (OEL's) for sulphur dioxide.

Country -organisation	OEL		TWA	Type of OEL	Note	Year of adoption	Reference
	ppm	mg/m^3					
The Netherlands							
- Ministry	2	5	8 h	legal MAC	-	1985	SZW02
- DECOS	0.5	1.3	8 h	HBROEL	-		WGD85
	1.0	2.6	15 min	Short-term	-		WGD85
Germany							
- DFG MAK-kom.	0.5	1.3	8 h	MAK	C[b]	2000	DFG02
	1.0	2.7	-	Ceiling[a]	-	2000	DFG02
The United Kingdom	2	5.3	8 h	OES	-	1991	HSE02
	5	13	15 min	Short-term	-	1991	HSE02
Sweden	2	5	8 h	OEL	-	1987	SNB00
	5	13	-	Ceiling	-	1987	SNB00
Denmark	0.5	1.3	8 h	OEL	-	1996	Arb02
The USA							
- ACGIH	2	5.2	8 h	TLV	A4[c]	1996	ACG02
	5	13	15 min	STEL	A4[c]	1996	ACG02
- OSHA	5	13	8 h	PEL		1993	ACG02
- NIOSH	2	5	10 h	REL		1988	ACG02
	5	13	15 min	STEL		1988	ACG02
European Union							
- SCOEL	0.5	1.3	8 h	OEL	-	1998	SCO98
	1.0	2.7	15 min		-	1998	SCO98

[a] Momentary value should not be exceeded at any time.
[b] Pregnancy risk group C: there is no reason to fear a risk of damage to the embryo or foetus when MAK and BAT values are observed.
[c] A4 designation refers to "not classifiable as human carcinogen" (group 3).

Chapter 8

Hazard assessment

8.1 Hazard identification

Inhaled sulphur dioxide affects mainly the upper respiratory tract and to a lesser extent the lower part of the respiratory tract. This is caused by the fact that sulphur dioxide is highly water soluble and thus quickly absorbed by the nasal mucosa. However, lung absorption is increased when sulphur dioxide is deeply inhaled through the mouth, for instance during physical exercise or heavy work.

Symptoms after acute exposure include: rhinorrhae; coughing; shortness of breath; and, chest tightness. Also symptoms on the eyes are reported, such as ocular irritation and lacrimation. Several human and animal studies have been presented, in which effects on lung function, including airway resistance, nasal irritation and other adverse health effects of sulphur dioxide have been investigated. The following paragraphs contain short evaluations on the relevant toxic effects of sulphur dioxide after single en repeated exposure.

Single and short-term repeated exposure

A number of laboratory studies in healthy volunteers associate acute exposure to sulphur dioxide with: upper respiratory tract and eye irritation; reduced lung function; and, enhanced pulmonary and nasal airway resistance. In more detail, volunteers were exposed to low concentrations of sulphur dioxide for minutes to several hours under controlled conditions. At 2.7 mg/m^3, several investigators, but not all, reported

increased nasal irritation or pulmonary airway resistance. No such effects on respiratory function have generally been described at an exposure level of 2.0 mg/m^3 sulphur dioxide or lower, with the exception of three studies (Isl92, Isl94 and Tun01). However, the committee did not include these three studies, because of limitations in study design and lack of toxicological relevance. For instance, the mild effects on the autonomic heart function observed in healthy and asthmatic subjects at 0.53 mg/m^3 were considered of little relevance, because they did not lead to visible changes in heart and lung functions (Tun01). Concerning the other two studies, both from the same research group (Isl92, Isl94), no control exposure at rest was included and the exposure itself was limited; subjects had been exposed to 1.6-2.0 mg/m^3 (exact concentration not given) for only 5 minutes under forced eucapnic hyperventilation.

Animal studies support the findings in humans, in that acute and subchronic exposure to sulphur dioxide causes irritation to the respiratory tract and eyes. At high exposure (13 and 267 mg/m^3), also signs of secondary infections and systemic effects, such as on the cardiovascular system (>100 mg/m^3) and on the lipid metabolism have been found. However, in none of these studies clear concentration-response relationships were reported.

Long-term repeated exposure

Epidemiological studies have reported an association between chronic exposure to sulphur dioxide and chronic coughing or bronchitis. Furthermore, data from the general population suggest that chronic exposure to air pollutants, such as sulphur dioxide, may facilitate airway infections or allergy to airborne allergens. However, limitations in the design of these studies preclude using these data for deriving a health-based recommended exposure limit (HBR-OEL). Of particular concern is the possibility of confounding from co-exposures to other toxic substances. Also failure to control adequately for smoking, other lifestyle factors and for adaptation is a point of concern. Hence, epidemiologic data are insufficient for quantitative risk assessment.

A few long-term animal studies have been carried out with low exposure levels. Unfortunately, also in these type of studies clear concentration-response relationships were reported.

Asthmatics

Available data do not indicate that at low exposure concentrations, persons with asthma are more vulnerable to sulphur dioxide. However, when other factors are involved, such as the presence of other lung diseases or heart diseases, or when doing heavy physical

exercise, asthmatic persons could be more at risk to sulphur dioxide exposure than normal healthy persons.

Carcinogenesis

In a few epidemiological studies, sulphur dioxide was suspected to cause lung and stomach cancer. However, for the committee it is unclear to what extent these cancers may be attributable to sulphur dioxide exposure, since combined exposure with other substances, smoking habits and other lifestyle factors were not taken into account. Few animal studies have been directed at the carcinogenicity of sulphur dioxide. Although tumour formation was observed, the studies were very limited, in that for instance highly susceptible animals and high exposure levels were used. In addition, a few studies on the tumour promoting activity of sulphur dioxide were incomplete. For these reasons, the committee considers these studies inadequate to draw any conclusion about the carcinogenicity of sulphur dioxide in humans.

Mutagenicity tests in bacteria were positive, but only in conditions not relevant to humans. Furthermore, sulphur dioxide induced chromosomal aberrations *in vitro,* and micronuclei *in vivo* and *in vitro*.

Overall, since data are limited, the committee is not able to make a definite conclusion about the carcinogenic potential of sulphur dioxide in humans. It, therefore, recommends not classifying sulphur dioxide.

Reproduction toxicity

Sulphur dioxide has been insufficiently investigated to allow any conclusion to be made, as for whether or not the substance causes adverse effects on reproduction or on the development of the offspring.

Conclusion

From the current data, the committee concludes that the acute effects on the respiratory tract, such as nose and throat irritation, depressed lung function and increased airway resistance, should be prevented. Therefore, the committee recommends deriving a health-based recommended occupational exposure limit for short-term exposure (STEL, 15-min TWA). This STEL is derived from human data obtained from single-exposure studies.

8.2 The derivation of an HBR-OEL

Overall, the committee considers the exposure level of 2.0 mg/m^3 as the no-observed-adverse effect level (NOAEL) for short-term exposure (see Table in annex F). This NOAEL is derived from two studies, one published by Stacy *et al*. (Sta83) and the other by Schachter *et al*. (Sch84). In the study by Stacy *et al.,* healthy volunteers were exposed for 4 hours, whereas in the study by Schachter *et al*., they were exposed for 40 minutes. In both studies, moderate physical exercise sessions were included and lung function tests were performed before and after exposure.

The committee adjusted the NOAEL by a factor of 3 for possible differences between individuals. This factor was included, because of the limited number of studies and the limited number of participants in those studies. In addition, referring to the studies by Islam *et al*. (Isl92, Isl94), data show variation in responses in the normal population under certain circumstances. Thus, the committee proposes a health-based recommended occupational exposure limit for sulphur dioxide to be at 0.7 mg/m^3 (0.3 ppm), as a 15-minute time weighted average concentration (15-min TWA, STEL).

This STEL value is lower than the one recommended by the committee in 1985 (2.6 mg/m^3). However, at that time fewer data were available and variations between individuals were not taken into account. Furthermore, in the old report, the committee commented that the STEL value of 2.6 mg/m^3 was probably not low enough to protect the most sensitive workers. Also, the STEL value differs from the one recommended recently by the SCOEL (2.7 mg/m^3). Yet, this is well explained by the way the evaluations are carried out (see section 7.2, European Commission).

Both epidemiological and animal data suggest that chronic exposure to sulphur dioxide may lead to chronic irritation (bronchitis) and increased susceptibility to airway infections. According to the committee, this warrants the need for deriving a health-based recommended exposure limit (HBR-OEL) to prevent chronic adverse health effects. However, the committee did not find reliable data from epidemiological studies. In addition, animal data on long- and mid-term exposure were insufficient to allow any scientific conclusion to be made on the concentration-response relationships. For this reason, the committee does not recommend an HBR-OEL (8-h TWA). Further studies on the long-term concentration-response relationships in both human and animals are needed.

8.3 Groups at extra risk

Workers with a history of asthma are at higher risk when not only exposed to sulphur dioxide, but also to other (non-specific) factors, which incite asthma. Also, the committee cannot exclude that workers with ischaemic heart diseases may be more vulnerable.

8.4 Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Standards recommends a health-based occupational exposure limit for sulphur dioxide of 0.7 mg/m^3 (≈0.25 ppm), with a 15-minute time weighted average (15-min TWA) (STEL).

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A	Request for advice
B	The Committee
C	Comments on the public review draft
D	Recommendations from the SCOEL for sulphur dioxide
E	IARC Monograph
F	Summary of data concerning acute physical effects in healthy humans
G	Abbreviations
H	DECOS-documents

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances in the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality in the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the

case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- LJNGM Bloemen
  epidemiologist; Dow Benelux NV, Terneuzen
- PJ Boogaard
  toxicologist; Shell International Petroleum Company, The Hague
- PJ Borm
  professor of inhalation toxicology; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- DJJ Heederik
  epidemiologist; IRAS, Utrecht University, Utrecht
- AAJP Mulder, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- TM Pal
  occupational physician; Netherlands Centre for Occupational Diseases, Amsterdam
- IM Rietjens
  professor of toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- RA Woutersen,
  toxicologist and pathologist; TNO Nutrition and Food Research, Zeist
- P Wulp
  occupational physician; Labour Inspectorate, Groningen
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- JM Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of the present advisory report was prepared by AAE Wibowo, PhD, of the Coronel Institute, Academic Medical Center of Amsterdam, the Netherlands, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: R Aksel-Gauri en F Smith.
Lay-out: J van Kan.

Annex C

Comments on the public review draft

A draft of the present report was released in 2002 for public review. The following organisations and persons have commented on the draft document:

- RD Zumwalde, L Murthy and GK Hatfield
  National Institute for Occupational Safety and Health, USA
- PE Schwarze, JA Holme and M Refsnes
  Norwegian Institute of Public Health, Norway
- JJH Koning
  VNO-NCW, The Netherlands

Annex **D**

Recommendations from the SCOEL for sulphur dioxide

SCOEL/SUM/27final, December 1998

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

Substance:

Sulphur dioxide:	SO_2
Synonyms:	Sulphurous oxide, sulphurous anhydride, sulphur oxide,
EINECS N°:	231-195-2
EEC N°:	016-011-00-9
Classification:	T; R23, Xi; R36/37
CAS N°:	7446-09-5
MWt:	64.06
Conversion factor (20°C, 101 kPa):	2.66 mg/m^3 = 1 ppm

Occurrence/use:

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. It has a vapour density of 2.26 times that of air at 0°C. The odour threshold is about 3-5 ppm (8-13 mg/m^3).

Sulphur dioxide is a normal component of air due to emissions from natural sources (volcanic activity and forest fires) and industrial activities. It 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. Highest exposures are generally encountered during manufacture of cellulose pulp.

Health Significance:

Sulphur dioxide is highly water soluble and, on inhalation, a large proportion is absorbed through the nasal mucosa (Speizer and Frank, 1966). 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. Sulphite is converted to sulphate by the action of sulphite oxidase and individuals deficient in this enzyme constitute a higher risk group (Calabrese *et al*, 1981).

The critical effect of sulphur dioxide is irritation of the upper respiratory tract. In most epidemiological studies, the workers were exposed to complex mixtures of sulphur dioxide with particulate material, 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 NaCI 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 (Stacey *et al*, 1983). However, electron microscopic examinations 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).

Asthmatic subjects are a high risk group with respect to sulphur dioxide. Effects are exacerbated by increasing levels of exercise. 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 bronchoconstricting 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 suggest 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.

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). 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). No relevant positive results have been identified in animal studies (Renner and Wever, 1983). Among the human studies there are a lot of 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). Therefore, genotoxicity of SO_2 is not relevant in the establishment of an occupational health-based limit value.

Recommendation:

Effects on lung function in healthy people are associated with exposures in the region of 1 ppm or more. However, individuals with compromised respiratory function (asthmatics or persons with chronic bronchitis) represent a large and increasing proportion of the working population, which has to be considered in setting an occupational exposure limit for the general workforce.

In this context, the study reported in Frank (1980), showed functional changes in healthy adult volunteers exposed to sulphur dioxide at 1 ppm (2.7 mg/m^3), which could be considered an LOAEL. Studies in asthmatics have shown no appreciable effects in the region of 0.25 to 0.75 ppm (0.67 to 2.0 mg/m^3). Taking into account all of the available data, an 8-hour TWA of 0.5 ppm (1.3 mg/m^3) is recommended. A STEL (15 mins) of 1.0 ppm (2.7 mg/m^3) is proposed to limit peaks in exposure which could result in irritation. No skin notation was considered to be necessary.

It should be noted that the proposed values should afford protection to most, but not all, individuals suffering from bronchial asthma or chronic bronchitis. At the levels recommended, no measurement difficulties are foreseen.

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Annex **E**

IARC Monograph

Summary of data reported and evaluation of sulfur dioxide and some sulfites, bisulfites and metabisulfites (Volume 54, 92).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Sulfur dioxide is produced commercially by burning sulfur or various sulfides or by recovering it from flue gases or non-ferrous metal smelting gases. Large quantities are used as intermediates in the manufacture of sulfuric acid and sulfite pulp. It is also used in agriculture and in the food and beverage industries as, among other things, a biocide and a preservative. Sulfite pulp workers have been exposed to fluctuating levels of sulfur dioxide, often exceeding 10 ppm (26 mg/m^3), but levels have decreased with modernization of facilities and processes. In metal industries, the roasting of ores and the combustion of various sulfur-containing fuels have resulted in mean exposures to sulfur dioxide in the range of 1-10 ppm (2.6-26 mg/m^3) in copper smelters, but at about 1 ppm (2.6 mg/m^3) or less in other facilities. Mean levels exceeding 1 ppm (2.6 mg/m^3) have also been reported in the manufacture of sulfuric acid and of superphosphate fertilizers, as weIl as at certain fire sites during fire fighting. Levels of sulfur dioxide in ambient air do not usually exceed 0.05 ppm (0.1 mg/m^3), except in same urban areas.

Sodium sulfite is used mainly in the pulp industry. Both sodium and potassium metabisulfure are used in food processing, chemical industries, water treatment.

photoprocessing and the textile industry. Levels of occupational exposure have not been reported.

5.2 Human carcinogenicity data

In four US and one Swedish cohort studies of copper smelters, increased lung cancer risks were observed in relation to exposure to arsenic, but no independent effect of sulfur dioxide was seen.

One proportionate mortality Study from the USA and Canada, as well as two US and one Finnish cohort studies, analysed cancer risks among sulfite pulp mill workers. Three of them suggested an increase in risk for stomach cancer; however, potential confounding factors were not adequately controlled. Lung cancer risks were not elevated in any of these studies.

In case-control studies performed at a chemical facility in Texas with a complex exposure environment, increased risks for lung cancer and brain tumours were indicated in workers with high exposure to sulfur dioxide; however, the findings using two different control groups were not consistent.

A population-based case-control study from Canada suggested an increased risk for stomach cancer in men exposed to sulfur dioxide, but no excess was indicated for lung cancer.

No epidemiological study was available on cancer risks associated with exposure to sulfites, bisulfites or metabisulfites.

5.3 Carcinogenicity in experimental animals

Sulfur dioxide was tested for carcinogenicity in one study in mice by inhalation exposure. A significant increase in the incidenc8 of lung tumours was observed in females.

Sulfur dioxide was tested for enhancement of carcinogenicity when administered with benzo[*a*]pyrene in two studies in rats and in one study in hamsters. One incompletely reported study found an increase in the incidence of lung tumours in rats exposed to sulfur dioxide in conjunction with benzo[*a*]pyrene. The other study in rats suffered from limitations owing to the high incidence of lung tumours in controls given benzo[*a*]pyrene. The study in hamsters was inadequately reported.

Potassium metabisulfite was tested for carcinogenicity in one study in mice by oral administration in the drinking-water and *sodium metabisulfite* in one study in rats by oral administration in the diet. No increase in tumour incidence was observed in mice, and there was no indication of a dose-related increase in tumour incidence in rats, but bath studies had same inadequacies in reporting of data.

Potassium metabisulfite was tested for enhancement of carcinogenicity in one study in rats. It significantly increased the incidence of gastric adenocarcinoma after initiation with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine.

No data were available on the carcinogenicity in experimental animals of sulfites or bisulfites.

5.4 Other relevant data

At high concentrations, sulfur dioxide irritates the upper airways and can induce acute and chronic bronchitis. At lower levels (less than 0.25 ppm [0.65 mg/m^3]), no effect of sulfur dioxide is seen on the airways of sensitive individuals in the general population who take exercise, presumably since this relatively hygroscopic gas is removed by the nose and mouth.

Conflicting results for the induction of chromosomal aberrations in lymphocytes were obtained in two studies of workers exposed to sulfur dioxide, among other agents. In a single study, no increase was reported in the frequency of sister chromatid exchange in lymphocytes of exposed workers.

Sulfur dioxide and its aqueous forms did not induce sister chromatid exchange, chromosomal aberrations or micronucleus formation in bone marrow of mice or Chinese hamsters. In a single study, sister chromatid exchange and chromosomal aberrations were induced in human lymphocytes. In cultured mammalian cells, bisulfite induced transformation and sister chromatid exchange but not gene mutation, chromosomal aberrations or DNA repair synthesis. In plants, chromosomal aberrations, micronuclei and gene mutation were induced. Sulfur dioxide and bisulfite induced gene mutation but not gene conversion in yeast. Mutations were induced in bacteria and phage.

Bisulfite solutions at high concentrations caused deamination of cytosine in DNA *in vitro.*

5.5 Evaluation

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)*.

Annex **F**

Summary of data concerning acute physical effects in healthy humans

Text in italic: the same authors reported also on higher exposure concentrations.

Exposure mg/m^3	Duration	Subjects	Effects	Ref.
0.5	1 hour with exercise	n=24	No change in lung function, including specific airway resistance.	Lin87
0.5	1 hour at rest	n=12, non-smoking	No changes in pulmonary function and on heart rate. Parameters of the spectral analysis of heart rate variability were increased ($p<0.05$ for total power).	Tun01
0.7	40 minutes with exercise	n=10	No changes in lung function, including airway resistance with exercise or at rest.	Sch84
1.0	1 hour with exercise	n=24	No change in lung function, including specific airway resistance.	Lin87
1.0	20 minutes with exercise	n=8, non-smoking	No significant changes in lung function, heart rate and eye symptoms. Two subjects reported of mild throat irritation.	San88
1.3	40 minutes with exercise	n=10	No changes in lung function, including airway resistance with exercise or at rest.	Sch84
1.6	1 hour with exercise	n=24	No change in lung function, including specific airway resistance.	Lin87
1.6 – 2.0	5 min eucapnic hyper-ventilation	n=26, non-smoking	A significantly increase in specific airway resistance (sRaw) was noted. Values turned to normal between 20-40 min after exposure. Thirteen individuals were considered to be responders (increase of sRaw ≥ 100%). No SO_2-exposure data were presented without hyperventilation.	Isl92

1.9	5 min eucapnic hyper-ventilation	n=37, non-smoking	Specific airway resistance was increased significantly 3 minutes after exposure. Values turned to normal between 20 and 40 minutes after exposure. Fourteen volunteers were considered responders (increase of sRaw 100%). No SO_2-exposure data were presented without hyperventilation.	Isl94
2.0	4 hours with exercise	n=11	No changes in airway resistance, lung volume and air flow responses.	Sta83
2.0	40 minutes with exercise	n=10	No changes in lung function, including airway resistance with exercise or at rest.	Sch84
2.7	10 minutes (face mask)	n=4	Slight increase in respiratory rate and cardiovascular pulse rate.	SCO93 (Amdur *et al*., 1953)
2.7	30 minutes at rest	n=6	No changes in pulmonary flow resistance during exposure or after 15 minutes of recovery period.	Fra64
2.7	6 hours	n=15, including four smokers	Significant decrease in nasal airway resistance, but decrease in forced respiratory flow. No effects on nasal mucociliary flow rate.	And74
2.7	1 hour	n=12-13	No significant changes in lung function and airway resistance with normal breathing. Twenty-five maximum deep breaths lowered airway resistance.	Law75
2.7 (+ 1 mg/m^3 NaCl)	2 hours with exercise	n=7	Significantly increased pulmonary flow resistance. Half of the exposed subjects experienced shortness of breath and wheezing.	Fra80
2.7	2 hours with and without exercise	n=9, non-smoking n=23, non-smoking	Significant increase in specific airway resistance. No changes in airway resistance.	Bed84
2.7	4 hours with exercise	n=10/sex, non-smoking	No significant changes in pulmonary function and non-specific bronchial reactivity to metacholine. Four subjects reported of upper respiratory irritation and one reported of eye irritation during exposure. At t = 17 minutes: significant decrement of $FEF_{25-75\%}$ and FEV_1/FVC. Also, statistically significant increases in nose and throat irritation.	Kul84
		n=10/sex, non-smoking	No statistically significant changes in pulmonary function, and nose and throat irritation, were observed 24 hr postexposure.	Kul86
2.7	40 minutes with exercise	n=10	No changes in lung function, including airway resistance with exercise or at rest.	Sch84
5.0	20 minutes with exercise	n=8, non-smoking	No significant changes in lung function, heart rate and eye symptoms. Six subjects reported of mild throat irritation, four subjects reported of mild nasal irritation.	San88
5.3	2 hours with and without exercise	n=9, non-smoking	Increased specific airway resistance.	Bed84
5.3	30 minutes with exercise	n=14, non-smoking	No changes in lung function, including airway resistance following normal breathing, forced oral or forced nasal breathing.	Bed89
8.0	Eight deep breaths	n=12-13	Significant increase in airway resistance following deep breathing. No changes in subjects breathing normally.	Law75

10.0	20 minutes	n=12	Significant increase in lung macrophages and lymphocytes.	San89a San89b
10.0	20 minutes with exercise	n=8, non-smoking	No significant changes in lung function, heart rate and eye symptoms. Eight subjects reported of mild throat irritation, five subjects reported of mild nasal irritation.	San88
13.4	30 minutes at rest	n=6 males	A small but statistically significant increase in mean R_{aw}. The increase was maximal after 10 min of exposure (mean %Raw: 38% (after 10 min), 30.0% (after 20 min), 24.8% (after 30 min) and 26.6% (after 15 min recovery period) compared to control values).	Fra64
13.4	15 minutes with forced inhalation	n=9	Small but significant decrease in expiratory flow in the middle of expired vital capacity.	SCO93 (Snell *et al*., 1969)
13.4	6 hours	n=15, including four smokers	Significant decrease in nasal airway resistance, but significant decrease in respiratory forced flow and nasal mucociliary flow rate.	And74
20.0	20 minutes	n=12	Significant increase in lung macrophages and lymphocytes.	San89a, San89b
40.5	30 minutes	n=6	A statistically significant increase in mean R_{aw}. The increase was maximal after 10 min of exposure (mean %Raw: 139% (after 10 min), 99.3% (after 20 min), 64.7% (after 30 min) and 50.4% (after 15 min recovery period) compared to control values).	Fra64
66.8	6 hours	n=15, including four smokers	Increased nasal airway resistance, but decreased forced expiratory flow and volume. Nasal mucociliary stasis occurred in 14 of 15 subjects with 4 having developed colds during the week following exposure.	And74

Annex **G**

Abbreviations

bp	boiling point
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
HBR-OEL	health based recommended occupational exposure limit
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{10}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{10}	lowest lethal dose
LOAEL	lowest observed adverse effect level
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAEL	minimal adverse effect level
MAK	Maximale Arbeitsplatz Konzentration
MOAEL	minimal observed adverse effect level
MTD	maximum tolerated dose
NAEL	no adverse effect level
NEL	no effect level
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
PEL	permissible exposure limit
ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}

RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
REL	recommended exposure limit
STEL	short term exposure limit
tgg	tijd gewogen gemiddelde
TLV	threshold limit value
TWA	time weighted average
V_{max}	maximal reaction velocity of an enzyme

Organisations

ACGIH	American Conference of Governmental Industrial Hygienists
CEC	Commission of the European Communities
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
INRS	Institut National de Recherche et de Sécurité (France)
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OSHA	Occupational Safety and Health Administration (USA)
RTECS	Registry of Toxic Effects of Chemical Substances
SER	Social and Economic Council (Sociaal-Economische Raad NL)
WATCH	Working Group on the Assessment of Toxic Chemicals (UK)
WHO	World Health Organisation

Toxicological terms

bid	*bis in diem* (twice a day)
bw	body weight
CARA	chronic non-specific respiratory diseases
CHD	coronary heart disease
CNS	central nervous system
ECG	electrocardiogram
EEG	electro encephalogram
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FSH	follicle stimulating hormone
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione

HLiA	hamster liver activated
IHD	ischaemic heart disease
im	intramuscular
ip	intraperitoneal
ipl	intrapleural
it	intratracheal
iv	intravenous
LH	lutheinising hormone
MAC	minimal alveolar concentration
MFO	mixed function oxidase
NA	not activated
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RLiA	rat liver activated
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis

Statistical terms

GM	geometric mean
OR	Odds Ratio
RR	Relative Risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

AAS	atomic absorption spectroscopy
BEEL	biological equivalent exposure limit
BEI	biological exposure index
BEM	biological effect monitoring
BM	biological monitoring
ECD	electron capture detector
EM	environmental monitoring
FID	flame ionisation detector
GC	gas chromatography
GLC	gas liquid chromatography
GSC	gas solid chromatography
HPLC	high performance liquid chromatography
IR	infrared

MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography
UV	ultraviolet

Additional abbreviations in the present report

ERV	expiratory reserve volume
$FEF_{25/50/25-75}$	forced expiratory flow at 25, 50 or between 25 and 75% of FVC
FEV_1	forced expiratory volume in 1 second
FIF_{25-75}	forced inspiratory flow between 25 and 75% of FIVC
$FIF_{200-1200}$	forced inspiratory flow between inspired volumes of 200 to 1200 mL
FIV_1	forced inspiratory air at 1 second
FIVC	forced inspritory capacity
FVC/VC	forced vital capacity/vital capacity
IC	inspiratory capacity
PEF/PIF	peak expiratory flow/peak expiratory flow
SR_{aw}	specific airway resistance

Annex **H**

DECOS-documents

Aanpassing van grenswaarden bij flexibele werktijden	2001/06OSH
Acetone cyanohydrin	1995/05WGD
p-Aramid fibres	1997/07WGD
Azathioprine	1999/04OSH
Aziridine (ethyl imine)	2000/13OSH
Azobisisobutyronitril	2002/01OSH
1,2,3-Benzotriazole	2000/14OSH
Bisphenol A and its diglycidylether	1996/02WGD
Bromoethane	1998/10WGD
1,2-and t-Butanol	1994/10WGD
n-, iso-, sec-, tert-Butylacetaten	2001/03OSH
β-Butyrolactone	1999/05OSH
Cadmium and inorganic cadmium compounds	1995/04WGD
Calculating cancer risk	1995/06WGD
Carbadox	1999/06OSH
Carbon disulphide	1994/08
Chlorine dioxide	1995/07WGD
p-Chloroaniline	1998/09WGD
4-Chloro-o-toluidine	1998/08WGD
Chlorotrimethylilane	2001/05OSH
Chromium and its inorganic compounds	1998/01WGD
Chromium VI and its compounds	2001/01OSH
Cresols	1998/15WGD

Copper sulphate	1999/01OSH
1996-1997 WGD-rapporten/1996-1997 DECOS reports	1999/01WGD
1,2-Dibromoethane	1999/07OSH
1,2-Dichloroethane	1997/01WGD
Diethylsulphate	1999/08/OSH
Diglycidyl resorcinol ether	1999/09OSH
Diphenylamine	1997/05WGD
	1998/03WGD
Epichlorohydrin (1-Chloro-2,3-epoxypropane)	2000/10OSH
1,2-Epoxybutane	1998/11WGD
1,2-Ethanediamine	1996/03WGD
Ethyleneglycol ethers	1996/01WGD
Ethylene oxide	2001/11OSH
Ethylene thiourea	1999/03OSH
Formaldehyde	2003/02OSH
Formamide and dimethylformamide	1995/08WGD
Halothane	2002/14OSH
Hydrazinoethanol, phenylhydrazine, isoniazid, maleic hydrazide	1997/03WGD
Hydrogen cyanide, sodium cyanide, and potassium cyanide	2002/15OSH
Isopropyl acetate	1997/04WGD
Lactate esters	2001/04OSH
Lindane	2001/07OSH
Man made mineral fibers	1995/02WGD
Manganese and its compounds	2001/02OSH
2-Methylaziridine (propylene imine)	1999/10OSH
Methyl Methacrylate	1994/09
Methacrylates. Ethyl methacrylate, n-butyl methacrylate and isobutyl methacrylate	1994/11
Methyl-t-butylether	1994/23
Methyl chloride	1995/01WGD
4,4'-Methylene bis (2-Chloroaniline)	2000/09OSH
4,4'-Methylene dianiline	2000/11OSH
Metronidazole	1999/11OSH
2-Nitropropane	1999/13OSH
N-Nitrosodimethylamine (NDMA)	1999/12OSH
2-Nitrotoluene	1998/12WGD
Pentaerythritol	1997/06WGD
Phenol	1996/04WGD
o-Phenylenediamine	1998/06WGD
Piperidine	1997/08WGD
Procarbazine hydrochloride	1999/14OSH
1- and 2-Propanol	1994/24

Propylene oxide	1997/02WGD
Ronidazole	1998/05WGD
Styrene	1998/07WGD
Styrene	2001/08OSH
Tetrachloroethylene (PER)	2003/01OSH
Quartz	1998/02WGD
Toluene	2001/09OSH
1,1,1-Trichloroethane	1995/03WGD
1,2,3-Trichloropropane	1994/25
1,2,3-Trichloropropane	1998/14WGD
Urethane (ethyl carbamate)	2000/12OSH
Vinylbromide	1999/15OSH
Xylene	2001/10OSH
Wood dust	1998/13WGD