Health Council of the Netherlands

Aerosols of mineral oils and metalworking fluids (containing mineral oils)

Health-based recommended occupational exposure limits

Aerosols of mineral oils and metalworking fluids (containing mineral oils)

Health-based recommended occupational exposure limits

to:

the State Secretary of Social Affairs and Employment

No. 2011/12, The Hague, June 29, 2011

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, Agriculture & Innovation, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

The Health Council of the Netherlands is a member of the International Network of Agencies for Health Technology Assessment (INAHTA), an international collaboration of organisations engaged with *health technology assessment*.

INAHTA

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Aerosols of mineral oils and metalworking fluids (containing mineral oils). Health-based recommended occupational exposure limits. The Hague: Health Council of the Netherlands, 2011; publication no. 2011/12.

ISBN: 978-90-5549-839-0

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Aerosols of mineral oils and metalworking fluids (containing mineral oils)*
Uw kenmerk : DGV/MBO/U-932342
Ons kenmerk : U 6599/HS/fs/459-N65
Bijlagen : 1
Datum : 29 juni 2011

Geachte staatssecretaris,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan minerale olienevels.

Dit advies maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige adieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. Het genoemde advies is opgesteld door de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. L.J. Gunning-Schepers,
voorzitter

Bezoekadres
Parnassusplein 5
2511 VX Den Haag
Telefoon (070) 340 70 04
E-mail: h.stouten@gr.nl

Postadres
Postbus 16052
2500 BB Den Haag
Telefax (070) 340 75 23
www.gr.nl

Contents

10 Aerosols of mineral oils and metalworking fluids (containing mineral oils)

Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS) van de Gezondheidsraad gezondheidskundige advieswaarden af voor stoffen in de lucht op de werkplek waaraan werknemers beroepsmatig kunnen worden blootgesteld.

In het voorliggende rapport bespreekt de commissie de gevolgen van de beroepsmatige blootstelling aan nevels van minerale oliën. Eerst komen de minerale oliën zelf aan bod. Vervolgens worden advieswaarden afgeleid voor de blootstelling aan nevels daarvan.

In de bespreking van de effecten en bij het afleiden van advieswaarden maakt de commissie onderscheid in verschillende soorten minerale oliën. Zij hanteert hiervoor de indeling die in de Europese Unie gebruikelijk is en die is gebaseerd op de mate van raffinage. Drie groepen worden onderscheiden: niet of matig geraffineerde oliën, hooggeraffineerde oliën en overige oliën. Binnen de groep van de overige oliën gaat de aandacht vervolgens uit naar de toepassing in metaalbewerkingsvloeistoffen, omdat daar de meeste gegevens over zijn. Bij de metaalbewerkingsvloeistoffen worden vier categorieën onderscheiden: minerale oliën, en oplosbare, semisynthetische en synthetische vloeistoffen. De metaalbewerkingsvloeistoffen uit de eerste drie categorieën bevatten een afnemende concentratie minerale basisoliën, de synthetische bevatten geen minerale oliën.

De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór 1 mei 2010 zijn verschenen.

Samenstelling van minerale oliën en hun toepassing in metaalbewerkingsvloeistoffen

Minerale oliën worden verkregen uit ruwe aardolie. Dat gebeurt door vacuümdestillatie toe te passen op het residu dat overblijft na de eerste destillatie onder atmosferische druk. De uiteenlopende kookpunten van de fracties in het residu worden dan benut om verschillende oliestromen te produceren. De oliën in deze oliestromen worden gezamenlijk aangeduid als minerale basisoliën. Deze basisoliën worden vervolgens verder gezuiverd (geraffineerd) in de olieraffinaderijen.

Het gevolg is dat minerale basisoliën een uiteenlopende samenstelling kunnen hebben, die deels afhankelijk is van de samenstelling van het beginproduct, de ruwe aardolie, en deels van de mate van raffinage. Drie groepen kunnen worden onderscheiden: niet of matig geraffineerde basisoliën, hooggeraffineerde basisoliën, en de groep van de overige basisoliën die daar qua raffinagegraad tussenin ligt. Verreweg het grootste deel van de uiteindelijk verkregen basisoliën valt in deze laatste productgroep van de overige basisoliën.

Alle minerale basisoliën zijn bij kamertemperatuur vloeibaar en niet vluchtig. Ze hebben kookpunten variërend van ongeveer 300 tot 600°C. De niet of matig geraffineerde basisoliën bevatten kankerverwekkende polycyclische aromatische verbindingen. Deze verbindingen worden grotendeels verwijderd uit de basisoliën tijdens het raffinageproces. In hooggeraffineerde oliën zijn ze nauwelijks meer aanwezig; deze oliën bestaan bijna geheel uit verzadigde koolwaterstoffen, overwegend rechte en vertakte ketens met ten minste 15 koolstofatomen. Oliën uit de groep van de overige basisoliën bevatten variërende percentages polycyclische aromatische verbindingen. Het gewichtspercentage dat met dimethylsulfoxide (DMSO) kan worden geëxtraheerd, wordt vaak gebruikt als maat voor het gehalte aan deze aromatische verbindingen. Op basis hiervan onderscheidt de Europese Unie oliën met 3 gewichtsprocent of meer DMSO extraheerbaar materiaal en oliën met minder dan 3 gewichtsprocent DMSO extraheerbaar materiaal.

De belangrijkste toepassing van de minerale basisoliën is als smeermiddel. Daarom worden deze oliën ook wel smeeroliën genoemd. Afhankelijk van de toepassing kunnen verschillende basisoliën worden vermengd. Vervolgens worden er nog diverse chemicaliën aan toegevoegd om de smerende eigenschappen te verbeteren.

Een van de toepassingen als smeermiddel vindt plaats in de metaalbewerking. Daar worden minerale basisoliën gebruikt in zogenoemde metaalbewer-

kingsvloeistoffen of snij- en koelvloeistoffen. Deze vloeistoffen bevatten vaak ook water en verschillende additieven, zoals emulgatoren, biociden en corrosieremmers. Er zijn overigens ook metaalbewerkingsvloeistoffen die helemaal geen minerale olie bevatten; die zijn dan gemaakt op basis van synthetische vloeistoffen en water. Metaalbewerkingsvloeistoffen zijn dus complexe mengsels die kunnen bestaan uit koolwaterstoffen, synthetische vloeistoffen, diverse toegevoegde chemicaliën en water.

Monitoring

In de eerste plaats is er een methode om de blootstelling aan nevels van minerale oliën te meten: NIOSH-methode 5026. Dat gebeurt met infrarood spectrometrie. De blootstelling aan nevels van metaalbewerkingsvloeistoffen is daarmee echter niet altijd goed te meten – voor (semi)synthetische vloeistoffen is hij namelijk ongeschikt. Daarom stelde NIOSH in 2003 een nieuwe methode vast: 5524. Hiermee kan de blootstelling worden gemeten aan nevels die afkomstig zijn van alle soorten metaalbewerkingsvloeistoffen.

Er bestaan geen methoden voor de biomonitoring van de blootstelling aan minerale olie of metaalbewerkingsvloeistoffen.

Huidige grenswaarden

In Nederland geldt voor de blootstelling aan minerale olienevels een wettelijke grenswaarde van 5 mg/m^3, gemiddeld over een achturige werkdag, gemeten als inhaleerbare deeltjes in de lucht. Voor de blootstelling aan nevels van metaalbewerkingsvloeistoffen is in Nederland geen wettelijke grenswaarde.

Een Europese norm voor de blootstelling aan minerale olienevels is er niet, maar in maart 2011 heeft de *Scientific Committee on Occupational Exposure Limits* (SCOEL), een commissie van de Europese Commissie, een grenswaarde van 5 mg/m^3 aanbevolen voor aerosolen van hooggeraffineerde minerale oliën. Verschillende landen hanteren vooralsnog verschillende grenswaarden. Een aantal EU-landen baseert zich op de oude Threshold Limit Value van de Amerikaanse ACGIH (een vereniging van arbeidshygiënisten) voor minerale olienevels van 5 mg/m^3. Zweden en Denemarken hebben een grenswaarde van 1 mg/m^3, gemiddeld over een achturige werkdag. In 2010 heeft de ACGIH een grenswaarde van 5 mg/m^3 aanbevolen die uitsluitend geldt voor aerosolen van hooggeraffineerde minerale oliën.

De Duitse MAK-commissie vindt de vastgestelde MAK-waarde van 5 mg/m^3 voor zuivere minerale olie niet geschikt voor de beroepsmatige blootstelling aan

metaalbewerkingsvloeistoffen vanwege de complexe samenstelling van deze vloeistoffen en het feit dat de minerale oliecomponent niet representatief is voor het mogelijke effect. Volgens deze commissie is het onmogelijk één grenswaarde vast te stellen die van toepassing is op alle soorten metaalbewerkingsvloeistoffen. Tot dezelfde conclusie kwam de Advisory Committee on Toxic Substances van de Engelse Health and Safety Commission.

Carcinogene classificatie

Minerale basisoliën kunnen in principe kankerverwekkende eigenschappen hebben, die samenhangen met het gehalte aan polycyclische aromatische verbindingen. Blootstelling aan niet of matig geraffineerde basisoliën kan onder andere huidtumoren veroorzaken. Door het raffinageproces wordt het gehalte aan deze aromatische verbindingen aanzienlijk teruggebracht, en daardoor neemt ook de mate van kankerverwekkendheid van minerale basisoliën af. Zoals hiervoor al is beschreven, wordt het gewichtspercentage dat met dimethylsulfoxide (DMSO) kan worden geëxtraheerd, vaak gebruikt als maat voor het gehalte aan polycyclische aromatische verbindingen in minerale basisoliën.

In de Europese Unie zijn de niet of matig geraffineerde basisoliën ingedeeld in categorie 1A: stoffen waarvan bekend is dat ze kankerverwekkend zijn voor de mens (‘GHS’ Verordening). De hooggeraffineerde basisoliën hebben geen classificatie in een van de categorieën. Oliën uit de groep van de overige basisoliën worden beoordeeld op grond van de gewichtshoeveelheid die met DMSO wordt geëxtraheerd: van oliën met 3 gewichtsprocent of meer extraheerbaar materiaal wordt verondersteld dat zij kankerverwekkend zijn voor de mens; oliën die minder dan 3 gewichtsprocent extraheerbaar materiaal bevatten, worden in de Europese Unie niet geclassificeerd voor kankerverwekkendheid (EU categorie 1B; ‘GHS’ Verordening).

Kinetiek en toxisch werkingsmechanisme

Bij proefdieren is de opname van minerale oliën in de longen traag. Na inademing van olienevels stapelen met olie gevulde macrofagen zich op in de longblaasjes. Opname via de huid is vermoedelijk langzaam en beperkt.

Orale inname bij proefdieren leidt nauwelijks tot opname van de olie via het maag-darmkanaal: 95-99% van de op die manier ingenomen minerale olie verlaat het lichaam onveranderd. De kleine hoeveelheid die niet wordt uitgescheiden, 1 tot 5%, wordt verdeeld over alle delen van het lichaam, maar komt in het bijzonder terecht in de vetrijke delen, waar de olie kan worden opgeslagen. Er

zijn vrijwel geen gegevens over het metabolisme van de verschillende koolwaterstoffen van minerale olie.

Gegevens over effecten

Hieronder wordt de kennis over de effecten per groep van minerale basisoliën besproken. Daarbij kunnen verschillende blootstellingsroutes aan bod komen, afhankelijk van het gebruik in de praktijk en de gegevens die daarover beschikbaar zijn.

Niet of matig geraffineerde basisoliën

In de Europese Unie zijn de niet of matig geraffineerde basisoliën geclassificeerd als kankerverwekkend in categorie 1A: stoffen waarvan bekend is dat ze kankerverwekkend zijn voor de mens (‘GHS’ Verordening). De International Agency for Research on Cancer (IARC) heeft in 1984 geconcludeerd dat er uit proefdieronderzoek voldoende was gebleken dat de volgende basisoliën kankerverwekkend zijn: onbehandelde vacuümdestillaten, zuurbehandelde oliën, aromatische oliën, matig met oplosmiddel geraffineerde oliën, en matig gehydrogeneerde basisoliën.

De niet of matig geraffineerde basisoliën bevatten aromaten waaronder (gealkyleerde) polycyclische aromatische verbindingen. Aanwijzingen dat deze oliën kankerverwekkend zijn voor de mens, dateren al van omstreeks 1920, toen men huidkanker vond bij werknemers die chronisch waren blootgesteld aan matig geraffineerde oliën. Spoedig daarna bleek dat polycyclische aromatische verbindingen in de basisoliën hiervoor verantwoordelijk waren.

Ook uit proefdieronderzoek blijkt dat de niet of matig geraffineerde basisoliën kankerverwekkend zijn. Dermale blootstelling aan deze oliën kan papillomen en carcinomen veroorzaken op de huid.

Hooggeraffineerde basisoliën

Blootstelling aan hooggeraffineerde basisoliën kan op verschillende manieren plaatsvinden, afhankelijk van de toepassing: via de mond, via de huid en via de luchtwegen.

Er is geen epidemiologisch onderzoek met kwantitatieve gegevens over blootstelling en effecten van hooggeraffineerde oliën. Incidenteel is longontsteking beschreven en zijn granulomen met olie gevonden na inhalatie of aspiratie van zuivere oliën. Macrofagen in de long kunnen de oliedruppeltjes opnemen en

transporteren naar het lymfevatenstelsel, en van daar naar verschillende delen in het lichaam. Er zijn geen humane gegevens beschikbaar over de schadelijke effecten op de voortplanting.

Hooggeraffineerde oliën veroorzaken geen kanker bij dieren, ongeacht de blootstellingsroute. Wel kunnen bij chronische blootstelling via de ademhaling macrofagen in de longen ontstaan, die gevuld zijn met minerale olie. Bij hoge blootstellingen kunnen dan microgranulomen ontstaan en kan het longgewicht toenemen. Een klein aantal van deze macrofagen kan al gezien worden na chronische blootstelling aan 5 mg/m^3 gedurende 12 tot 24 maanden, overigens zonder enige andere reactie van het longweefsel. Dit is gevonden bij honden en knaagdieren. Chronische blootstelling aan 100 mg/m^3 veroorzaakt bij honden en ratten microgranulomen in het longweefsel. Gegevens bij dieren over de schadelijke effecten op de voortplanting zijn er nauwelijks, en laten geen effect zien na orale toediening.

Overige basisoliën

Blootstelling aan overige basisoliën vindt voornamelijk plaats via de huid en de luchtwegen: deze oliën worden voornamelijk gebruikt als smeermiddel in automobielen en in industriële toepassingen.

Er is epidemiologisch onderzoek beschikbaar met kwantitatieve gegevens over de blootstelling aan minerale olienevels, maar dit betreft bijna uitsluitend onderzoek bij werknemers die in aanraking waren gekomen met nevels van metaalbewerkingsvloeistoffen. De beoordeling van dit onderzoek is niet eenvoudig, als gevolg van de wisselende samenstelling van deze vloeistoffen (zowel in de tijd als per werkplaats), de vervuiling van deze vloeistoffen tijdens het gebruik en de vroegere verschillen in de methoden voor het monitoren van de blootstelling. Zo mogen smeeroliën en metaalbewerkingsvloeistoffen tegenwoordig uitsluitend oliën bevatten met minder dan 3 gewichtsprocent DMSO extraheerbaar materiaal. Dat was vroeger anders: toen werden ook minder zuivere oliën gebruikt. In epidemiologisch onderzoek is echter nooit vermeld hoe zuiver de oliën zijn geweest waaraan werknemers in het verleden waren blootgesteld.

Uit het beschikbare onderzoek bij de mens blijkt dat de huid en de ademhalingsorganen de belangrijkste organen zijn die schade kunnen ondervinden na blootstelling aan metaalbewerkingsvloeistoffen. Vanwege de complexe samenstelling van deze vloeistoffen is de commissie echter niet in staat een specifieke stof of specifieke stoffen aan te wijzen die verantwoordelijk zijn voor de waargenomen effecten. Daarom heeft zij een advieswaarde afgeleid die van toepassing is op *het werken met* metaalbewerkingsvloeistoffen die minerale olie bevatten.

Effecten op de huid. Ontsteking van de haarfollikels, olie-acne en keratose zijn gezien na langdurige blootstelling aan nevels van metaalbewerkingsvloeistoffen die enkel minerale olie bevatten. De waterige vloeistoffen zijn in staat irriterende en soms allergische ontstekingsreacties op de huid te veroorzaken. Het is onbekend in hoeverre de toegevoegde chemicaliën en/of verontreinigingen hieraan debet zijn.

Effecten op het ademhalingsysteem. Schadelijke effecten na herhaalde blootstelling aan nevel van minerale olie bevattende metaalbewerkingsvloeistoffen zijn ontsteking van de longblaasjes, astma en bronchitis. Deze verschijnselen kunnen gepaard gaan met vermindering van de longfunctie. Ook over andere luchtwegklachten is gerapporteerd, zoals piepen bij het ademhalen en het ophoesten van slijm. In het algemeen zijn deze effecten gevonden na blootstelling aan concentraties van de inhaleerbare deeltjes in de lucht die hoger zijn dan 0,2 mg/m^3.

Ontsteking van longblaasjes als overgevoeligheidsreactie, ook bekend als extrinsieke allergische alveolitis, is uitsluitend gevonden na blootstelling aan water bevattende metaalbewerkingsvloeistoffen. *Mycobacterium* en *Pseudomonas* worden hiervoor verantwoordelijk gehouden, maar ook andere micro-organismen kunnen betrokken zijn.

Over het geheel genomen is de commissie niet in staat de verschillende typen metaalbewerkingsvloeistoffen apart te beoordelen. Schadelijke effecten op de ademhalingswegen en vermindering van de longfunctie zijn bij alle typen gevonden, ook na blootstelling aan de vloeistoffen die geen minerale olie bevatten. Ook kan de commissie niet aangeven welke stoffen hiervoor verantwoordelijk zijn, omdat nevels van metaalbewerkingsvloeistoffen niet alleen minerale olie kunnen bevatten maar ook water, diverse chemicaliën, metaalslijpsel en micro-organismen.

Kankerverwekkendheid. Er zijn zwakke, positieve associaties gevonden tussen de cumulatieve hoeveelheid ingeademde deeltjes afkomstig van metaalbewerkingsvloeistoffen en kanker van het strottenhoofd, maag, slokdarm en endeldarm. Deze associaties zijn gevonden in een cohort-onderzoek in de Verenigde Staten, onder werknemers in de automobielindustrie. In een vervolgonderzoek met nieuwe gegevens is alleen de associatie met kanker van het strottenhoofd bevestigd. Een verklaring is dat de polycyclische aromatische verbindingen in de ‘oude’ oliën de oorzaak van kanker zijn geweest en dat het risico is afgenomen door het tegenwoordige gebruik van relatief zuivere oliën in metaalbewerkingsvloeistoffen.

Evaluatie en afleiding van gezondheidskundige advieswaarden

De advieswaarden die de commissie hierna afleidt kunnen niet op zichzelf staan. Indien namelijk in minerale basisoliën, of in nevels daarvan, stoffen voorkomen of ontstaan waarvoor al grenswaarden zijn vastgesteld, dan zijn uiteraard die grenswaarden (inclusief eventueel gekoppelde huidnotatie) ook van toepassing.

Kankerverwekkendheid van minerale oliën

Minerale basisoliën kunnen in principe kankerverwekkende eigenschappen hebben, die samenhangen met het gehalte aan polycyclische aromatische verbindingen. Blootstelling aan niet of matig geraffineerde oliën kan onder andere huidtumoren veroorzaken. Producten die zijn afgeleid van minerale basisoliën kunnen eveneens in principe kankerverwekkend zijn. Daarom zijn de risicogetallen van polycyclische aromatische koolwaterstoffen en de gekoppelde huidnotatie van toepassing op alle minerale basisoliën en afgeleide producten.

Advieswaarde voor nevels van **uitsluitend** hooggeraffineerde basisoliën

Een klein aantal met olie gevulde macrofagen is aangetoond in de longen van honden en knaagdieren na chronische (12 tot 24 maanden) inhalatie van 5 mg/m^3 minerale olienevel. De vorming van deze macrofagen is volgens de commissie een normale fysiologische reactie en daarom nog geen schadelijk effect. Schadelijk is pas de vorming van microgranulomen die er op wijzen dat de macrofagen tekort schieten in hun functie en de geïnhaleerde oliedruppeltjes niet meer naar behoren kunnen afvoeren. Daarom beschouwt de commissie de vorming van deze microgranulomen als het kritische effect. Deze microgranulomen zijn gevonden in longweefsel van honden en ratten na chronische inhalatie van 100 mg/m^3 minerale olienevel.

Zij concludeert vervolgens dat de waarde van 5 mg/m^3 het hoogste blootstellingsniveau is waarbij dit kritische effect nog niet is waargenomen in verschillende diersoorten. Deze waarde van 5 mg/m^3 is daarom volgens de commissie een no-observed-adverse-effect-level (NOAEL). Hierop past zij de standaard onzekerheidsfactor van 3 toe om rekening te houden met individuele verschillen in gevoeligheid. Een onzekerheidsfactor voor extrapolatie van dier naar mens acht zij niet nodig omdat de vorming van microgranulomen een locaal effect is.

Met deze onzekerheidsfactor van 3 berekent de commissie een gezondheidskundige advieswaarde van 1,6 mg/m^3 inhaleerbare massa, gemiddeld over een

achturige werkdag, voor nevels van hooggeraffineerde minerale olie. Deze waarde is uitsluitend van toepassing op nevels van hooggeraffineerde minerale olie, zonder additieven en slechts eenmaal gebruikt (niet gerecycled).

Een huidnotatie wordt toegekend als blootstelling via de huid voor tien procent of meer bijdraagt aan een systemisch-toxisch effect of indien huidblootstelling huidtumoren kan veroorzaken. Over de systemische toxiciteit van hooggeraffineerde minerale basisoliën zijn onvoldoende gegevens bekend, maar de beschikbare gegevens wijzen op geringe systemische toxiciteit. Daarnaast is blootstelling van de huid aan hooggeraffineerde basisoliën niet in staat huidtumoren te veroorzaken. Om deze redenen acht de commissie een huidnotatie niet nodig.

Carcinogene classificatie van **het werken met** metaalbewerkingsvloeistoffen die minerale olie bevatten

In epidemiologisch onderzoek zijn associaties gevonden tussen de (cumulatieve) blootstelling aan metaalbewerkingsvloeistoffen en kanker van strottenhoofd, slokdarm en endeldarm. Deze associaties zijn zwak en laten geen consistent beeld zien. Het afnemende gehalte aan polycyclische aromatische verbindingen in de smeeroliën sinds de jaren zestig kan hiervoor een verklaring zijn. Een andere verklaring voor het wisselende beeld is dat op specifieke werkplekken kankerverwekkende stoffen zouden kunnen ontstaan door het gebruik van metaalbewerkingsvloeistoffen met specifieke additieven. In het verleden zijn bijvoorbeeld nitrosaminen en formaldehyde gevonden in gebruikte vloeistoffen die (een) bepaalde (combinatie van) additieven bevatten.

Voor de beoordeling van de kankerverwekkendheid van het werken met metaalbewerkingsvloeistoffen heeft de Commissie GBBS advies gevraagd aan de Subcommissie Classificatie van carcinogene stoffen. De subcommissie merkt op dat aan de huidige metaalbewerkingsvloeistoffen geen mutagene of kankerverwekkende stoffen mogen worden toegevoegd. Er zijn evenwel geen gegevens beschikbaar waaruit daadwerkelijk blijkt dat de huidige ongebruikte metaalbewerkingsvloeistoffen niet mutageen en niet kankerverwekkend zijn.

Tijdens (her)gebruik vervuilen metaalbewerkingsvloeistoffen. Op grond van de ervaringen in het verleden is het denkbaar dat er dan genotoxische stoffen in kunnen ontstaan en dat metaalbewerkingsvloeistoffen kankerverwekkende eigenschappen kunnen krijgen. Daarom is er volgens de subcommissie reden tot zorg. Zij voegt hieraan toe dat er extra reden is tot zorg omdat het ontstaan van kanker mogelijk pas over ongeveer twintig jaar kan worden beoordeeld vanwege

de latentietijd. De bewijslast voor het ontstaan van kanker is echter zwak en er is meer onderzoek nodig voordat een definitieve conclusie kan worden getrokken.

De subcommissie concludeert dat er onvoldoende gegevens zijn over de carcinogeniteit en de genotoxiciteit van de huidige *ongebruikte* metaalbewerkingsvloeistoffen. Daarom beveelt de subcommissie aan *ongebruikte* metaalbewerkingsvloeistoffen niet te classificeren.

Bovendien is de subcommissie van mening dat het werken met metaalbewerkingsvloeistoffen (waarbij sprake is van recycling) onvoldoende is onderzocht, maar dat de beschikbare gegevens niettemin reden geven tot zorg. Daarom beveelt de subcommissie aan *het werken met* metaalbewerkingsvloeistoffen te classificeren als verdacht kankerverwekkend voor de mens. Deze classificatie is te vergelijken met classificatie in categorie 2 van de Europese Unie ('GHS' Verordening).

Advieswaarden voor nevels die ontstaan bij **het werken met** metaalbewerkingsvloeistoffen die minerale olie bevatten

Alles afwegende concludeert de commissie dat de waargenomen effecten van metaalbewerkingsvloeistoffen die minerale olie bevatten verbonden moeten worden met *het gebruik ervan*, en met de nevels die daarbij ontstaan. Dit gebruik is beoordeeld als verdacht kankerverwekkend voor de mens vanwege de mogelijkheid dat er kankerverwekkende stoffen in kunnen ontstaan tijdens hun gebruik bij het metaalbewerken. Indien kankerverwekkende stoffen ontstaan, zijn automatisch de daarvoor bestaande grenswaarden of risicogetallen van toepassing, inclusief een eventueel daaraan gekoppelde huidnotatie.

Volgens de commissie is er voldoende onderzoek waaruit blijkt dat beroepsmatige blootstelling aan nevels van metaalbewerkingsvloeistoffen niet-carcinogene schadelijke effecten kan hebben. Die vloeistoffen kunnen naast minerale olie ook nog andere stoffen bevatten. Bovendien raken ze vervuild in het gebruik. De resultaten van deze onderzoeken zijn echter wel consistent, ongeacht het type metaalbewerkingsvloeistof. Daarom heeft de commissie er voor gekozen alle typen metaalbewerkingsvloeistoffen die minerale olie bevatten samen in ogenschouw te nemen.

De commissie kan de effecten van de minerale olie echter niet onderscheiden van de effecten van andere componenten, inclusief de verontreinigingen die ontstaan tijdens het werken met deze vloeistoffen. Een complicerende factor is nog dat de effecten niet alleen zijn waargenomen bij blootstelling aan vloeistoffen die minerale olie bevatten, maar ook bij vloeistoffen die geen minerale olie bevatten en voor vergelijkbare arbeidsprocessen gebruikt worden. Het gevolg hiervan

voor de toepasbaarheid van de gezondheidskundige advieswaarde heeft de commissie beschreven in een beschouwing aan het einde van hoofdstuk 11.

In verschillende epidemiologische onderzoeken zijn schadelijke effecten beschreven op de luchtwegen met vermindering van de longfunctie als mogelijk gevolg. Deze effecten beginnen op te treden bij concentraties boven de 0,2 mg/m^3 inhaleerbare deeltjes in de lucht, afkomstig van metaalbewerkingsvloeistoffen. Vanwege de geringe omvang van de effecten bij deze concentratie beschouwt de commissie de waarde van 0,2 mg/m^3 als het laagste niveau waarbij schadelijke effecten op de gezondheid kunnen optreden. Verder kiest zij voor een kleine onzekerheidsfactor, namelijk 2. Toepassing van deze factor leidt voor bovengenoemde deeltjes tot een concentratie in de lucht van 0,1 mg/m^3. Bij deze concentratie treden naar verwachting geen effecten op.

Volgens de commissie bevatten de onderzoekspopulaties ook gevoelige personen. Daarom oordeelt de commissie dat er geen extra onzekerheidsfactor nodig is voor interindividuele verschillen in gevoeligheid. Ze concludeert dan ook dat de waarde van 0,1 mg/m^3, gemiddeld over een werkdag van acht uur, een gezondheidskundige advieswaarde is die alle werknemers, ook die uit gevoelige groepen, beschermt tegen de niet-carcinogene schadelijke effecten op de luchtwegen en vermindering van de longfunctie.

Er zijn geen gegevens beschikbaar over systemische effecten van *ongebruikte* metaalbewerkingsvloeistoffen. Tijdens (her)gebruik vervuilen deze vloeistoffen echter en kunnen er misschien genotoxische stoffen in ontstaan, en als gevolg daarvan schadelijke systemische effecten na blootstelling aan gebruikte vloeistoffen. Aangezien een huidnotatie wordt toegekend als blootstelling via de huid voor tien procent of meer bijdraagt aan een systemisch-toxisch effect of indien huidblootstelling huidtumoren kan veroorzaken, zou de huidnotatie eventueel van toepassing kunnen zijn. De commissie is echter niet in staat de noodzaak hiertoe te beoordelen, omdat er volgens de commissie vele verschillende, grotendeels onbekende, verontreinigingen kunnen ontstaan in metaalbewerkingsvloeistoffen tijdens hun gebruik. Niettemin zou toekenning van de huidnotatie moeten worden beoordeeld voor iedere component in de gebruikte metaalbewerkingsvloeistoffen, die verantwoordelijk zou kunnen zijn voor het ontstaan van schadelijke systemische effecten.

Conclusies en aanbevelingen

De advieswaarden die de commissie hieronder geeft zijn niet de enige waarden die van toepassing zijn op de beroepsmatige blootstelling aan nevels van minerale oliën. Indien namelijk in minerale basisoliën, of in nevels daarvan, stoffen

voorkomen of ontstaan waarvoor al grenswaarden zijn vastgesteld, dan zijn die grenswaarden (inclusief eventueel gekoppelde huidnotatie) ook van toepassing. Daarom zijn de risicogetallen van polycyclische aromatische koolwaterstoffen en de gekoppelde huidnotatie van toepassing op alle minerale basisoliën en afgeleide producten.

Nevels van **uitsluitend** hooggeraffineerde basisoliën

De Commissie GBBS geeft een gezondheidskundige advieswaarde van 1,6 mg/m^3 inhaleerbare deeltjes in de lucht, gemiddeld over een achturige werkdag, voor de beroepsmatige blootstelling aan nevels van *uitsluitend* hooggeraffineerde minerale basisoliën, zonder additieven en slechts eenmaal gebruikt (niet gerecycled). De commissie voegt hieraan toe dat zelfs hooggeraffineerde minerale basisoliën kunnen veranderen in verdacht kankerverwekkend voor de mens, vergelijkbaar met classificatie in categorie 2 van de Europese Unie ('GHS' Verordening), indien ze worden gebruikt in of als metaalbewerkingsvloeistof.

Bij blootstelling van de huid aan hooggeraffineerde basisoliën ontstaan geen huidtumoren. Over de systemische toxiciteit zijn onvoldoende gegevens bekend, maar die is vermoedelijk gering. Om deze redenen acht de commissie een huidnotatie niet nodig.

Carcinogene classificatie van **ongebruikte** metaalbewerkingsvloeistoffen die minerale olie bevatten

De Subcommissie Classificatie van carcinogene stoffen van de Commissie GBBS concludeert dat er onvoldoende gegevens zijn over de carcinogeniteit en de genotoxiciteit van *ongebruikte* metaalbewerkingsvloeistoffen. Daarom beveelt de subcommissie aan *ongebruikte* metaalbewerkingsvloeistoffen niet te classificeren als kankerverwekkend voor de mens.

Carcinogene classificatie van **het werken met** metaalbewerkingsvloeistoffen die minerale olie bevatten

De Subcommissie Classificatie van carcinogene stoffen van de Commissie GBBS concludeert dat *het werken met* metaalbewerkingsvloeistoffen onvoldoende is onderzocht. Hoewel de gegevens het niet toelaten *het werken met* metaalbewerkingsvloeistoffen te classificeren als kankerverwekkend voor de mens of als moet worden beschouwd als kankerverwekkend voor de mens, is waakzaamheid geboden. De commissie adviseert daarom *het werken met* metaal-

bewerkingsvloeistoffen te classificeren als verdacht kankerverwekkend voor de mens. Dit is vergelijkbaar met classificatie in categorie 2 van de Europese Unie ('GHS' Verordening).

Gezondheidskundige advieswaarde voor **het werken met** metaalbewerkingsvloeistoffen die minerale olie bevatten

Het gebruik van metaalbewerkingsvloeistoffen geeft reden tot zorg omdat er mogelijk kankerverwekkende stoffen bij kunnen ontstaan. Indien kankerverwekkende stoffen ontstaan, zijn automatisch de bestaande grenswaarden en risicogetallen van die stoffen van toepassing, inclusief gekoppelde huidnotaties.

Als bescherming tegen de niet-carcinogene schadelijke effecten geeft de Commissie GBBS een gezondheidskundige advieswaarde van 0,1 mg/m^3, gemiddeld over een achturige werkdag, voor de beroepsmatige blootstelling aan inhaleerbare deeltjes in de lucht, inclusief aanwezige verontreinigingen, die ontstaan tijdens *het werken met* metaalbewerkingsvloeistoffen die minerale olie bevatten. Deze gezondheidskundige advieswaarde dient te worden gerespecteerd naast andere bestaande grenswaarden en risicogetallen voor specifieke stoffen in nevels van metaalbewerkingsvloeistoffen.

De commissie is niet in staat de noodzaak van een eventuele huidnotatie te beoordelen omdat er vele verschillende – vaak onbekende – verontreinigingen in de verschillende metaalbewerkingsvloeistoffen kunnen ontstaan. Niettemin zou toekenning van de huidnotatie moeten worden beoordeeld voor iedere component in gebruikte metaalbewerkingsvloeistoffen, die verantwoordelijk zou kunnen zijn voor het ontstaan van schadelijke systemische effecten.

Executive summary

Scope

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for existing substances in the air in the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Safety (DECOS).

In this advisory report, the Committee discusses the consequences of occupational exposure to aerosols of mineral oils. In describing the effects of exposure, the Committee has followed the generally used division of the mineral base oils into three product groups, based on the severity of the refining process: unrefined or mildly refined base oils, highly refined base oils, and other lubricant base oils. Within the latter group, the attention is focused on their application in metalworking fluids (MWF) as most of the data on adverse health effects of occupational exposure specifically concern the exposure to MWF. Four categories of MWF are distinguished: straight oils, soluble MWF, semi-synthetic fluids, and synthetic fluids. Fluids from the first 3 categories contain a decreasing amount of mineral base oils. The synthetic fluids are free from mineral oils.

The Committee's conclusions are based on scientific papers published before May 1, 2010.

Composition of mineral oils and their application in metalworking fluids

Mineral oils are obtained by vacuum distillation of the residue of the atmospheric distillation of crude petroleum oils. Depending on their boiling points, different oil streams are collected. These oils, commonly called mineral base oils, are further refined by solvent treatment, hydrotreatment, and/or hydrocracking. The base oil composition, therefore, depends on the original crude petroleum oil and on the refining process. Essentially, 3 product groups can be distinguished: unrefined or mildly refined base oils, highly refined base oils, and other lubricant base oils. Most of the mineral base oil production falls in this latter product group of the other lubricant base oils.

Mineral base oils have carbon numbers of 15 or more and boiling points in the range of 300-600°C. At ambient temperatures, virtually all mineral base oils are liquids and have negligible vapour pressures.

Unrefined mineral base oils contain carcinogenic polycyclic aromatic compounds (PAC). These compounds are largely removed during the refining process. Highly refined base oils contain relatively small amounts of these PAC. These oils mainly consist of paraffinic and cycloparaffinic (naphthenic) hydrocarbons, with only traces of other substances. Oils belonging to the other lubricant base oils have varying amounts of PAC. Dimethyl sulfoxide (DMSO) has been found to be a good extraction solvent for aromatic compounds including PAC, and the DMSO extractable fraction is often used as a surrogate measure of the amount of PAC present. In the European Union, 2 subgroups can be distinguished within the group of the other lubricant base oils: base oils having a DMSO extractable fraction equal to or greater than 3% (w/w) and base oils having a DMSO extractable fraction less than 3% (w/w).

Depending on the application, different base oils may be mixed and chemicals added to yield mineral lubricant oil products of the desired specifications. Their main use is in automotive and industrial applications.

An important application associated with adverse health effects due to occupational exposure is in MWF. Several types of these fluids exist, based on the amount of mineral oil, water, and synthetic fluids present. Overall, MWF may contain mineral oil, water, and a variety of additives such as emulsifiers, biocides, and corrosion inhibitors. Some MWF do not contain mineral oil but are based on water and synthetic water-miscible fluids. MWF fluids may also contain synthetic hydrocarbons in addition to or instead of mineral hydrocarbons. Consequently, MWF are complex mixtures and may contain hydrocarbons

(mineral or synthetic), water, water-miscible fluids, and various added chemicals.

Environmental and biological monitoring

NIOSH method 5026 is available to monitor aerosols of mineral oils. This method is based on infrared spectrophotometry. This method appeared to be unsuitable for the monitoring of (semi)synthetic MWF. In 2003, NIOSH published method 5524 for monitoring aerosol particles from all categories of MWF.

No validated methods are available for the biological monitoring of exposure to mineral oils.

Limit values

In the Netherlands, the current legally-binding occupational exposure limit for mineral oil mist is 5 mg/m^3 of inhalable particulate mass, as an 8-hour time-weighted average (TWA). In the Netherlands, no limit value exists for the occupational exposure to MWF.

There is currently no limit value for oil mist exposures at the European level but in March 2011, the Scientific Committee on Occupational Exposure Limits (SCOEL), a committee of the European Committee, recommended an occupational exposure limit of 5 mg/m^3 for aerosols of severely refined mineral oils. A number of EU member countries have set limits numerically equivalent to the 'old' TLV (5 mg/m^3). Sweden and Denmark have an occupational exposure limit of 1 mg/m^3 mineral oil particulate mass, as an 8-hour TWA. In 2010, ACGIH recommended a TLV of 5 mg/m^3 for highly refined mineral oil aerosols only. The German MAK Commission has specified that it considers its previously established MAK value of 5 mg/m^3 for pure mineral oil not applicable to work environments with present-day MWF because of, as a rule, the complex composition of these fluids and because the mineral oil component alone is not representative of the potential effect. The same conclusion was reached by the Advisory Committee on Toxic Substances of the UK Health and Safety Commission.

Classification as a carcinogen

Mineral base oils may have carcinogenic properties that appear to be related to their PAC content. Severe refining processes remove or substantially reduce the

amount of PAC, and eliminate or reduce the carcinogenic activity of mineral base oils. As described above, the DMSO extractable fraction is often used as a surrogate measure of the amount of PAC present in the base oils.

For carcinogenic classification, the European Union has divided mineral base oils into 3 groups, based on the severity of the refining process: unrefined or mildly refined base oils, highly refined base oils, and other lubricant base oils. Unrefined or mildly refined base oils are classified in category 1A: substances known to have carcinogenic potential to humans ('CLP' Regulation). Highly refined base oils do not have a classification in any of the carcinogenic categories in the European Union. The group of the other lubricant base oils contains a large number of individual CAS numbers with unspecified refining severity. Oils with a DMSO extractable fraction equal to or greater than 3% by weight are classified in category 1B: substances presumed to have carcinogenic potential for humans. Oils with less than 3% by weight DMSO extractable material are not classified in the European Union ('CLP' Regulation).

Kinetics and mechanism of action

Animal studies with mineral oils suggest that absorption after inhalation exposure is slow and that lung clearance may be mediated by macrophage phagocytosis. Oil-filled macrophages have been found to accumulate in the lungs. Particle size and composition may influence the absorption of inhaled mineral oil components. Dermal absorption of mineral oil hydrocarbons is expected to be slow and limited. Almost all (95-99%) of ingested food-grade mineral oil leaves the body unchanged in the faeces, 1-5% being absorbed as such by the intestinal mucosa. Studies in rats show that absorption of ingested *n*-alkanes, isoparaffins and naphthenes is inversely related to molecular weight.

Clinical observations in man have shown that deposition takes place in the hilar nodes from where they may be transported to other organs such as the spleen. After absorption, mineral oils are transported throughout the body by the blood circulation and the lymph system. Storage takes place in adipose tissue or in fat. After excessive exposure, mineral oil droplets have been identified in mesenteric and portal lymph nodes, and in liver, spleen and adipose tissue in man. Data on the biotransformation of mineral-oil hydrocarbons are limited.

Effects

In the European Union, mineral base oils are generally divided into 3 product groups, based on the severity of the refining process: the unrefined or mildly

refined base oils, the highly refined base oils, and the other lubricant base oils. The Committee has followed this division.

Unrefined or mildly refined mineral base oils

In the European Union, the unrefined and mildly refined mineral base oils are classified in carcinogenicity category 1A: substances known to have carcinogenic potential to humans ('CLP' Regulation). In 1984, IARC concluded that there was sufficient evidence for the carcinogenicity in experimental animals for the following base oils: untreated vacuum distillates, acid-treated oils, aromatic oils, mildly solvent-refined oils, and mildly hydrotreated oils.

The unrefined and mildly refined base oils contain aromatics including (alkylated) PAC. Studies dating back to the early 1920's showed that exposure to unrefined and mildly refined mineral base oils was associated with skin cancer in humans and that these cancers were caused by the PAC present in these oils.

Animal data are in line with these observations. Many studies have shown that mildly refined mineral lubricant base oils, when applied to the skin, cause skin papillomas and carcinomas in various animal species.

Highly refined mineral base oils

No epidemiological studies exist with exposure-response data for highly refined mineral base oils. Case reports have described lipid pneumonia and lipid granulomas after inhalation or aspiration of white oils and petrolatums. The oils are taken up by macrophages in the lungs. No human data on reproduction toxicity, immunological effects, or neurological effects of highly refined mineral oil mists are available.

Animal studies show that highly refined mineral base oils do not have carcinogenic potential. No increase in incidence of any tumour was observed after inhalation, oral administration, dermal administration, or subcutaneous injections of highly refined base oils in animal species.

Animal studies show that chronic inhalation exposure to highly refined mineral oils may cause the formation and accumulation of oil-filled lung macrophages and increased lung weights. In general, these studies showed that few oil-filled macrophages without other tissue response occur in the lungs of several animal species, including dogs and rodents, after 12-24 months of inhalation exposure to 5 mg/m^3. At inhalation exposure levels of 100 mg/m^3, microgranulomas were found in lung tissue of dogs and rats.

The few animal studies available did not show evidence for reproduction toxicity of highly refined white mineral oils after oral administration. Overall, the data on reproduction toxicity are limited.

Other lubricant base oils

Nowadays, the other lubricant base oils that have less than 3% (w/w) DMSO extractable material are being used in lubricant oil products and MWF. In the past, however, less refined oils have been used in lubricant oil products and MWF. The available epidemiological studies, however, do not give details on the composition and purity of the mineral base oils used in workplaces in the past.

Several epidemiological studies with quantitative exposure-response data describe adverse health effects in workers exposed to mineral oils, but these studies mainly concern workers exposed to MWF, *i.e.*, to fluids that may contain mineral oil, water, additives, and contaminants. Therefore, the Committee decided to focus on these MWF. Several factors appear to hamper the evaluation of these studies. Main factors include co-exposure to non-mineral oil components and contaminants, differences in the methods used to monitor occupational exposure, and the variable composition of in particular the water-containing MWF.

From the available human data, the major sites that appear to be affected are the skin and the respiratory system. It is, however, not possible to pinpoint the substance(s) responsible for the observed effects. For this reason, the Committee decided to derive a health-based occupational exposure limit for *working with* MWF that contain mineral oil.

Skin effects. Skin effects that may be observed after repeated exposure to straight oil MWF include folliculitis, oil acne, and keratosis. The soluble and semi-synthetic MWF (*i.e.*, the water-based emulsions) primarily cause irritant and occasionally allergic contact dermatitis. It is not clear to what extent additives and contaminants of MWF contributed to the observed irritant and allergic skin effects.

Effects on the respiratory system. Respiratory effects that have been observed after exposure to mists of mineral-oil-containing MWF include asthma, bronchitis, and respiratory symptoms (wheezing, cough, phlegm), sometimes accompanied by decreases of pulmonary function (baseline and cross-shift). Generally, adverse effects on lung function have been described at exposure levels above 0.2 mg/m^3 inhalable particulate mass, originating from MWF; no adverse effects have been observed at levels below 0.2 mg/m^3 inhalable particulate mass.

Outbreaks of hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis) have occurred in workers exposed to water-containing MWF. Both *Mycobacterium* and *Pseudomonas* species have been implicated in the aetiology but other species (*e.g., Acinetobacter*) may be involved, too. The evidence indicates that the observed hypersensitivity pneumonitis after exposure to MWF is associated with exposure to water-containing fluids and not to mineral oils *per se*.

Overall, it is not possible to separately evaluate the different types of MWF. Adverse health effects appear to be associated with exposure to any of the 4 types of MWF. No conclusions can be drawn on the components that are responsible for the observed effects in metal workers. The observed effects are associated with occupational exposure to mists of MWF and these mists may contain mineral oil and many other substances, including MWF additives and contaminants like metal fines and microorganisms.

Carcinogenicity. Several studies among automotive workers in the US show associations between cumulative exposures to mineral-oil-containing MWF and cancer of the larynx, oesophagus, and rectum, but the associations were weak and not consistent. In a re-examination, with improved case definition in a case-cohort design and new cases identified from 1985 to 2000, the main finding was an association between larynx cancer incidence and cumulative exposure to straight MWF with a 7% increase in risk for each 5-mg/m^3·year increment in cumulative exposure. No other fluid types were associated with laryngeal cancer risk. The results for oesophageal cancer were inconsistent and stomach cancer risk was not associated with any fluid type. Overall, the results suggest that one or more common agents in the early straight and soluble MWF may have been the causative agent(s), possibly the PAC that were present at higher levels in the pre-1980 mineral oils as compared to the relatively pure mineral base oils, used in MWF nowadays.

Evaluation and derivation of health-based recommended occupational exposure limits

The occupational exposure limits that the Committee will derive in this section are not the only limits to be applied. For specific substances in mineral base oils, including substances that are newly formed during the use of these oils, existing occupational exposure limits (including skin notations if attached) are to be applied as well.

Carcinogenicity of mineral base oils

Mineral base oils may have carcinogenic properties related to their PAC content: occupational exposure to unrefined or mildly refined mineral base oils is able to induce skin tumours. Consequently, products derived from mineral base oils may as well have carcinogenic properties related to their PAC content. As a consequence, the existing occupational cancer risk values and the skin notation of polycyclic aromatic hydrocarbons apply to all mineral base oils and derived products.

Aerosols of **exclusively** highly refined mineral base oils

Few oil-filled macrophages with no other tissue response were found in the lungs in several animal species at chronic (12-24 months) inhalation exposure levels of 5 mg/m^3. Microgranulomas were found in dogs and rats at 100 mg/m^3 chronic inhalation exposure levels. According to the Committee, the occurrence of oil-filled macrophages is a normal physiological reaction and not an adverse health effect. The formation of microgranulomas, however, is adverse as it indicates that the inhaled oil droplets can not completely be removed anymore by the macrophages. Therefore, the Committee considers the occurrence of microgranulomas as the critical effect and concludes that 5 mg/m^3 is the no-observed-adverse-effect-level for this effect.

A factor correcting for exposure duration is not necessary as the Committee considers an exposure period of 24 months in dogs and rats sufficiently representative of long-term exposure. An interspecies factor is not needed as the occurrence of microgranulomas is a local effect. To cover intraspecies variation, the Committee uses the default assessment factor of 3. Applying this factor of 3 yields a health-based recommended occupational exposure limit (HBROEL) of 1.6 mg/m^3 inhalable particulate mass, as an 8-hour time-weighted average. This value exclusively applies to aerosols of highly refined mineral base oils, used without additives and only once (not recycled).

A skin notation is indicated if occupational skin exposure adds for 10% or more to systemic toxicity, or if skin exposure may induce skin cancer. Insufficient data are available on the systemic toxicity of highly refined mineral base oils, but the available studies indicate minor systemic toxicity. In addition, skin exposure to highly refined base oils does not induce skin tumours. For these reasons, the Committee considers a skin notation not needed.

Carcinogenic classification of **working with** mineral-oil-containing metalworking fluids

Several studies show associations between cumulative exposures to mineral-oil-containing MWF and cancer of the larynx, oesophagus, and rectum, but the associations were weak and inconsistent. Overall, one or more common agents in the early MWF may have been the causative agent(s), possibly the PAC. Another explanation may be the formation of carcinogenic compounds from specific (combinations of) additives during the continuous re-use of MWF. For example, nitrosamines and formaldehyde have been detected in specific workplaces in *used* MWF, in the past.

DECOS has consulted the Subcommittee on the Classification of Carcinogenic Substances for the assessment of carcinogenicity of working with MWF. The Subcommittee notes that mutagenic or carcinogenic additives are not allowed to be used in present-day MWF. However, no data are available that allow to conclude that *unused* MWF are indeed not genotoxic and not carcinogenic. Besides, based on the experiences in the past, it is conceivable that during (re-)use of present-day MWF genotoxic compounds might be formed and that MWF might acquire carcinogenic properties. This indicates that there is cause for concern for man. According to the Subcommittee, there is additional concern as the possible carcinogenicity of working with MWF can only be assessed after a latency period of about 20 years. However, the evidence for the carcinogenicity of working with MWF is weak and further experiments are needed before a final conclusion can be reached.

The Subcommittee concludes that there is a lack of carcinogenic and genotoxic data on *unused* MWF. Therefore, the Subcommittee recommends not to classify *unused* MWF.

In addition, the Subcommittee's opinion is that *working with MWF* has been insufficiently investigated. While the available data do not warrant a classification as is known or as presumed to be

carcinogenic to man, they indicate that there is cause for concern. Therefore, the Subcommittee recommends classifying *working with MWF* as suspected to be carcinogenic to man. This recommendation is comparable to EU classification in category 2 ('CLP' Regulation).

Aerosols formed during **working with** mineral-oil-containing metalworking fluids

Taking all the available information into consideration, DECOS concludes that the observed adverse health effects are associated with the *use* of MWF and the aerosols then formed, and that *working* with MWF may result in exposure to mineral oil, additives, and contaminants. *Working with MWF* is recommended for classification as suspected human carcinogenic as carcinogenic substances might be formed during their (re-)use. For specific carcinogenic substances being formed, existing occupational exposure limits, cancer risk values, and skin notations if attached, automatically apply.

Non-carcinogenic effects of occupational exposure to mineral-oil-containing MWF have been frequently described. Several epidemiological studies exist with quantitative dose-response data (Table 11.1). The results of these studies show a consistent picture. For this reason, the Committee decided to evaluate these studies.

Occupational exposure to inhalable particulate mass originating from mineral-oil-containing MWF has adverse effects on worker's health. However, the Committee cannot separate the effects of mineral oil from the effects of other components in MWF, including contaminants formed during the use of these fluids. Next to this, it appears that the hazard is not only associated with exposure to mineral-oil-containing MWF but also to MWF that do not contain mineral oil. The Committee describes the consequence of this for the applicability of the HBROEL in an additional consideration at the end of Chapter 11.

Several epidemiological studies have described adverse effects on the respiratory system after occupational exposure to MWF, including a decrease of the lung function. These adverse health effects started to occur at exposure levels above 0.2 mg/m^3 (arithmetic mean) inhalable particulate mass, originating from MWF. Because of the small effect size, the Committee considers the level of 0.2 mg/m^3 the lowest level at which adverse health effects may start to occur. This small effect size also justifies a small factor to extrapolate the lowest-observed-effect-level (LOEL) into a no-effect-level (NEL). For this, the Committee applies a factor of two, resulting in a no-effect-level of 0.1 mg/m^3 (arithmetic mean) inhalable particulate mass originating from MWF.

In the epidemiological studies, sensitive workers were likely included. This makes an additional factor for interindividual variability in sensitivity unnecessary. Therefore, the Committee concludes that the value of 0.1 mg/m^3 inhalable particulate mass including contaminants represents the occupational exposure limit that protects all workers, including those from sensitive groups,

against the non-carcinogenic adverse effects of MWF on the respiratory system and the lung function.

In conclusion, DECOS recommends a health-based occupational exposure limit of 0.1 mg/m^3 inhalable particulate mass including contaminants, as an 8-hour time-weighted average, applying to aerosols that are formed during working with MWF that contain mineral oil. The Committee adds that this value should be respected next to other occupational exposure limits that exist for specific (carcinogenic) substances occurring in MWF.

No data on systemic toxic effects are available for the exposure to *unused* MWF. During (re-)use, however, MWF become contaminated and the contaminants cause concern for carcinogenicity and, consequently, systemic toxicity. As a skin notation is indicated if occupational skin exposure adds for 10% or more to systemic toxicity or if skin exposure may induce skin cancer, a skin notation might be indicated for used MWF. However, the Committee is not able to evaluate the need as such, as the contaminants in used MWF are diverse and largely unknown. Nevertheless, the need for a skin notation should be evaluated for each individual component that may be formed in MWF and that might be responsible for adverse systemic effects.

Conclusions and recommendations

The occupational exposure limits that DECOS has derived are not the only limits to be applied. For specific substances in mineral base oils, including substances that are newly formed during the use of these oils, existing occupational exposure limits (including skin notations if attached) are to be applied as well. This includes the occupational cancer risk values and the skin notation of polycyclic aromatic hydrocarbons.

Aerosols of **exclusively** highly refined mineral base oils

DECOS recommends a health-based occupational exposure limit of 1.6 mg/m^3 inhalable particulate mass, as an 8-hour time-weighted average, applying *exclusively* to aerosols of highly refined mineral base oils, used without additives and only once (not recycled). The Committee recognizes that in some applications, *e.g.*, in MWF, even highly-refined mineral base oils may end up as suspected human carcinogens, comparable to EU category 2 (‘CLP’ Regulation).

Insufficient data are available on the systemic toxicity of highly refined mineral base oils, but the available studies indicate that the systemic toxicity is

small. In addition, skin exposure to highly refined base oils does not induce skin tumours. For these reasons, the Committee considers a skin notation not needed.

Carcinogenic classification of **unused** metalworking fluids

The Subcommittee on Classification of Carcinogenic Substances of DECOS concludes that there is a lack of carcinogenic and genotoxic data on *unused* MWF. Therefore, the Subcommittee recommends not to classify *unused* MWF.

Carcinogenic classification of **working with** metalworking fluids

The Subcommittee on Classification of Carcinogenic Substances of DECOS is of the opinion is that *working with MWF* has been insufficiently investigated. While the available data do not warrant a classification as known or as presumed to be carcinogenic to man, they indicate that there is cause for concern**.** Therefore, the Subcommittee recommends classifying *working with MWF* as suspected to be carcinogenic to man. This recommendation is comparable to the EU classification in category 2 ('CLP' Regulation).

Health-based recommended occupational exposure limit for **working with** mineral-oil-containing metalworking fluids

DECOS recognizes that there is cause for concern that carcinogenic substances might be formed during the (re-)use of mineral-oil-containing MWF. For specific carcinogenic substances being formed, existing occupational exposure limits, cancer risk values, and skin notations if attached, automatically apply.

In addition to existing exposure limits for specific substances, DECOS recommends a health-based occupational exposure limit of 0.1 mg/m^3 inhalable particulate mass including its contaminants, as an 8-hour time-weighted average. This value applies to aerosols formed during *working with* mineral-oil-containing MWF and should be respected next to other occupational exposure limits that exist for specific (carcinogenic) substances occurring in MWF.

DECOS is not able to evaluate the need for a skin notation as the contaminants formed by the use of MWF are diverse and largely unknown. Nevertheless, the need for a skin notation should be evaluated for each individual component that may be formed in MWF and that might be responsible for adverse systemic effects.

Chapter 1

Scope

1.1 Background

At the request of the Minister of Social Affairs and Employment (Annex A), the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of existing substances that are used in the workplace. The purpose of the evaluations is to recommend a health-based occupational exposure limit for the concentration of a substance in the air, provided that the database allows the derivation of such a value. In the Netherlands, the recommendations serve as the basis in setting occupational exposure limits by the Minister.

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the Committee, of the health hazard of aerosols of mineral oils. The members of the Committee are listed in Annex B.

In 2008, the President of the Health Council released a draft of the report for public review. The individuals and organisations 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

The Committee's recommendation has been based on scientific data, which are in the public domain. Data were obtained from the online databases Toxline, Medline, Current Contents and Chemical Abstracts, using combinations of the key words mineral*, lubricant*, oil*, mist*, base oil, adverse effects, occupational exposure, kinetics, toxic*, industrial oil, lubrication, human, and animal. The literature from this search was selected based on titles and abstracts. The last search was performed in April 2010.

Chapter 2

Introduction

This advisory report is on the consequences of occupational exposure to aerosols of mineral oils. The term mineral oil has a broad meaning. It has been used to describe crude petroleum oil and virtually all materials obtained by the refining of these crude oils (*e.g.*, including middle distillates, fuel oils, and base oils). From the perspective of occupational health protection, the term is used here to describe the mineral base oils prepared from crude petroleum oil. These base oils are primarily used as lubricants in a wide variety of lubricant oil products including metalworking fluids (MWF).

Epidemiological data on adverse health effects of occupational exposure to mineral base oil products primarily concern the exposure to MWF. Several studies with quantitative exposure-response data are available, and these studies show that exposure to aerosols of MWF may have adverse health effects. For this reason, the Committee decided to include a review of these studies and to evaluate the adverse health effects of occupational exposure to mineral-oil-containing MWF as well.

2.1 Identity of mineral base oils

The refining of crude petroleum oil produces basically three types of products: fuels, lubricating oils, and bitumen.[61] Atmospheric distillation fractionates crude petroleum oil into fuel components of various boiling ranges and these are used to produce the different fuel products. The residue from the atmospheric

distillation is further fractionated by vacuum distillation to yield the different base oils. These base oils are further processed in refineries to produce refined base oils. The base oils are also described as lubricant basestocks as their main application is in the production of lubricants. Finally, the residue from vacuum distillation is bitumen.

The refining processes have changed considerably over the years. Originally, processing of crude mineral base oils consisted of acid and clay treatment, and dewaxing by chilling. Solvent refining was introduced in the 1930s and hydrotreating (catalytic hydrogenation), as a more thorough process than 'hydrofinishing' (mild hydrogenation), was introduced in the 1960s. Since then, the trend has been increasingly towards the production of highly refined base oils with associated removal of unwanted components like the PAC. Originally, the mineral oil products used for lubrication were poorly or mildly refined and contained PAC and other impurities. Nowadays, mineral lubricant oil products are prepared from base oils that are refined to such a degree that they contain trace amounts of PAC and other impurities.

For carcinogenic classification, the mineral base oils can be divided in three product groups: the *unrefined or mildly refined base oils*; the *highly refined base oils*; and the *other lubricant base oils*. This last group contains a large number of individual CAS numbers with unspecified refining severity.[125] Most of the mineral base oil production falls in this product group of the *other lubricant base oils*.[125] Depending on the application, different base oils may be mixed and several chemicals added. Consequently, many different mineral oil products exist and these may considerably vary in composition.

Aerosols of mineral oils may arise in a variety of applications. Important applications associated with the potential generation of oil mists include metal-working, textile machinery, rock drills, mist lubrication, agricultural sprays, concrete mould release agents, corrosion preventives, printing inks, rubber extenders, lubricant blending and open processes, and food and pharmaceutical preparations.

2.2 Chemical composition

2.2.1 Mineral base oils

Mineral base oils are primarily composed of straight and branched-chain paraffinic, cycloparaffinic (naphthenic) and aromatic hydrocarbons with carbon numbers of 15 or more.[61] Also traces of organic sulphur, oxygen, nitrogen, and a number of metal compounds may be present.

The residual content of (polycyclic) aromatic hydrocarbons in the finished base oils is mainly determined by the severity of the refining process.[20,79] Severe hydrogenation of mineral oil streams produces mineral base oils as complex mixtures of straight and branched-chain paraffinic and cycloparaffinic (naphthenic) hydrocarbons.[61] High-pressure hydrogenation (hydrocracking) is able to break down long-chain and cyclic paraffins, and yields a mixture of straight and branched short-chain alkanes.

2.2.2 *Mineral lubricant oil products*

Products derived from mineral base oils are obtained by mixing several base oils and/or adding one or more performance enhancers (additives).[61] Typically, individual additives may be added in concentrations up to 2%.[61] Total amount of additives may account for up to about 30% of the formulated lubricant oil products. It concerns a variety of chemicals to modify physical and chemical properties.[110]

Additives to modify physical characteristics:

- viscosity index improvers: polymers or co-polymers based on methacrylates, olefins, or styrenes
- pour point depressants: usually polymers related to those used as viscosity index improvers, but of higher molecular weight
- tackiness agents: normally high molecular weight polymers such as polybutenes
- anti-foam additives: normally silicones or organic co-polymers
- emulsifiers: alkali and alkanolamine soaps, naphthenates, sulphonates, sulphates, ethoxylates, sorbitan esters
- friction modifiers: including organic acids, amines, fats, oils, and waxes and their additives.

Additives to modify chemical characteristics:

- anti-oxidants: including amines, phenols and a variety of zinc, calcium, barium, and magnesium salts, including thiophosphates, salicylates, phenolates, and sulphonates
- corrosion inhibitors: alkali and alkanolamine soaps, naphthenates, amines, amides, boron compounds
- anti-rust additives: including derivatives of dibasic organic acids, salts of alkali and alkaline earth metals, nitrites, and amine derivatives

- metal deactivators: substituted diamines or ring compounds containing nitrogen, *e.g.*, triazoles or thiazoles
- anti-wear and extreme pressure additives: including fats, oils, and waxes, and their derivates, compounds of sulphur, chlorine, and phosphorus, elemental sulphur, and salts of zinc or occasionally lead
- detergents/dispersants: often amines, imides, ether derivatives or salts of various kinds
- biocides: including phenol derivatives and compounds which slowly release formaldehyde under conditions of uses, *e.g.*, substituted triazines.

From the foregoing, it may be clear that the composition of the mineral lubricant oils and formulated products like *e.g.*, MWF is complex and may vary widely. The original crude petroleum oil, the refining process, and the additives are the main factors that determine the final composition of the end products.

2.3 Physical properties of mineral base oils

The properties of main mineral oil refinery streams are presented in Table D-1 (Annex D). Each type of refinery stream is identified by a CAS registry number. The mineral base oils are arranged according to the last refining process they have gone through.[61]

The components of mineral base oils have boiling points ranging from circa 300 to 600°C. Those produced from vacuum residues may contain components boiling as high as 800°C. At ambient temperatures, virtually all mineral base oils are liquids with negligible vapour pressures.[20]

Paraffinic oil streams are characterized by high wax content, high natural viscosity index (low rate of change in viscosity with temperature) and relatively low aromatic hydrocarbon content. Naphthenic oil streams are normally low in wax and relatively high in cycloparaffins and aromatic hydrocarbons.[61]

The various mineral base oils have a range of physical properties (Table D-2 of Annex D). In general, mineral base oils are defined as either light or heavy according to their kinematic viscosities at 40°C. Those having viscosities above 19 mm^2/sec at 40°C are described as heavy and those below as light.[20]

2.4 EU classification and labeling of mineral base oils

The carcinogenic potential of mineral base oils has appeared to be related to their PAC content and, therefore, to depend on the severity of their refining.[79,125]

Severe refining processes remove or substantially reduce the amount of PAC, and eliminate or reduce the carcinogenic activity of unrefined base oils.

For carcinogenic classification, the European Union has divided the mineral base oils into three groups: the *unrefined or mildly refined base oils*; the *highly refined base oils*; and the *other lubricant base oils*. In Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures ('CLP' Regulation), unrefined or mildly refined base oils are classified as category 1A carcinogens (substances known to have carcinogenic potential for humans). Highly refined base oils (including white oils used in cosmetics, pharmaceutical preparations, textile machinery, and agricultural spraying) do not have a carcinogenic classification. The unspecified 'other lubricant base oils' are subject to Note L. Note L, specifically introduced in the legislation for base oils, describes the criterion for distinguishing oils considered carcinogenic from oils considered non-carcinogenic as follows: '*The classification as a carcinogen need not apply if it can be shown that the substance contains less than 3 % DMSO extract as measured by IP 346 'Determination of polycyclic aromatics in unused lubricating base oils and asphaltene free petroleum fractions - Dimethyl sulphoxide extraction refractive index method', Institute of Petroleum, London.*' Unspecified base oils are classified as category 1B carcinogens (substances presumed to have carcinogenic potential for humans) unless they contain less than 3% (w/w) DMSO-extractable material.[41]

An overview of carcinogenic classifications is given in Annex G.

2.5 Monitoring

2.5.1 Environmental monitoring of aerosols of mineral oil

NIOSH method 5026 is available to monitor mineral oil mist. Airborne mist samples are collected on 37-mm membrane filters (0.8 µm MCE, 2 µm PTFE, or glass fibre) at a flow rate of 1 to 3 litre per minute. The mineral oil is subsequently extracted from the filters into carbon tetrachloride, and analysed by infrared spectrometry near 2940 cm^{-1}. This method is applicable to all trichlorofluoroethane-soluble mineral oil mists, most likely also to the majority of semi-synthetic MWF but not to synthetic MWF.[84]

2.5.2 *Environmental monitoring of aerosols of metalworking fluids*

In 2003, NIOSH method 5026 has been replaced by NIOSH Method 5524 for monitoring particulate mass from airborne metalworking fluid. Method 5524 is a gravimetric method for measuring airborne MWF (all categories) after collection of aerosol particles (either as thoracic or as total particulate) on tared 37-mm, 2-µm PTFE-filters. For thoracic sampling, the filter is preceded by a cyclone. Filters are weighed before and after solvent extraction with dichloromethane:methanol:toluene (1:1:1) and methanol:water (1:1). The second solvent extraction step was included to assure complete extraction of MWF components that were incompletely removed by the first extraction step alone. The NIOSH manual cites an estimated limit of detection of 0.03 mg/sample for both total and extractable weight.[85]

Other monitoring methods are the infrared technique by the German IFA (BIA 7750) and two methods by the British HSE: the gravimetric technique (MDHS 84) and the marker element technique (MDHS 95/2).[55,56,60] None of these methods is applicable to all categories of MWF like NIOSH method 5524. BIA 7750 and MDHS 84 cannot be used for synthetic fluids, and MDHS 95/2 is not suitable for straight oils.

Sampling on filters, with personal impactor, or with electrostatic precipitator may result in the loss of volatile components of the mineral oil mist. Woskie *et al.* (2003) concluded that for MWF aerosols, especially for used MWF, losses of mineral oils by filter sampling are acceptable and do not necessitate backup sorbent tube sampling to collect volatile oils stripped from the filter. Collection by personal impactor, produced similar weight losses to those of typical filter cassette sampling, while fewer losses were reported with an electrostatic precipitator.[134] According to Woskie *et al.* (2003), further work is needed to evaluate the extent of the vapour exposure and the composition of the vapours.[134]

2.5.3 *Biological monitoring*

No validated methods are available for the biological monitoring of exposure to mineral oil (see section 5.5) from base oils or formulated lubricant oil products.

Chapter 3

Sources

3.1 Natural sources

The hydrocarbon constituents of mineral base oils, *i.e.*, straight- and branched-chain paraffins, and naphthenic hydrocarbons with carbon numbers in the approximate range of 15 to 50, occur naturally in crude petroleum.[61]

3.2 Man-made sources

3.2.1 Production of mineral base oils

Mineral base oils are produced by vacuum distillation of the residue of atmospheric distillation of crude petroleum oil. Atmospheric distillation of crude oils yields fuels and fuel oils. Vacuum distillation of the residue yields mineral base oil fractions, which are further processed in refineries to produce refined mineral base oils.[61] Most of the mineral base oil production falls in the product group of 'other lubricant base oils'.[125]

The refining processes have changed considerably over the years. Originally, processing of crude mineral oils consisted of acid and clay treatment, and dewaxing by chilling. Solvent refining was introduced in the 1930s and hydrotreating (catalytic hydrogenation), as a more thorough process than 'hydrofinishing' (mild hydrogenation), was introduced in the 1960s. Since then, the trend has been increasingly towards the production of highly refined oils with

associated removal of unwanted components including PAC. Aromatics are removed by solvent extraction and by high-pressure hydrogenation (hydrocracking) to yield mineral base oils that contain less than 3% (w/w) of aromatic compounds by IP 346 analysis. Hydrocracking breaks down long-chain paraffins into smaller molecules and is able to open the rings of naphthenes (cyclic paraffins) formed from aromatic compounds during hydrogenation.

According to Dalbey and Biles (2003), virtually all modern mineral base oils are highly refined, do not contain PAC, and are not carcinogenic.[26]

3.2.2 *Production of mineral lubricant oil products*

A wide range of additives may be added to the mineral base oils to modify the physical and/or chemical characteristics of the base oils in order to provide the performance requirements of specific applications. These additives include viscosity improvers, emulsifiers, friction modifiers, antioxidants, detergents, and biocides. Additives are often proprietary materials and composition details of formulated products will vary between individual suppliers.

Typically, individual additives may be added in concentrations of less than 2%. Total amount of additives may account for up to about 30% of the formulated lubricant oils.[61,110]

3.2.3 *Use of mineral base oils*

Mineral base oils and lubricant oil products are used to reduce friction between surfaces in relative motion. Other applications of mineral base oils include removal or transfer of heat; removal of waste, fines, and contaminants; protection of surfaces against corrosion; and their use as a dielectric medium (electric oils).[110]

The annual market for mineral base oils in the European Union is approximately 5 million tons.[125] More than 65% is used in automotive applications and the remainder is used in other industrial applications. In automotive applications, the mineral oils are used in closed systems (*e.g.*, in gear boxes) and aerosols are not formed.[61,125] In other applications, mineral oil mists may be generated, either intended or not. Examples include metalworking, mist lubrication, rock drilling, agricultural spraying, ink printing, in textile machinery, and as concrete mould releasing agents. Approximately 7% of the European mineral base oil supply is used to produce MWF.[125]

In summary, mineral base oils are used as engine oils, gear oils, automotive transmission fluids, hydraulic fluids/oils, circulation oils, bearing oils, general-

purpose machine oils, machine-tool oils, compressor and refrigeration oils, steam-engine oils, textile oils, air-tool oils, MWF (cutting oils, roll oils and can-forming oils, drawing oils), rust prevention oils, heat-treating oils, transformer oils, process oils (product extenders, processing aids, carriers and diluents, water repellents, surface-active agents, batching oils, mould-releasing oils, wash oils).[61] Highly refined white oils are used in cosmetics, pharmaceutical preparations, and in various food products.[2,133]

3.2.4 *Use of mineral base oils in metalworking fluids*

A reason to single out MWF from other mineral lubricant oils is that much information on adverse health effects of occupational exposure to mineral lubricant oil products is from epidemiological studies in workers exposed to MWF. MWF are used for lubrication and cooling of metallic workpieces and cutting tools during the machining and shaping of these workpieces.

Originally, MWF consisted primarily of straight mineral oils (also called neat or non-soluble oils) and did not contain any water.[19,86] Straight mineral oils have excellent lubricating properties. In Europe and the USA, the straight mineral oils have largely been replaced by water-miscible cutting fluids from which the users prepare the water-mixed fluids.[9] The water-containing fluids have superior cooling capacity and are preferred in metalworking operations with considerable heat formation. The term ‘coolants’ is commonly used today to describe these water-containing MWF.[19]

MWF are complex chemical mixtures that can be grouped into four major categories:[19,86]

- the straight oils (‘non-soluble’ MWF), containing 60-100% mineral base oils; these fluids do not contain water
- the oil-in-water emulsions (‘soluble’ MWF), containing 30-85% mineral base oils and emulsifiers (fatty oils, fatty acids or esters) in various amounts of water
- the semi-synthetic fluids, containing 5-20% emulsified mineral oils and various synthetic chemicals in water
- the synthetic fluids; these fluids do not contain mineral base oils, but are totally water-based fluids; they are clear and slightly opalescent solutions of synthetic chemicals, frequently polyalkylene glycols, in water; the water content may be 70-95%.

Part or even the total mineral oil content can be replaced by synthetic hydrocarbons such as polyalphaolefins.[9]

Overall, MWF may contain varying amounts of oils (mineral and/or synthetic) and water, as well as additives like emulsifiers, corrosion inhibitors, buffers, biocides, and extreme pressure additives. In use, the complexity of these fluids is compounded by contamination with substances from the metalworking process. Furthermore, the water-based fluids support microbial growth and the formation of biological contaminants. Aerosols of MWF, therefore, can be seen as the mist and all contaminants in the mist generated during the metalworking process.

Chapter 4

Exposure

4.1 General population

Highly purified white mineral oils are being used in food, cosmetics, and in pharmaceuticals.[2,133] The general population may therefore be exposed to mineral oils by the consumption of foods, and the use of cosmetics and pharmaceuticals containing these purified oils. Specific data on exposure are not available. It is highly unlikely that the general population is exposed to aerosols of these purified mineral oils.

4.2 Working population

4.2.1 Exposure to mineral oils

The primary routes of human occupational exposure to aerosols of mineral oils are inhalation and dermal contact. Exposure can occur in workers employed in the manufacturing of cars, aeroplanes, metal parts and tools; in mining, agricultural spraying, and in the entertainment industry during the production of artificial smoke.

In principle, workers may be exposed to vapours of mineral oils as well. Vapour pressures of the mineral oil hydrocarbons are, however, extremely low at room temperature (boiling ranges: 300-600°C at atmospheric pressure), and vapours of mineral oils are barely formed at room temperature. However, at

elevated temperatures, vapour formation may become significant in the workplace. During cooling down, these vapours may condense and form aerosols.

Applications of mineral oils associated with aerosol generation include metalworking, rock drilling, mist lubrication, ink printing, agricultural spraying, artificial smoke generation, textile machinery, and concrete mould releasing. Thus, occupational exposure to mineral oils occurs in a variety of industries.

4.2.2 *Exposure to mineral-oil-containing metalworking fluids*

Most epidemiological studies on adverse health effects of mineral oils in humans concern workers exposed to MWF.[15,61] Therefore, most data on exposure to mineral oil mists are obtained from exposures to these MWF.

The MWF used are held in machine sumps, pumped onto the point of machining and run back into the sump. MWF may be applied by high-pressure spraying, continuous jet, spray, or hand dispenser. During machining and shaping operations, these fluids easily form aerosols as a result of the violent and rapid fracturing of fluid streams. Aerosol generation is influenced by the composition (additives and contaminants) of the fluids as settling of individual particles varies with density and volume.

Exposure to MWF aerosols has been expressed as the airborne concentration of inhalable, total, or thoracic particulate mass. Preference is to express exposure as the concentration of *inhalable* particulate mass.

Woskie *et al.* (2003) used a conversion factor of 1.4 for conversion from thoracic to inhalable size fraction and a conversion factor of 0.55 for conversion from closed-face cassette to thoracic mass. With these conversion factors, their results suggested that across all studies the mean MWF *thoracic* particulate exposure of workers varied from 0.12 to 0.68 mg/m^3, while the mean MWF *inhalable* particulate exposures varied from 0.22 to 0.95 mg/m^3.[134]

In 2007, Verma published relationships between inhalable, thoracic, and respirable fractions of MWF as measured by gravimetry after collection with the Respicon sampler. This sampler simultaneously collects all three fractions. When forced through the origin, ratio of inhalable to thoracic was 1.38; inhalable to respirable was 1.51; and thoracic to respirable was 1.13.[127] The inhalable to thoracic ratio of 1.38 is in agreement with the ratio of 1.4 used by Woskie *et al.* (2003).

Hallock *et al.* 1994 estimated historical exposures of airborne MWF in the automotive industry. MWF concentrations declined significantly during the period 1958-1987, with an arithmetic mean concentration of 5.42 mg/m^3 (total

aerosol mass) observed before 1970, and 1.82 mg/m^3 (total aerosol mass) after 1980 (Hallock *et al.* 1994[52] cited in NIOSH[86]).

The Integrated Management Information System (IMIS) developed by OSHA tracks a substantial cross-section of industrial occupational exposures. An examination of airborne mineral oil mist exposure in industries found little evidence of substantial inter-industry differences in mean exposure concentrations. From 1979 to 1995, the occupational exposure data compiled in IMIS demonstrated a steady decline in airborne exposure concentration. The arithmetic mean concentration for all samples collected during this period was 0.92 mg/m^3 (total particulate mass). The percentage of total aerosol exposures of less than 0.5 mg/m^3 increased from 36.7% before 1980 to 73% after 1990. The arithmetic mean concentration for the period 1989-1994 was 0.49 mg/m^3 (total particulate mass).[86]

Since 1967, NIOSH has conducted more than 70 health hazard evaluations of industries with occupational exposures to MWF or mineral oil aerosols. Exposure data from 38 evaluations indicated that airborne MWF exposures have generally decreased over time. The arithmetic mean personal exposure concentrations (total particulate mass) were: 1.23 mg/m^3 (21 plants) in the 1970s; 0.57 mg/m^3 in the 1980s (15 plants); and 1.0 mg/m^3 in the 1990s (2 plants). The latter value is based on only two plants. The overall mean concentration for the 38 plants was 0.96 mg/m^3 (total particulate mass). The exposure data collected in these 38 plants show airborne concentrations similar to those in the OSHA IMIS data set. These two data sets indicated an overall reduction in airborne MWF exposures since 1980.[86]

From the foregoing data, the Committee concluded that the average occupational airborne MWF aerosol concentrations in the 1990s were approximately 1 mg/m^3 (total particulate, underestimated by the early methods used), equivalent to approximately 1 to 2 mg/m^3 inhalable particulate, or 0.5 to 0.8 mg/m^3 thoracic particulate, by conversion from total particulate.

Chapter 5

Kinetics

Mineral base oils have a complex and variable composition, with aliphatic and naphthenic (cycloparaffinic) hydrocarbons as their main constituents. The kinetic properties of the base oils will, therefore, depend on their composition, and relate to the properties and the interactions of the individual components. It is beyond the scope of this advisory report to evaluate the kinetics of each individual component. However, the kinetics of some specific mineral oils or groups of hydrocarbons has been studied, and a summary of the findings on these oils is given below.

5.1 Absorption

5.1.1 Inhalation exposure

Animal studies with a car (Penn oil®, SAE no. 10) and a diesel engine (SGF no. 1) lubricating oil aerosol suggest that absorption is not rapid and lung clearance is mediated by macrophages.[78]

Mice, rats, and rabbits that were continuously exposed for 343 days to a SGF no. 1 oil aerosol at a concentration of 63 mg/m^3 (aerosol production for 30 min/hour, every hour), had oil in alveolar macrophages of the mediastinal lymph nodes and in the lymphatic channels of the lung and the pleura; in mice, concentrations of hydrocarbons as percentage of total wet organ weight were 0.13% in the lungs and 0.03% in the livers.[78]

In another study in mice, oil droplets of liquid petrolatum (Nujol®) or motor oil (SAE no.10) penetrating into the lung were immediately phagocytosed. This process was essentially completed within 48 hours after aspiration of oil mists, except after prolonged exposures varying from 2 to 4 weeks, when large numbers of free droplets are seen in the lungs. The concentration of the liquid petrolatum and motor oil droplets in the lung remained essentially unchanged for ninety-six hours after a 2-hour exposure period.[105]

After inhalation of equal concentrations of aliphatic, aromatic, and naphthenic hydrocarbon vapour, the concentrations of aliphatic and naphthenic hydrocarbons in human and animal blood were lower than the concentrations of aromatic hydrocarbons.[33] According to Eide (1990), the reason for this is the lower blood solubility of naphthenic, and in particular aliphatic hydrocarbons. The uptake of aliphatic hydrocarbons increased with an increasing number of carbon atoms in the C8-C10 range, and decreased from C10 to C12.[33]

5.1.2 *Dermal exposure*

The skin barrier is only permeable to hydrocarbons of a certain molecular size. Paraffinic substances of up to 20 carbon atoms appear to be able to penetrate the skin. Recently medium-chain chlorinated paraffin (MCCP), a component of MWF, was estimated to be dermally absorbed in amounts comparable to inhalation uptake.[18]

Studies in monkeys show that dermal absorption is slow when radiolabelled mineral oil in an aqueous white oil emulsion is administered subcutaneously. Radioactivity remaining at the sites of injection accounted for 85-99% and 25-33% of the administered radioactivity, at 1 week and 10 months following injection, respectively.[61]

5.1.3 *Oral exposure*

Results from animal experiments suggest that 1 to 5% of ingested food-grade mineral oil is absorbed as such by the intestinal mucosa. Phagocytosis may play a role in this process of absorption.[133]

Studies in rats show that absorption of ingested *n*-alkanes, isoparaffins, and naphthenes (saturated cyclic hydrocarbons) is inversely related to molecular weight, ranging from complete absorption at the lower end of the molecular weight range to about 60% for C14 hydrocarbons, 5% for C28 hydrocarbons, and essentially no absorption for aliphatic hydrocarbons with more then 32 carbons.[2]

5.2 Distribution

Studies in mice, rats, hamsters, rabbits, and dogs showed that mineral oil droplets are phagocytosed in the lungs. Furthermore, clinical observations in man showed that deposition occurs in the hilar nodes from where mineral oils may be transported to the spleen and other organs.[133]

Absorbed mineral oil is transported throughout the body by the bloodstream and the lymph system. Storage takes place in adipose tissue or in fat in organs. After excessive exposure, mineral oil droplets have been detected in the mesenteric and portal lymph nodes, and also in the liver, the spleen, and in adipose tissue in man.[133]

Aliphatic and naphthenic hydrocarbons are rapidly distributed from the blood to other organs and tissues, particularly to those rich in lipids. The concentration in the brain of trimethyl cyclohexane (C9 naphthene) is about twice the concentration of trimethyl benzene (C9 aromatic) after inhalation of air containing equal concentrations (100 ppm) of either of the two compounds.[33]

Accumulation of mineral oils in the lung is of concern with prolonged or high-level inhalation exposure to aerosols or after aspiration, as indicated by numerous case reports of lipid pneumonia in humans who were exposed to mineral oil through intranasal application of liquid petrolatum in medicinal nose drops.[2] Following absorption, the hydrocarbons in mineral oils may be expected to accumulate to some degree in the liver and fatty tissues, as indicated by the observation that 24 hours after administration of an oral dose of tritiated mineral oil to rats, concentrations of tritiated oil were about 7-fold greater in fatty tissues and the liver than in the kidney and the brain.[2] Lipid granulomas (clusters of lipid droplets surrounded by lymphocytes and macrophages) have been found in man at autopsy, particularly in the liver, spleen, and abdominal lymph nodes.[2] These structures are associated with dietary exposure to mineral oils and waxes.[2]

5.3 Biotransformation

Few data are available on the biotransformation of this group of products, but data from observations in both humans and animals suggest that aliphatic hydrocarbons are generally inert and excreted in unchanged form.[133]

Aliphatic hydrocarbons in the 16 to 36 carbon range are expected to undergo slow metabolism by oxidative reactions in animals and humans. In monkeys, 2 days after intramuscular injection of a mineral oil emulsion spiked with radio-labelled *n*-hexanedecane, substantial portions (30-90%) of radioactivity in

various tissues existed as unmetabolised *n*-hexanedecane. The remainder of the radioactivity was found as phospholipids, free fatty acids triglycerides, and sterol esters.[2] No radioactivity was found in water-soluble factions. The common presence of lipid granulomas in human autopsies and the widespread dietary exposure to mineral oils and waxes are consistent with the concept that aliphatic hydrocarbons in this fraction are slowly metabolised.[2]

5.4 Elimination

Few data are available on the rate of elimination of mineral oils. Results from animal experiments suggest that 95 to 99% of ingested food-grade mineral oil is not taken up by the body and leaves the body unchanged in the faeces.[133] Aliphatic hydrocarbons having carbon numbers of 16 to 35, may be expected to be eliminated predominately in the faeces, based on experiments in rats, which were given oral or intraperitoneal doses of these compounds. In rats orally exposed to tritiated mineral oil, 90% of administered radioactivity appeared rapidly (within 2 days) in the faeces, predominantly as unchanged mineral oil. Less than 10% of the administered radioactivity appeared in the urine within 2 days of administration. After intraperitoneal exposure to tritiated mineral oil, radioactivity appeared more slowly in the faeces (11% of administered radioactivity appeared in the faeces within 8 days of dosing). Urinary excretion of metabolites, within 8 days of dosing, represented about 8% of administered radioactivity.[2]

5.5 Possibilities for biological monitoring

Because of the compositional complexity of mineral oils, detection of specific components (*e.g.*, specific hydrocarbons or their metabolites) in biological fluids or tissues cannot be expected to provide a reliable biomarker of exposure to mineral oil. However, detection of specific hydrocarbons (or their metabolites) from several aromatic and/or aliphatic fractions in biological fluids or tissues can provide reliable evidence of exposure. Lipid granulomas, for example, found in autopsied livers and spleens (*i.e.*, lipid droplets surrounded by lymphocytes and macrophages) may be useful as an index of exposure to petroleum hydrocarbons, especially aliphatic hydrocarbons having carbon numbers between 16 to 35.[2]

5.6 Summary

Animal studies with mineral oil aerosols suggest that absorption after inhalation is slow and that lung clearance may be mediated by macrophage phagocytosis. Particle size and composition influence the absorption of components of inhaled mineral oil mists. Dermal absorption of mineral oil mist is expected to be slow. Results from animal experiments suggest that almost all (95-99%) of ingested food-grade mineral oil leaves the body unchanged in the faeces, 1-5% being absorbed as such by the intestinal mucosa. Phagocytosis may play a role in this. Studies in rats show that absorption of ingested *n*-alkanes, isoparaffins, and naphthenes is inversely related to molecular weight.

Clinical observations in man have shown that deposition takes place in the hilar nodes from where they may be transported to other organs such as the spleen. After oral exposure, the absorbed part of the oil is transported throughout the body by the blood circulation and the lymph system. Storage takes place in adipose tissue or in fat. After excessive exposure, mineral oil droplets have been identified in the mesenteric and portal lymph nodes, and in the liver, spleen, and adipose tissue in man. Data on the biotransformation of mineral oil components are limited.

Chapter 6

Mechanisms of action

Mineral base oils contain hydrocarbons with a carbon number of 15 or more as their major constituents. Non-carcinogenic effects are related to the exposure to these hydrocarbons. Carcinogenic effects are related to the PAC content of mineral base oils and, as a corollary, to their stage of refining. As a generalization, the non-carcinogenic effects are, therefore, associated with the exposure to mineral base oils, irrespective of its stage of refining and its PAC content.

The main organs affected by inhalation exposure to mineral oil aerosols are the airways and the lungs.

According to ATSDR, pulmonary irritation and pneumonia from inhalation and oral exposure to complex mixtures of petroleum hydrocarbons are thought to involve direct parent hydrocarbon interaction with nerve cell membranes resulting in broncho-constriction and dissolution into membranes of lung parenchyma resulting in a haemorrhagic exudation of proteins, cells, and fibrin into alveoli.[2]

Aspiration of mineral oils can produce lipid pneumonia and lipid granulomas in the lungs.[61] Mineral oils that have entered the lung are taken up by macrophages (called lipophages), and may cause inflammatory and sometimes fibrotic responses of lung tissue, due to incomplete phagocytosis. Lipid granulomas of the lung are localized lipid pneumonias, usually found in adults as a result of habitual use of large amounts of mineral oil by nasal, oral, or pharyngeal administration for prolonged periods of time.[61]

The (micro)granulomas in the liver and mesenteric lymph nodes of rats fed mineral hydrocarbons might develop as a direct response in order to phagocytose the accumulated hydrocarbons or as an indirect response to chemo-attractive cytokines produced by the cells in the liver and the mesenteric lymph nodes activated by the presence of the mineral hydrocarbons.[17] The response was not considered typical of a foreign body reaction.

The carcinogenicity of mineral base oils is related to their PAC content.[79] In addition, the level of mutagenic activity has been shown to be a reflection of the PAC content.[99] Therefore, the carcinogenic mechanism of action of mineral base oils can be assumed to be identical to that of polycyclic aromatic hydrocarbons.

Chapter 7

Effects of exposure to unrefined or mildly refined mineral base oils

In the European Union, the unrefined and mildly refined mineral base oils are classified in carcinogenicity category 1: substances known to be carcinogenic to humans. IARC concluded that there was sufficient evidence for the carcinogenicity in experimental animals for the following base oils: untreated vacuum distillates, acid-treated oils, aromatic oils, mildly solvent-refined oils, and mildly hydrotreated oils.[61]

7.1 Observations in humans

Studies dating back to the early 1920's showed that exposure to unrefined and mildly refined mineral base oils was associated with various types of cancer in humans including cancer of the skin, pharynx, lung, stomach, kidney, rectum and scrotum, and leukaemia.[61,79] These studies are summarized in Tables E-9 to E-11 of Annex E.

7.2 Observations in animals

Animal data are in line with the observations on carcinogenicity of mildly refined mineral oils to the skin. Many studies have shown that mildly refined mineral lubricant base oils, when applied to the skin, cause skin papillomas and carcinomas in various animal species (Table F-5 of Annex F). The malignant effects were found to be caused by the presence of (alkylated) PAC and the

carcinogenic potential of the base oils appeared to be related to their PAC content.

Chapter 8

Effects of exposure to highly refined mineral base oils

Highly refined mineral base oils are mixtures of saturated hydrocarbons and contain straight and branched-chain paraffinic and cycloparaffinic (naphthenic) hydrocarbons having carbon numbers of 15 or more. (Cyclo)paraffinic hydrocarbons are also major constituents of less than highly refined mineral oils. Therefore, the effects described below may also be observed after exposure to less than highly refined mineral oils.

8.1 Observations in humans

8.1.1 Lipid granuloma in the lung and lipid pneumonia

Inhalation or aspiration of highly refined mineral oils may produce lipid pneumonia and lipid granulomas in the lungs.[61] Mineral oil may enter the trachea and bronchi in individuals with a reduced or absent cough reflex. It inhibits the action of respiratory cilia, allowing passage to the alveoli. Mineral oils are taken up by macrophages (called lipophages), which remain within the alveolar spaces and cause inflammatory and sometimes fibrotic responses of lung tissue. Lipid granulomas of the lung are localized lipid pneumonias, and may be found in adults as a result of habitual use of large amounts of mineral oil by nasal, oral, or pharyngeal administration for prolonged periods of time.[61] Numerous cases have been reported in the literature but these cases were related to oral administration of mineral oil, oil-based nose drops or intra-laryngeal injection of medicinal

mineral oil.[61] Most lipid pneumonia cases described in the literature are caused by liquid paraffin aspiration during extended laxative treatment of patients with swallowing or pharynx and oesophagus diseases.[92] These exposures do not represent occupational exposures. Case reports of lipid pneumonia resulting from occupational exposure to highly refined oils are not available.

8.1.2 Respiratory symptoms

Acute and chronic respiratory symptoms have been sparsely documented in workers in the entertainment industry where highly refined mineral oils may be used for the generation of artificial fog.[120,126] However, prevalence rates for chronic respiratory symptoms were presented for exposure to glycol and mineral oil aerosols combined. Similarly, adjusted odds ratios for acute respiratory symptoms were given for exposure to glycol and mineral oil aerosols combined. It is, therefore, not possible to distinguish between the adverse effects of mineral oil and glycol-based fogs.

8.2 Animal experiments

8.2.1 Irritation and sensitization

In the available studies, no or slight eye and skin irritation and no or slight skin sensitization was observed (Table F-2 of Annex F). In acute inhalation toxicity studies, sensory and pulmonary irritation was observed in mice (Table F-3 of Annex F).

8.2.2 Acute toxicity

Highly refined white mineral oils have low acute toxicity (Table F-3 of Annex F). After acute inhalation of white mineral oils, mild inflammatory reactions can be seen in mice at exposure levels of 200 mg/m^3. LD_{50} values derived from acute dermal toxicity studies are >2 g/kg bw for hydrotreated (light and heavy) naphthenic distillates. LD_{50} values derived from acute oral toxicity studies are over 5 g/kg bw for white mineral oil.[20]

8.2.3 Short-term and sub-chronic toxicity

Effects observed after short-term inhalation exposure to highly refined oils include the accumulation of foamy alveolar macrophages, increased lung weight,

and increased dry weight/wet weight of the lungs (Table F-4 of Annex F). Accumulation of macrophages in alveoli and increased lung weights were generally observed at the lowest concentration group (50 mg/m^3) and higher. Dalbey and Biles (2003) considered mild accumulation of alveolar macrophages in the absence of other significant toxicity not likely to constitute an adverse effect and considered a NOAEL of approximately 50-150 mg/m^3 appropriate on the basis of 13-week exposures to formulated mineral oil products.[26]

In two 90-day experiments, Fischer-344 rats were given diets containing oleum-treated or hydrotreated mineral hydrocarbon food-grade white oils at concentrations ranging from 5,000 to 20,000 mg/kg food in the first experiment, and 10 to 20,000 mg/kg food in the second experiment. Effects included increased liver weight and microscopic inflammation of the liver, and increased mesenteric lymph nodes weights. At necropsy, increases in weight of liver, kidney, and spleen were significant. Microscopic changes included multifocal lipogranulomata in mesenteric lymph nodes and liver. No changes were observed in rats fed either white oil for 90 days at dietary concentrations of 10 and 100 mg/kg food, equivalent to a minimum intake of 0.65 and 6.4 mg/kg bw/day, respectively.[6]

8.2.4 *Long-term non-carcinogenic toxicity*

After long-term (12-24 months) inhalation exposure to a 5 mg/m^3 oil mist prepared from a paraffinic or naphtenic oil base, foamy macrophages were detected in the lungs and in the hilar lymph nodes in dogs, rats, mice and gerbils.[114,129] There was no other tissue response found. In the study by Stula and Kwon (1978), the aerosol was prepared from a complex oil mixture (70% paraffinic oil, supplemented with vegetable oils, alkyl phosphate esters, polyalkylene oxide waxes, and resins) with acetone vapour.[114] Long-term exposure to 100 mg/m^3 resulted in lipid granulomas in dogs and rats.[114,129] After long-term oral exposure to concentrations of 25 and 5% mineral oil in the diet, granulomatous inflammation in mesenteric lymph nodes were found in rats of both sexes. Long-term exposure to intraperitoneal injections caused lipid granulomas in mice. For a summary, see Table F-5 (Annex F).

In a two-year dietary study carried out according to the OECD Guidelines, Fisher-344 rats were fed with white mineral oils in dietary concentrations of 60, 120, 240, and 1,200 mg/kg bw/day, adjusted periodically to account for body weight changes. Two different oils were investigated, designated as P70(H) and P100(H), respectively. The mineral oils were derived from paraffinic crude oil (P), with viscosities at 40°C of 70 and 100 centistoke, respectively, and highly

refined by hydrogenation (H). The investigators did not find treatment-related mortality, neoplastic lesions, or changes in clinical health, haematology, serum chemistry, or urine chemistry in any group. Higher mesenteric lymph nodes (MLN) weights were accompanied histopathologically by an increased number of infiltrating histiocytes. In the males, the higher MLN weights were only observed in the 1,200 mg/kg bw/day P70(H) group at both 12- and 24-month sacrifices; in the females, the increase in MLN weights was significant at all doses of P70(H) at 24 months. No other significant histopathological findings were reported. Mineral hydrocarbons were found in the liver, reaching maximal concentrations more rapidly with P70(H) than with P100(H), and returning to near-background levels during the reversibility phase. According to the authors, lifetime exposure of Fisher-344 rats to P70(H) and P100(H) white oils produced minimal changes and did not affect clinical health of the animals. The authors considered 1,200 mg/kg bw/day as the NOAEL for any effect seen in their study.[124]

8.2.5 *Carcinogenicity*

No increased tumour incidence was observed in dogs and rats after long-term inhalation exposures up to 100 mg/m^3 of highly refined oils (Table F-5 of Annex F).

After long-term oral, dermal or subcutaneous exposure to highly refined mineral oil, no increase of tumour incidence was found. In the dietary toxicity study by Trimmer *et al.* (2004) with highly refined oils (described above), no treatment-related neoplastic lesions were found.[124]

A single intraperitoneal injection of 0.4 mL or 0.5 mL to 2-month-old female BALB/c mice (bw not reported), or 3 intraperitoneal injections of 0.5 mL of highly refined mineral oil at 2-month intervals (or higher intraperitoneal doses) did cause increased plasma-cell tumours.

8.2.6 *Genotoxicity*

In genotoxicity studies (Table F-6 of Annex F), white mineral oils of medicinal quality did not induce mutations in *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA 1538). Negative results were also reported in mouse lymphoma studies, in bone marrow cytogenetic, and in micronucleus assays.

8.2.7 *Fertility and development*

Studies are summarized in Table F-7 (Annex F). In rats, no developmental toxicity was observed after dermal exposure to 2,000 mg/kg bw/day of several lubricating base oils. In addition, no teratogenic effects were observed after oral exposure to 5 ml/kg bw/day highly refined white oil by gavage. Overall, data on effects of mineral oils on fertility and development are limited.

8.3 Summary

Highly refined mineral oils with no additives have relatively low toxicity by all routes of exposure. In acute inhalation studies with white mineral oils, mild inflammatory reactions can be seen in mice at exposure levels of 200 mg/m^3. In short-term and subchronic inhalation studies, foamy alveolar macrophages may accumulate at exposure levels of 50 mg/m^3 and higher. In long-term inhalation studies, exposure to 100 mg/m^3 resulted in microgranulomas in the lungs of dogs and rats. After 12-month inhalation exposure to a paraffinic or naphthenic mineral oil mist of 5 mg/m^3, few vacuolated macrophages filled with oil particles could be detected in the lungs of dogs, rats, mice, and gerbils, without other cellular response.

Highly refined mineral base oils do not have carcinogenic potential and are not genotoxic. Data on effects of mineral oils on fertility and development are limited.

Chapter 9

Effects of human exposure to other lubricant base oils: mineral oil-containing metalworking fluids

The majority of the 'other lubricant base oils' is used as lubricants in automotive and industrial applications. As lubricants in automotive applications, aerosols are not expected to occur, but in industrial applications aerosol formation may well occur. In this Chapter, the Committee focuses on human data showing adverse health effects in metal workers after occupational exposure to different types of MWF. Most of these studies did not give details on the composition and purity of the oils used.

New and consistent information on adverse health effects from occupational exposure to MWF has become available in the last few decades, and these epidemiological studies in metal workers will be reviewed here. Focus will be on those studies that contain quantitative exposure-response data. The different types of MWF are described in Chapter 3.2.4.

9.1 Dermal effects of metalworking

Workers whose skin is repeatedly exposed to mineral metalworking oil (straight oils) may develop eczematous dermatitis, contact dermatitis, folliculitis, oil acne, lipid granuloma, and melanosis.[58,61,86,113] Straight oil MWF contain additives and it is not possible from the available studies to separate the effects of mineral oils from those of additives.

Both irritant and allergic contact dermatitis are thought to be caused by non-mineral oil components present in MWF.[45,86,117] As a generalization, the oil-in-

water emulsions (soluble and semi-synthetic MWF) primarily cause irritant and occasionally allergic contact dermatitis, and the straight mineral oils mainly cause irritant skin reactions.

9.2 Respiratory effects of metalworking

Adverse respiratory effects that have been reported after exposure to MWF include lipid pneumonia, hypersensitivity pneumonitis, pulmonary fibrosis, asthma, bronchitis, respiratory symptoms, and changes in pulmonary function.[61,86] Most epidemiological studies had a cross-sectional design. A few studies included repeated measures within one calendar year[95] or were followed-up for 2[71,119], 3[66], or 7 years[107]. Study details are given in Table E-1 (Annex E). A summary of the main findings is given in Table 11.1.

9.2.1 Lipid pneumonia

Case reports of lipid pneumonia resulting from occupational exposure to mineral oils during metalworking are relatively rare, when taking the frequency of exposure to mineral oils into account.[86,93] In recent decades, Penes *et al.* (1990) reported lipid pneumonia in a person who worked for 16 years as a machinist.[92] Perol *et al.* (1989) reported a 45-year-old patient who was occupationally exposed to motor oil spray[93]; and Cullen *et al.* (1981) reported on a case in a steelrolling tandem mill operator, who was exposed for 3 years to straight and soluble oil MWF in concentrations below 5 mg/m^3 (particle size <5 µm).[23]

Epidemiologic studies did not report on incidence or prevalence of lipid pneumonia among workers exposed to MWF. Apparently, lipid pneumonia associated with occupational exposure to oil mist in metalworking operations is rare. Overall, observational data on lipid pneumonia and lipid granuloma development after occupational exposure to mineral oil mists are limited.

9.2.2 Hypersensitivity pneumonitis

Many cases of hypersensitivity pneumonitis associated with occupational exposure to MWF have been reported.[42,59,86] Outbreaks have occurred up till recently.[10,14,27,51,87] Hypersensitivity pneumonitis is also known as extrinsic allergic alveolitis and involves an immunological reaction to inhaled antigen. In its acute phase, it is characterized by alveolar inflammation and flu-like symptoms; in its chronic phase, it is characterized by pulmonary fibrosis and decreased – potentially irreversibly – pulmonary function.

In a workshop held in 1997, in which eight clusters of hypersensitivity pneumonitis among MWF-exposed workers were discussed, it was concluded that a risk for hypersensitivity pneumonitis exists where water-based MWF are used, and unusual (among which the non-tuberculous *Mycobacterium chelonae*) microbial contaminants predominate.[73] Cases of hypersensitivity pneumonitis were only reported in plants using water-based fluids and the consensus view was that microbial contaminants – in particular, non-tuberculous mycobacteria and fungi – were the likely causes of this pneumonitis. More recently, Bukowski (2003) came to the same conclusion, when he reviewed outbreaks of hypersensitivity pneumonitis, and pointed to microbial exposure as the cause of these outbreaks.[15] Both *Mycobacterium* and *Pseudomonas* species have been implicated in the aetiology, but these organisms have not consistently been found in outbreaks.[27,94] Nevertheless, the evidence points to *Mycobacterium immunogenum* as one of the possible causative microorganisms, as it appeared to be able to induce histological changes in lung tissue of mice that resembled hypersensitivity pneumonitis in man.[49,122] These lung changes were obtained with heat-killed and lysed *M. immunogenum*, and with used MWF that was contaminated by *M. immunogenum*. Recent results from an investigation of an outbreak of alveolitis in the UK suggest that *Acinetobacter* species, too, may contribute to cases of extrinsic allergic alveolitis.[94]

9.2.3 *Pulmonary fibrosis*

Two epidemiological studies on pulmonary fibrosis after occupational exposure to mineral oil mist are available.[107,108] In both studies, the exposures have likely been underestimated because of high peak exposures. Besides, smoking and exposure to asbestos occurred which may have contributed to the chest X-ray changes observed.

In a Norwegian cross-sectional study with matched pairs, Skyberg *et al.* (1986) investigated 25 cable plant workers who were exposed to mists and vapours of mineral oils and kerosene for 5-35 years. Time-weighted average (8 hours) concentrations were reported as 0.15-0.30 mg/m^3 (extracted total particulate), but one hydrocarbon vapour measurement showed a short-time (time-period not specified) vapour exposure level of 2,000-4,000 mg/m^3. Increased prevalence of slight basal lung fibrosis was found (7 cases; 1 case in the control group; $p<0.05$). Vital capacity and % predicted FEV_1 were not decreased in the exposed workers. The authors concluded that the actual oil mist exposure levels might have been severely underestimated, and that exposure to

mists and vapours of petroleum distillates was the most probable cause of the basal lung fibrosis.[108]

The follow-up study through 1990 by Skyberg *et al.* (1992) included 37 workers employed for at least 3 years in oil impregnation of cables in the period from 1963 through 1983. The time-weighted average concentration of mineral oil vapours was estimated to be 50-100 mg/m^3. Time-weighted average concentrations of mineral oil mists were estimated to be 0.5-1.5 mg/m^3 (total particulate) in the cable impregnation area. Chest X-ray in 25 workers and 25 matched controls showed increased prevalence of lung fibrosis (10 cases; 1 case in the control group; $p<0.01$). In chest radiographs available from both 1979-1980 and 1989-1990 (n=16 impregnation workers), an increased profusion of small opacities was found in 6 workers at follow-up. No cases of regression were observed indicating that the fibrosis was progressive after cessation of exposure. The authors concluded that exposure to oil mist and vapour was the most plausible cause of the fibrosis, and that smoking and industrial exposure to asbestos might have contributed to the radiographic changes on chest X-ray. They considered it unlikely that smoking and asbestos exposure were the only causes of the radiographic changes.[107]

9.2.4 *Asthma and bronchial hyperresponsiveness*

The NIOSH Criteria Document on Occupational Exposure to Metalworking Fluids reviewed the literature on the occurrence of occupational asthma in workers exposed to mists of various MWF.[86] In Table E-2, an overview is given, containing the exposure-response data (exposure levels, prevalence and/or risk ratios) for asthma, derived from the studies that contained a quantitative exposure assessment.

The cross-sectional studies show a similar prevalence of asthma in MWF exposed (0-13%) workers compared to non-exposed (4-12 %) workers.[3,50,74] Risk ratios range from 0.5 to 3.5.[36,50,65,74,76] The observed increases in asthma risk ratios concern workers exposed to synthetic MWF. No statistically significant increases were observed for mineral-oil-containing MWF.

Only a few studies divided the data into asthma cases prior to employment and post-hire or new-onset asthma cases. When only new onset asthma is included, the data of Robins *et al.* (1997) give a prevalence of 3% (3/120) in soluble oil exposed workers and 1% (1/120) in non-exposed workers.[95] In the study of Rosenman *et al.* (1997), higher prevalences of 9.8% and 23.5% were found in those exposed to mineral oil only and to soluble (emulsified) oil, respectively. These percentages include individuals with only symptoms

suggestive of work-related asthma. A control group was not included in the Rosenman study.[98]

Kriebel *et al.* (1997) found a prevalence ratio for post-hire asthma of 3.2 (95% CI, 0.8-13.7) for machinists compared to non-machinists. The prevalence ratio for pre-hire asthma was 1.4 (95% CI, 0.7-2.8).[74] Eisen *et al.* (1997) tried to control for the healthy-worker effect by relating new-onset asthma to exposure to a specific type of metalworking fluid or operation within 2 years prior to the onset. This approach did not show elevated prevalence ratios for straight and soluble metalworking fluid exposure.[35]

In a few studies, the methacholine challenge test was used to find bronchial hyperresponsiveness as an indicator of asthma.[3,71,81,132] Exposures included straight oil and soluble and synthetic MWF. The prevalence of individuals, for which the forced expiratory volume in 1 second (FEV_1) had fallen by ≥20%, were similar for exposed (5-19.5%) and non-exposed (4-15%) workers. Normalized dose-response slope was, however, significantly steeper in exposed workers and related to cumulative exposure to soluble (but not straight) oil mist.

In a cross-sectional study, Massin *et al.* (1996) investigated 114 ball-bearing workers and 55 blue-collar workers as the controls, using a questionnaire and the methacholine challenge test. Geometric mean concentration of soluble oil mists in the cutting and machining area were 0.65 mg/m^3 in 1990, 1.49 mg/m^3 in 1989, and 2.2 mg/m^3 in 1979, as dichloromethane extracted total particulate. After adjustment for baseline FEV_1 and age, a significantly steeper normalised dose-response slope to methacholine, defined as 1/((% fall in FEV_1/µmol methacholine) + 2.5), was found among the exposed workers compared to the controls (p=0.01), indicating airway hyperresponsiveness in the exposed workers. This normalized dose-response slope was significantly related to the cumulative exposure to soluble oil mist.[81]

In another cross-sectional study, Ameille *et al.* (1995) investigated 230 exposed and 78 unexposed workers of a large car-making plant, using questionnaires and the methacholine challenge test. The geometric mean oil mist concentration was 2.19 mg/m^3 (GSD, 1.9 mg/m^3) and the arithmetic mean was 2.6 mg/m^3 (SD, 1.83 mg/m^3) measured as the extracted total particulate in areas using straight oils.[3] After reanalysis of the original data by Wild and Ameille, a significantly steeper normalized dose-response slope to methacholine, defined as 1/((% fall in FEV_1/µmol methacholine) + 2.5), was reported in the workers exposed to soluble mineral oil compared to the workers not exposed to soluble oil. However, the trend with duration of exposure to soluble oil mist was not statistically significant.[132]

These findings were confirmed in a 2-year prospective cohort study by Kennedy *et al.* (1999) among newly apprenticed machinists attending the provincial technology school and a comparison group of apprentices from construction painting, insulation, and electrician apprenticeship classes. Tests included respiratory questionnaires, spirometry, methacholine challenge, and allergy skin tests. Baseline testing was carried out while participants were attending their year 1 apprenticeship training class at school. Follow-up testing was conducted approximately 2 years after baseline. A complete baseline and follow-up data set was obtained for 82 machinists and 157 control subjects. Details on duration of exposure were collected by interview and 68 representative full shift personal samples for 'total aerosol' were obtained from 13 different machine shops (arithmetic mean, 0.46 mg/m^3; geometric mean, 0.31 mg/m^3; GSD, 2.39 mg/m^3). In all of these shops, straight oil was used in combination with synthetic and soluble oils. The prevalence of a positive allergy skin test did not differ between groups, although in both groups, a greater proportion developed a new positive test reaction at follow-up than the proportion who were positive at the first visit and negative at the second. Machinists and control subjects did not differ at baseline. An equal percentage of individuals (5%) with a FEV_1 fallen by ≥20% at the highest methacholine test concentration (8 mg/mL) was found among exposed and non-exposed workers at baseline testing, but an increased percentage (not statistically significant) among exposed (10% versus 4% in controls) was found at follow-up. The dose-response slope to methacholine among exposed was comparable with that of the non-exposed at baseline testing, but significantly steeper in exposed at follow-up testing. This steeper methacholine slope at follow-up was associated with increased duration of exposure to both soluble and synthetic MWF, but not with exposure to straight oils. The authors concluded that exposure to water-based MWF (especially synthetic fluids) is associated with increased bronchial hyperresponsiveness to methacholine at follow-up and that straight oils may be less likely to be associated with bronchial hyperresponsiveness than the water-based fluids.[71]

9.2.5 *Bronchitis*

In Table E-3, an overview is given of the exposure-response data for bronchitis, derived from the studies that contain a quantitative exposure assessment.

Prevalences of bronchitis are slightly higher in exposed (2-19.8%) compared to non-exposed (2-10.6 %).[3,50,81,95,98,118] Risk ratios range from 0.80 to 8.6.[50,65,66,95,118] The only longitudinal study on bronchitis found a risk ratio of

1.8 (95% CI, 1.1-2.9).[66] Generally, a higher prevalence or risk ratio for bronchitis was observed after exposure to synthetic MWF as compared to other MWF classes.

In a longitudinal study, Jarvholm (1982) re-examined workers 3 years after a previous cross-sectional study on respiratory symptoms in 1978. The workers had been exposed to straight and emulsified cutting oil at concentrations ranging from 1 to 4.5 mg/m^3 in the mechanical engineering industry. Fifty-eight exposed and 27 non-exposed men who previously reported respiratory symptoms, and 49 exposed and 17 non-exposed men who reported no respiratory symptoms in 1978 participated in the study. All men were clinically examined by a physician, after spirometry and a respiratory symptom questionnaire. Chronic bronchitis was more prevalent among the exposed men with respiratory symptoms in 1978 (prevalence ratio, 1.8; 95% CI, 1.1-2.9).[66,67]

In a cross-sectional study by Robins *et al.* (1997), 83 machinists exposed to soluble oils and 46 assembly workers of an automotive transmission machining plant were investigated. Pulmonary function tests were taken at 3 time points and a questionnaire was included in the study. Exposure measurements taken at the same time points with personal 2-stage samplers measured mean exposure concentrations of 0.41 mg/m^3 (thoracic particulate) among machinists and 0.13 mg/m^3 among assemblers. The percentage of subjects reporting chronic bronchitis was higher among machinists than among assemblers (odds ratio, 6.8; $p<0.05$).[95]

In a cross-sectional study by Greaves *et al.* (1997), 1,042 machinists and 769 assemblers were examined by questionnaires. Current and past exposure was measured by personal and area sampling. Mean current exposure levels were 0.43, 0.55, and 0.41 mg/m^3 (thoracic particulate) for straight, soluble, and synthetic MWF, respectively. After adjustment for confounding, chronic bronchitis was only statistically significantly associated with increasing levels of current exposure to synthetic MWF.[50]

In another cross-sectional study by Ameille *et al.* (1995) (described before), no statistically significant increase in the prevalence of bronchitis was observed after exposure to straight MWF at arithmetic and geometric mean concentrations of 2.6 mg/m^3 and 2.2 mg/m^3, respectively (dichloromethane extracted total particulate).[3]

A more recent cross-sectional study among 726 male Finnish machine workers and 84 male office workers was performed by Jaakkola (2009). Information on exposure to MWF and health effects of the respiratory tract were collected during a telephone interview. Also air measurements (mass concentration of aerosols determined by light scatter, size range 0.1-10 µm) were

performed in 60 (out of 64 participating) companies. Exposure involved all types of MWF with 87% being water-miscible. The aerosol concentration (median) in the breathing zone of the machine workers was 0.12 mg/m^3 (range, 0.001-3.00) and the geometric mean 0.12 mg/m^3 (SD, 4.07). The median and geometric concentrations in the general air of the machine workshops were 0.17 (range: 0.007- 0.67) mg/m^3 and 0.15 (SD, 2.41) mg/m^3 respectively. Exposure to 0.17 mg/m^3 MWF (median) in workshop air was associated with a significantly increased risk for chronic bronchitis (adjusted odds ratio, 2.8; 95% CI, 1.0-7.5). The adjusted odds ratio for the highest exposed machine workers (0.28-0.67 mg/m^3) was 8.6 (95% CI, 1.1-69.7). Also a job history of >15 years of machining work was associated with an increased risk of chronic bronchitis (odds ratio, 2.7; 95% CI, 1.0-7.3).[65]

In another recent cross-sectional study Lillienberg *et al.* (2010) investigated 1,048 Swedish metal workers (923 men, 125 women) and 451 (374 men, 77 women) controls. Exposure levels determined by personal sampling were: arithmetic mean, 0.21 mg/m^3; geometric mean, 0.19 mg/m^3 (SD, 1.62; range, 0.04-0.57).[77] Prevalence ratios for chronic bronchitis were significantly increased for workers exposed to 'mostly emulsion' or 'mostly synthetic' MWF (prevalence ratio, 2.20; 95% CI, 1.01-4.78; prevalence ratio, 3.05, 95% CI, 1.16-8.01, respectively) When the prevalence ratio for chronic bronchitis was related to the assessed current exposure, a statistically significant increase was found at 0.41 mg/m^3 (inhalable particulate).[76]

In summary, in 4 cross-sectional studies a statistically significant increased risk for bronchitis was associated with exposure to MWF concentrations ranging from 0.17 to 1 mg/m^3.[65,66,76,95] Together these studies cover all categories of MWF from straight oils to synthetic. In contrast, no statistically significant differences in the prevalence or rate ratio for bronchitis were found in the cross-sectional studies of Ameille *et al.* (1995)[3] and Greaves *et al.* (1997)[50] after exposure to straight and soluble MWF at concentrations of 2.6 mg/m^3 (arithmetic mean; extracted total particulate) and 0.43-0.55 mg/m^3 (thoracic particulate), respectively.

9.2.6 *Cough and phlegm*

The NIOSH Criteria Document on Occupational Exposure to Metalworking Fluids reviewed a large number of studies, in which workers who were exposed to mists of MWF reported chronic respiratory symptoms.[86] Table E-4 and E-5 give an overview of the exposure-response data for cough and phlegm, derived from the studies that contained a quantitative exposure assessment.

Cough

In most studies, the prevalence for cough is higher in exposed (2-50%) compared to non-exposed (10-35 %).[3,74,75,81,95,118] Risk ratios range from 0.93 to 5.3.[3,66,81,89,111] Generally, workers exposed to synthetic and semi-synthetic MWF had higher prevalence and/or risk ratios for cough than workers exposed to straight or soluble MWF.[50,90,98]

Sprince *et al.* (1997) found a dose-related increase in odds ratios for chronic and post-shift cough in workers exposed to soluble or semi-synthetic aerosol (significant in the highest exposure category with mean exposure level of 0.90 mg/m^3).[111] Kriebel *et al.* (1997) found that machinists with straight MWF exposure reported more frequently chronic cough than non-machinists (prevalence ratio, 2.2; 95% CI, 1.1-4.6; arithmetic mean exposure concentration, 0.24 mg/m^3).[74] Oudyk *et al.* (2003) found small dose-related increases in odds ratios for coughing up phlegm in workers exposed to semi-synthetic or soluble MWF when peak exposures were added in the statistical model: odds ratio, 1.56 (95% CI, 1.09-2.22) in the mid-upper peak-exposure category (mean 95th-percentile exposure level, 0.27 mg/m^3); odds ratio, 1.78 (95% CI, 1.04-3.06) in the upper peak-exposure category (mean 95th-percentiles exposure level, 1.37 mg/m^3).[89] Jaakkola *et al.* (2009) (described before) observed an increased risk for cough in machine workers exposed to 0.12 mg/m^3 MWF (median concentration, all types) in the breathing zone, or 0.17 mg/m^3 in general air (median concentration, total mass, light scatter): odds ratios, 2.2 (95% CI, 1.0-4.8) and 3.1 (95% CI, 1.5-6.4), respectively. The odds ratio for workers of the highest exposed quartile (0.28-0.67 mg/m^3) was 18.5 (95% CI, 1.6-101.6).[65]

Greaves *et al.* (1997) and Robins *et al.* (1997) found no significant increases in the prevalence or odds ratio for cough among workers exposed to straight and/or soluble MWF at mean aerosol concentrations of 0.4-0.6 mg/m^3 (thoracic particulate).[50,95]

Since different sampling and analytical methods were used in the different studies, exposure measurements are difficult to compare. Based on the Kriebel, Oudyk, and Jaakkola studies[65,74,89], a statistically significant increase in prevalence or odds for chronic cough is seen in workers exposed to straight, soluble, or (semi)synthetic MWF at mean aerosol concentrations of 0.12 mg/m^3 (total particulate by light scatter measurements) or at mean peak exposures of 0.27 mg/m^3 (total particulate by light scatter measurements). However, Greaves *et al.* (1997) and Robins *et al.* (1997) did not find statistically significant prevalence/odds ratio for cough among workers exposed to mean aerosol concentrations of 0.4-0.6 mg/m^3 (thoracic particulate).[50,95]

Phlegm

Prevalence ratios for phlegm are generally higher in exposed (8-60%) compared to non-exposed (8-26 %).[3,50,81,90,95] Risk ratios range from 0.8 to 7.3.[50,65,66,81,89,111] No consistent differences existed in the prevalence or risk ratios of phlegm between the different MWF classes. Oudyk *et al.* (2003) and Sprince *et al.* (1997) found small dose-related increases in odds ratios for workers exposed to soluble or semi-synthetic MWF aerosols. Increases became significant at mean category aerosol concentrations of 0.17 mg/m^3 (total particulate by light scatter) and mean peak levels of 0.27 mg/m^3 (mean of 95th percentiles), respectively.[89,111]

9.2.7 Pulmonary function

The NIOSH Criteria Document on Occupational Exposure to Metalworking Fluids described several studies of associations between current and past exposure to MWF and current pulmonary functions.[86] Sometimes changes in pulmonary functions after a follow-up period (follow-up pulmonary function) or after a work shift (cross-shift pulmonary function) were also determined. With baseline pulmonary function, the pulmonary function measured without or before a follow-up period or work-shift is meant. Table E-6 and E-7 give an overview of the exposure-response data for the effects on baseline, follow-up, and cross-shift pulmonary function, derived from the studies that contain a quantitative exposure assessment.

Baseline and follow-up pulmonary function

Several investigators reported on decreased baseline pulmonary function in exposed workers compared to non-exposed workers.[5,36,71,74,75,119] However, several other studies did not find significant differences in baseline pulmonary function in exposed compared to non-exposed workers.[3,39,66,67,72,81,90,95,107,108,111]

Eisen *et al.* (2001) found a negative association between cumulative exposure to straight MWF and FVC (borderline significant with p=0.055), but not so for FEV_1. Exclusion of workers who transferred to assembly jobs, increased the strength of this association.[36]

Kennedy *et al.* (1999) found a decrease in FVC (but not in FEV_1) after 2 years of exposure.[71] Jarvholm (1982), however, found no statistically significant differences in FEV_1 or FVC after 3 years of exposure.[66]

Kriebel *et al.* (1997) observed a significant decrease in baseline FEV_1 in machinists exposed to soluble MWF. Compared to non-machinists, the machinists had a significant lower pre-shift FEV_1 (approximately 115 mL less; that is 3% of average FEV_1 value in this population) at arithmetic mean levels of 0.22 mg/m^3 soluble MWF (inhalable particulate). However, no statistically significantly differences in pulmonary function were observed in machinists exposed to straight MWF (arithmetic mean, 0.24 mg/m^3; inhalable particulate).[74]

Other investigators did not observe significant changes in baseline pulmonary function in workers exposed to different types of MWF aerosols at mean concentrations of 0.3-1.2 mg/m^3 (total particulate).[71,81,111] In the Sprince study, a negative association between total culturable bacteria and FEV_1 was observed.[111] In contrast, Kriebel *et al.* (1997) found no evidence of an association between endotoxin exposure and decreased lung function which was consistent with the low levels of endotoxin observed.[74]

Cross-shift pulmonary function

Three of the 4 cross-shift pulmonary function studies show increased prevalence in cross-shift FEV_1 decline. Risk ratios for a cross-shift ΔFEV_1 ($\geq$ 5% or $\geq$10%) range from 0.36 to 8.43. A dose-response relation was found by Kriebel *et al.* (1997) and, for obstructed workers only, by Robins *et al.* (1997).[74,95]

Kriebel *et al.* (1997) found an increased incidence of 5% cross-shift ΔFEV_1 among workers in the high-exposure category (straight and soluble MWF combined) with a mean inhalable mass particulate concentration of 0.31 mg/m^3 (relative risk, 3.2; 95% CI, 1.2-8.7 in the adjusted model).[74]

The effects observed by Robins *et al.* (1997) were dose-related for obstructed workers only, with an odds ratio of 4.6 (95% CI, 1.8-11.6) at 0.34 mg/m^3 (thoracic mass particulate), and an odds ratio of 6.2 (95% CI, 2.2-17.8) at 0.57 mg/m^3 (thoracic mass particulate). For non-obstructed workers, no such effect was found.[95] From this observation, the Committee concludes that obstructed workers are at increased risk.

Kennedy *et al.* (1989) also found increased odds ratios for 5% cross-shift ΔFEV_1 with increasing exposure categories from low (<0.2 mg/m^3) through medium (0.20-0.55 mg/m^3) to high (>0.55 mg/m^3), but this increase was significant only for Friday measurements, and not on Mondays. Aerosol concentrations were measured as thoracic mass particulate and the exposure-response regression analysis was done for straight, soluble, and synthetic MWF combined.[72] In contrast, Sprince *et al.* (1997) did not observe statistically significant differences in cross-shift pulmonary function between non-exposed

workers and workers exposed to semi-synthetic or soluble MWF at 0.33 mg/m^3 (geometric mean; total aerosol particles by light scatter measurements).[111]

9.2.8 *Evaluation of respiratory effects*

In several studies, respiratory effects such as lung fibrosis, asthma, bronchitis, rhinitis, cough, phlegm, and changes in baseline, follow-up, and cross-shift pulmonary function, have been found in workers exposed to MWF aerosols. A summary of the main findings is given in Table 11.1.

Assuming that the reported aerosol concentrations represent inhalation exposure levels to mineral oil, adverse effects can be observed at exposure levels above 0.2 mg/m^3 inhalable particulate mass. Kriebel *et al.* (1997) showed that machinists with soluble MWF exposure at 0.22 mg/m^3 (arithmetic mean) had approximately 115 mL lower pre-shift FEV_1 on average (significant difference at p=0.05) than non-machinists.[74] Kennedy *et al.* (1989) showed an increased number of workers with 5% ΔFEV_1 on Fridays (but not on Mondays) in the exposure category of 0.20-0.55 mg/m^3 ($p<0.05$) as the thoracic particulate fraction (any MWF) which corresponds to approximately 0.3-0.8 mg/m^3 as the inhalable fraction.[72] In addition, Kennedy *et al.* (1999) observed a decreased FVC at follow-up (p=0.03) at mean arithmetic aerosol levels of 0.46 mg/m^3, however without an effect on FEV_1. In the logistic regression model in their study, a predictor of bronchial hyperresponsiveness was the exposure to synthetic MWF, and not the exposure to soluble or straight MWF.[71] The other two studies (Ameille *et al.* 1995; Massin *et al.* 1996) that included the methacholine challenge test found slightly increased bronchial hyperresponsiveness at higher levels of soluble MWF mist exposure.[3,81] In the recent study by Lillienberg *et al.* (2010) exposure to aerosols of MWF (all types) was related to significant increases in prevalence ratios of wheeze, chronic bronchitis, chronic rhinitis, and eye irritation at a concentration of 0.41 mg/m^3 (inhalable particulate fraction).[76]

In summary, adverse effects on lung function can be seen at levels above 0.2 mg/m^3 inhalable particulate mass originating from MWF. No adverse effects have been described at levels below 0.2 mg/m^3 inhalable particulate mass from MWF.

9.3 Carcinogenic effects of working with metalworking fluids

Many studies have examined the risk of cancer among metal workers. Unfortunately, most of these did not identify the type of mineral base oil used or

the type of MWF used. It is likely that in most cases exposure was to used and unused formulated products.

Several reports have identified cancer of the skin, scrotum, and other sites in the body among MWF-exposed workers (see Table E-8 in Annex E). In scrotal cancer patients, excess numbers of secondary cancers were found in the skin, the respiratory system, and the upper alimentary tract.[61]

Many epidemiological studies on carcinogenicity of mineral oils typically deal with exposure to MWF. Therefore, co-exposure to non-mineral oil components is likely to have occurred in the populations studied. Epidemiological studies include cohort studies and case-control studies (Table E-8 in Annex E). The cohort study by Eisen *et al.* (1992)[38] and the extended follow-up study[34] from 1941 through 1994 represent important advancements on the evidence of relationships between MWF exposure and cancer. The relevant case-cohort and case-control studies within this cohort are described in detail below.

9.3.1 *Cohort studies in metal workers*

Eisen *et al.* (1992) and Tolbert *et al.* (1992) studied cancer mortality in a large cohort of over 46,000 workers exposed to MWF. This cohort (the United Autoworkers/General Motors, UAW/GM, cohort) was from 3 car parts manufacturing plants in Michigan (USA) and included workers with hire dates from 1917 to 1981 who had worked for at least 3 years prior to 1985. Standardised mortality ratios (SMRs) were estimated with both USA and local populations as reference and gross measure of exposure. Significantly elevated SMRs were found for leukaemia (1.57; 95% CI, 1.21-2.00) and pancreatic cancer (1.70; 95% CI, 1.05-2.61) at a plant with exposure to straight and soluble MWF, laryngeal cancer (1.85; 95% CI, 1.03-3.05) and lung cancer (1.16; 95% CI, 1.01-1.32) at a plant with straight, soluble and synthetic MWF, and liver cancer (2.77; 95% CI, 1.26-5.25) at a plant with straight oils. Poisson regression analysis yielded significantly elevated relative risks of 1.52 (95% CI, 1.01-2.29) for prostatic cancer in the highest straight-oil exposure category, 1.94 (95%CI, 1.23-3.07) for stomach cancer in the lowest straight-oil exposure category, and 3.17 (95% CI, 1.62-6.24) for rectal cancer in the highest straight oil exposure category. No significantly elevated risks were found for soluble-MWF exposure, and only oesophageal cancer risk was significantly elevated (2.22; 95% CI, 1.14-4.32) for synthetic-fluids exposure in the lowest exposure category.[38,123]

In an extended follow-up to 1994, Eisen *et al.* (2001) estimated adjusted relative risks in Poisson regression models with categorical variable of cumulative exposure to each type of MWF and in proportional hazards models

with continuous exposure variables. In this study, quantitative exposure estimates of the different types of MWF are assessed. The authors found weak associations between cumulative exposure to straight MWF and oesophageal, laryngeal, and rectal cancer; cumulative exposure to soluble MWF and cancer of the oesophagus, larynx, skin, and brain; and cumulative exposure to synthetic MWF and cancer of the oesophagus, liver, and prostate. For straight MWF, the relative risks were modestly elevated (1.1-2.0) and, at cumulative levels of >3 mg/m^3·years, only significantly increased for rectal cancer (relative risk, 2.0; 95% CI, 1.2-3.5). The authors concluded that their results provided further evidence that exposure to MWF can cause cancer among workers in the car manufacturing. They added that the risk seemed to decrease with the more severely refined oils and that modestly increased risks might still persist at current levels of exposure to water-based MWF.[34]

Zeka *et al.* (2004) re-examined the cancer risk with improved case definition in a case-cohort design and new cases identified from 1985 to 2000. Their main finding was an association between larynx cancer incidence and cumulative exposure to straight MWF with a 7% increase in risk for each 5-mg/m^3·year increment in cumulative exposure (rate ratio, 1.07; 95% CI, 1.01-1.12). No other fluid types were associated with laryngeal cancer risk. The results for oesophageal cancer were inconsistent and stomach cancer risk was not associated with any fluid type.[135] In a subsequent analysis, Malloy *et al.* (2007) used survival models with penalized splines to estimate the relationship between cumulative exposure to MWF and mortality from rectal cancer, and found that the hazard ratio increased linearly with cumulative exposure to straight MWF up to a maximum of 2.2 at the 99th centile of exposure.[80]

Friesen *et al.* (2009) investigated a subcohort of 21,999 men with a focus on bladder and lung cancer incidence. The follow-up period lasted from 1985 to 2004. Only a cumulative exposure to straight MWF >9 mg/m^3.years and a 20-year lag period was associated with an increased risk of bladder cancer (hazard ratio, 2.07; 95% CI, 1.19-3.62). According to the authors, the association with straight oils provides support for the role of polycyclic aromatic hydrocarbons (PAH) in the aetiology of bladder cancer. No association was observed between exposure to straight, soluble, or synthetic MWF and the incidence of lung cancer.[43]

9.3.2 *Case-control studies in metal workers*

Within the UAW/GM cohort, Eisen *et al.* (1994) carried out a case-control study of larynx cancer (108 cases; 538 controls). Risks associated with specific types

of MWF, as well as specific components of MWF were evaluated. Lifetime exposures to straight and soluble MWF, grinding particulate, biocides, selected metals, sulphur, and chlorine were examined. Exposure to asbestos and acid mists at 2 of the 3 study sites was also characterized. Their results indicated that straight mineral oils and elemental sulphur (commonly added to straight mineral oil) were associated with an excess of larynx cancer. However, it was not clear whether sulphur or straight mineral oil were causally related to an excess relative risk of larynx cancer or whether the observed associations were the result of unmeasured confounding by other contaminants or process features (*e.g.*, PAH).[37]

Sullivan *et al.* (1998) used this UAW/GM cohort to study oesophageal cancer in a case-control design (53 cases and 971 controls). They found that oesophageal cancer was significantly associated with exposure to both soluble and synthetic fluids in grinding operations. For grinding with soluble MWF, the odds ratio was elevated at 2.5, but the exposure-response trend was statistically significant only when exposure was measured as duration. Ever working with synthetic MWF was associated with a 3.9-fold (95% CI, 1.1-14.3) risk of oesophageal cancer mortality, after controlling for cumulative exposure to soluble MWF in grinding operations. Elevated risk was also associated with nitrosamines and biocides found in synthetic and soluble fluids, but the specific risks to these agents could not be separated from the risk of oesophageal cancer associated with synthetic fluids exposure.[116] In a subsequent study of this cohort, Sullivan *et al.* (2000) found increased risks of stomach cancer mortality for grinding with water-based fluids (synthetic and soluble). Grinding with synthetic MWF (cumulative exposure >1.3 mg/m^3·years during the ten years prior to death) was associated with an elevated risk of 4.4 (95% CI, 1.5-13.1) and grinding with soluble MWF had an increased risk of 1.9 (95% CI, 1.0-3.6). In plant-specific analysis, they additionally found evidence of increased risk of stomach cancer associated with exposure to straight MWF (risk not given in the abstract).[115]

In an analysis of pancreatic cancer incidence in the UAW/GM cohort (case-control design), Bardin *et al.* (1997) found associations between pancreatic cancer (n=97; controls=1825) and cumulative exposure to synthetic fluids in grinding operations. No clear risk patterns were found for exposure to straight or soluble MWF, whether in machining or grinding operations. According to the authors, there was some evidence that nitrosamines and/or biocides might explain some of the risk.[7]

Bardin *et al.* (2005) also used this UAW/GM cohort (46,400 workers; at least 3 years employed before 1984) to study liver and biliary tract cancer in a case-

control study. Follow-up began in 1941 and ended in 1994. Three time windows of exposure were built: the most recent 10 years, >10-20 years, and >20 years prior to the date of risk age. Overall, hepatobiliary cancer (n=63) was not associated with exposure to MWF. However, the risk was not homogeneous across liver (n=39) and biliary tract (n=24) cancer, and a slight excess risk of biliary tract cancer was found for workers with cumulative exposure to straight MWF above 1.0 mg/m^3·years (odds ratio, 2.7; 95% CI, 0.9-7.6). When straight MWF exposures were separated into 10-year periods, the adjusted odds ratio increased to 6.24 (95% CI, 1.6-24.2 in the >1.0 mg/m^3·years exposure category) for exposures occurring >20 years prior to the risk date. This finding suggests a relatively long latency period between straight MWF exposure and cancer development and supports the higher PAH content of these earlier straight mineral oils as the likely cause.[8]

In this UAW/GM cohort, Thompson *et al.* (2005) studied breast cancer among female workers (99 cases; 626 matched controls). They found a weak positive association between lifetime cumulative exposure to soluble MWF and breast cancer risk. The association was strongest in the decade preceding diagnosis: when controlling for earlier exposures, the authors found an odds ratio of 1.18 (95% CI, 1.02-1.35) per mg/m^3·year of cumulative exposure to soluble MWF in this decade. There was no evidence of an association with either straight or synthetic fluids.[121]

Agalliu *et al.* (2005) studied prostate cancer incidence (nested case-control design) in a subset of this UAW/GM cohort and examined exposure-response relationships in linear dose-response models with different lagging periods (10, 15, 20, and 25 years) to account for latency. After examining lags, they evaluated 2 consecutive windows of exposure to MWF: 25 or more years before (early window) and less than 25 years before risk age (*i.e.*, the age of the case). Study subjects had been hired between 1921 and 1984, and followed for cancer incidence from 1985 through 2000. The subset consisted of 31,648 male workers who had worked at least 3 years before 1985, and were still alive at the time of the study. Risk of prostate cancer increased modestly with increasing exposure to straight and soluble fluids that occurred 25 years or more before risk age, but not with exposure in the later 25 years. This supports a latency period of at least 25 years. The relationship with straight fluids in the early window was linear with a relative risk of 1.12 (95% CI, 1.04-1.20) per 10 mg/m^3·years; the relationship with soluble fluids in the early window was nonlinear (relative risk of 1.10 per 10 mg/m^3·years; 95% CI, 0.84-1.42).[1] In summary, the Agalliu study suggests that one or more common agents in straight and soluble MWF may be associated with prostate cancer. According to Agalliu *et al.*, the observed association of

prostate cancer with soluble and straight fluids in the early window could be due to the PAH content, which was higher in MWF before the 1970s, and has steadily decreased over time as the result of more severe refining of the mineral oils. Agalliu *et al.* also mention chlorinated paraffin as a possible common agent involved.

9.3.3 *Cohort and proportionate mortality studies in other workers*

Other cohort and proportionate mortality studies can be found in Tables E-9, E-10, and E-11 (Annex E). These early studies date from the seventies and co-exposure to PAC is likely to have occurred in the study populations with exposures that date back to the first half of the twentieth century.

9.3.4 *Evaluation of carcinogenic effects*

Several studies show associations between cumulative exposures to mineral-oil-containing MWF and cancer of the larynx[37,38], oesophagus[34], and rectum[34] but the associations were weak and not consistent. For instance for cumulative straight MWF exposure, stomach cancer was not increased in the Zeka study[135] and the results for oesophageal cancer were inconsistent in this study. Nevertheless, Zeka *et al.* (2004) could find an association between larynx cancer and cumulative exposure to straight MWF (in particular in the time window 10-20 years before risk age)[135] and Malloy *et al.* (2007) were able to show that the rectal cancer risk increased with cumulative exposure to straight MWF.[80]

The results of Bardin *et al.* (2005) show a latency period of at least 20 years between straight MWF exposure and the development of biliary tract cancer[8] and support the view of the earlier oils with their higher PAC content as the likely cause. A similar conclusion can be drawn from the study by Agalliu *et al.* (2005) who found that the risk of prostate cancer modestly increased with cumulative exposures to straight and soluble MWF that occurred 25 years or more before risk age, but not with exposure in the last 25-years. The risk in the early window increased linearly with cumulative straight fluid exposure and non-linearly with cumulative soluble fluid exposure.[1] These results suggest that one or more common agents in the early straight and soluble MWF are the likely cause, possibly the polycyclic aromatic hydrocarbons present at higher levels in the pre-1980 mineral oils as compared to the severely refined oils used nowadays.

9.4 Genotoxicity of working with mineral oils

There is strong evidence that the PAH content of mineral lubricant oils increases during use. The extent of this increases appears to depend on the type of application and, in particular, on the use of mineral oils at high temperatures as engine oils and heat-treating oils.[61]

Used steel-hardening oils appeared to contain significant more PAH than unused oils, and in *S. typhimurium* assays, used crankcase oils and used steel-hardening oils showed mutagenic activity whereas unused oils were negative.[61] Overall, the available data indicate that the use of mineral oils at high temperatures is associated with the formation of PAH and that such used oils have acquired mutagenic activities.

One study in humans indicates a significant increase in the frequency of aberrant cells and number of chromosomal breaks per cell in blood lymphocyte cultures from glass workers. These workers were occupationally exposed to mineral oils suspected to contain relatively high concentrations of PAH formed at high temperatures.[112] Matched controls (n=23) were included in the analysis. In glass-forming operations, mineral oils were used to cool hot glass and came into contact with hot surfaces of 600-800°C. The authors considered PAH formed at these high temperatures as a likely cause and concluded that glass workers might run serious risk of acquiring genetic injury as the result of exposure to PAH formed in mineral oils at high temperatures of 600-800°C.

9.5 Genotoxicity of working with metalworking fluids

Other genotoxic compounds have occasionally been identified in used MWF, but their formation is associated with aqueous MWF and not with mineral base oils. Examples are N-nitrosodiethanolamine and formaldehyde.[86] In a German study of 65 male workers exposed to synthetic fluids, those working in areas with N-nitrosodiethanolamine concentrations greater than 500 ng/m^3 had increased numbers of DNA single strand breaks in mononuclear blood cells, compared to those working in areas with less than 50 ng/m^3.[44] N-nitrosodiethanolamine has also been detected in the urine of workers exposed to ‘nitrite-formulated’ MWF, at higher levels than in the urine of workers exposed to ‘nitrite-free’ fluids.[31,32]

9.6 Summary

In several studies, respiratory effects such as lung fibrosis, asthma, bronchitis, rhinitis, cough, phlegm, and changes in baseline, follow-up, and cross-shift pulmonary function, have been found in workers exposed to MWF aerosols.

Overall, it is not possible to separately evaluate the different types of MWF. Adverse effects appear to be associated with exposure to MWF, irrespective of the type of MWF. Generally, adverse effects on lung function can be seen at exposure levels above 0.2 mg/m^3 inhalable particulate mass, originating from MWF. No adverse effects have been described at levels below 0.2 mg/m^3 inhalable particulate mass from MWF.

From the available studies, no conclusions can be drawn on the components that are responsible for the observed adverse health effects in metal workers. The observed effects are associated with occupational exposure to mists of MWF and these mists may contain mineral oil and many other substances, including MWF additives, metal fines, microorganisms, and other contaminants.

Several studies show associations between cumulative exposures to mineral-oil-containing MWF and cancer of the larynx, oesophagus, and rectum, but the associations were weak and not consistent. Zeka *et al.* (2004) re-examined the cancer risk with improved case definition in a case-cohort design and new cases identified from 1985 to 2000. Their main finding was an association between larynx cancer incidence and cumulative exposure to straight MWF with a 7% increase in risk for each 5-mg/m^3·year increment in cumulative exposure (rate ratio, 1.07; 95% CI, 1.01-1.12). No other fluid types were associated with laryngeal cancer risk.[135] Friesen *et al.* (2009) observed an increased risk of bladder cancer (hazard ratio, 2.07; 95% CI, 1.19-3.62) when the cumulative exposure to straight MWF exceeded 9 mg/m^3 • years with a 20-year lag period.[43] The results for oesophageal cancer were inconsistent and stomach cancer risk was not associated with any fluid type.

Overall, the results suggest that one or more common agents in the early straight and soluble MWF may have been the causative agent(s), possibly the PAC that were present at higher levels in the pre-1980 mineral oils as compared to the relatively pure mineral base oils, used in MWF nowadays.

Chapter 10

Existing guidelines, standards and evaluations

10.1 General population

No health-based guidance values or environmental values have been established to protect the general population against adverse health effects of exposure to vapours and aerosols of mineral oils or lubricant oil products.

10.2 Working population

10.2.1 Occupational exposure limits for mineral oils

The current legally-binding occupational exposure limit for mineral oil mist in the Netherlands is 5 mg/m^3 as an 8-hour time-weighted average.[82]

At the European level, no limit value currently exists, but in March 2011, the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European commission has recommended an occupational exposure limit of 5 mg/m^3 (inhalable; 8-hour TWA) for aerosols of severely refined mineral oils.[40] A number of EU member countries have set limits numerically to 5 mg/m^3 as an 8-hour time-weighted average.

ACGIH has recommended a Threshold Limit Value (TLV®) of 5 mg/m^3 (time-weighted average; inhalable particulate matter) for highly refined mineral

oil aerosols encountered in industries where additives and contamination are not commonplace. ACGIH stated that this limit value should not be applied to poorly or mildly refined mineral oil since insufficient data were available to address the toxicity of poorly refined mineral oil.[4]

The National Institute for Occupational Safety and Health (NIOSH) has a Recommended Exposure Limit (REL) of 5 mg/m^3 (10-hour time-weighted average) and a Short-Term Exposure Limit (STEL, 15-minute time-weighted average) of 10 mg/m^3 for mineral oil mist. The Occupational Safety and Health Administration (OSHA) has a Permissive Exposure Limit (PEL) of 5 mg/m^3 (8-hour time-weighted average).

10.2.2 Occupational exposure limits for mineral oil containing metalworking fluids

The German MAK commission has specified that it considers its previously established MAK value of 5 mg/m^3 for pure mineral oil no longer applicable to work environments with MWF due to presence of many potential harmful additives.[103]

After consultation of the Advisory Committee on Toxic Substances (ACTS), the UK Health and Safety Commission adopted a similar conclusion and agreed to remove MWF from the scope of the Occupational Exposure Standards because – given the substantial variability in the composition of MWF and the contamination during industrial use – it was considered impossible to derive revised Occupational Exposure Standards values for mineral oil MWF which would be valid for all possible combinations of such fluids.[113] Sweden and Denmark have an occupational exposure limit of 1 mg/m^3 mineral oil particles as an 8-hour time-weighted average.

In its recommendation, ACGIH stated that mineral oils as commonly used in industry often contain additives and contaminants and that it is difficult to distinguish between the effects of mineral oils alone and other components in the mixture. Similarly, it is difficult to attribute acute and chronic effects, *e.g.*, respiratory symptoms and pulmonary function changes, reported at exposure to mineral oil aerosols in entertainment industry below 1 mg/m^3, to mineral oil-based or glycol-based fog particles. Studies in laboratory animals using highly refined mineral oils with no or few additives have generally shown that few and minimal effects occurred after exposure to 50 mg/m^3. Based upon animal toxicology studies and exposure assessment of exposure to mineral oil fogs in the entertainment industry, a TLV® was recommended for highly refined mineral oil aerosols encountered in industries where additives and contamination are not

commonplace. This limit value does not apply to occupational exposure to mineral oil aerosols encountered in metalworking operations. It was not clear whether additives or contaminants or mineral oils attributed to respiratory symptoms and pulmonary function changes associated with exposure to mineral oil aerosols in metalworking industries.[4]

In 1998, NIOSH recommended 0.4 mg/m^3 of thoracic particulate mass (or 0.5 mg/m^3 of total particulate mass) as limit value for the occupational exposure to aerosols from MWF.[86]

In 1999, the OSHA Metalworking Fluids Standards Advisory Committee recommended a permissible exposure limit (PEL) of 0.4 mg/m^3 of thoracic particulate (0.5 mg/m^3 of total particulate), and the introduction of systems management (*i.e.*, a holistic approach for managing MWF and machining processes that results in improved exposure control and enhances productivity), an active medical surveillance program, and a training program for everyone involved in MWF.[88]

10.2.3 *Carcinogenic classification*

The European Union and IARC have classified certain mineral base oils with respect to carcinogenicity. An overview of these classifications is given in Annex G.

In the European Union, mineral base oils are divided into three groups based on the severity of the refining process: unrefined or mildly refined base oils, highly refined base oils, and other lubricant base oils. Unrefined or mildly refined base oils are classified as category 1A carcinogens (substances known to have carcinogenic potential for humans). Highly refined base oils have no classification in any of the categories in the European Union. The group of the other lubricant base oils contains a large number of individual CAS numbers with unspecified refining severity. Oils with a DMSO extractable fraction equal to or greater than 3% (w/w) are classified as category 1B carcinogens (substances presumed to have carcinogenic potential for humans). Oils with a DMSO extractable fraction less than 3% (w/w) are not classified in any of the categories in the European Union ('CLP' Regulation).[40]

Up to now, none of the EU member countries has assigned a carcinogenicity category to the occupational exposure limit for mineral oil mist.[125]

IARC divided mineral oil refinery streams are into two broad groups: those that are 'highly refined' and those that have undergone at best only 'limited refining'.[61] In 1987, IARC concluded that there was sufficient evidence for the carcinogenicity in experimental animals for the following base oils: untreated

vacuum distillates, acid-treated oils, aromatic oils, mildly solvent-refined oils, and mildly hydrotreated oils.[61] IARC concluded that the evidence for carcinogenicity to humans was sufficient for 'untreated and mildly-treated oils' (Group 1), and inadequate for 'highly refined oils' (Group 3).[63]

ACGIH classified pure, highly and severely refined mineral oils in carcinogenicity category A4 ('not classifiable as a human carcinogen') and poorly and mildly refined mineral oils in category A2 ('suspected human carcinogen').[4]

Table 10-1 Established limits for occupational exposure to mineral oils in various countries.

Country - Organisation	Occupational exposure limit (mg/m^3)	Aerosol fraction	Time-weighted average	Note	Reference
Denmark	1		8 h	OEL	
The Netherlands					
- Ministry of Social Affairs and Employment	5	Inhalable particulate mass	8 h	OEL	[82]
Germany					
- AGS	-				
- DFG	-				
Sweden	1		8 h	OEL	
UK					
- HSE	-				[54]
USA					
- ACGIH	5	Inhalable particulate mass	8 h	TLV	[4]
- NIOSH	5[a]	Thoracic particulate mass	10 h	REL	[86]
	10	Thoracic particulate mass	15 min	STEL	
- OSHA	5[a]	Thoracic particulate mass	8 h	PEL	[88]
European Union	5[b]	Inhalable	8 h	IOELV	[40]

a For the exposure to MWF aerosols, NIOSH and OSHA have recommended 0.4 mg/m^3 thoracic particulate mass, corresponding to approximately 0.5 mg/m^3 total particulate mass.

b Recommendation by SCOEL (March 2011).

Chapter 11

Hazard assessment

Mineral lubricant base oils are obtained from crude petroleum by vacuum distillation of the residue remaining after atmospheric distillation, and subsequent refining by solvent treatment, hydro treatment and/or hydrocracking. Unrefined mineral base oils contain carcinogenic PAC. These compounds are largely removed during the refining process. Highly refined base oils mainly consist of paraffinic and naphthenic hydrocarbons, with only traces of other substances.

In the European Union, the mineral base oils are usually divided into different groups, based on the severity of refining (see Annex G): the unrefined or mildly refined base oils, the highly refined base oils, and the other lubricant base oils. The Committee has followed this division.

To mineral base oils, additives may be added up to 30% of the total content, depending on their application. An important application is in their use in MWF. Different base oils may be mixed and various additives added before being used in MWF. Nowadays, the majority of MWF is water-based and may contain mineral oil, water, emulsifiers, corrosion inhibitors, biocides, and synthetic oils as well.

The Committee noted the large number of different mineral base oils (see Annex D) and concluded that it is not possible to derive a health-based occupational exposure limit for aerosols of mineral oils in general, because of the complexity and varying amounts of impurities present in these oils. On the other hand, the highly refined base oils are clean oils with a high degree of purity.

Animal data on adverse health effects of highly refined mineral oils are consistent and can be used to recommend a health-based occupational exposure limit.

In addition to this, the Committee noted that several epidemiological studies exist that describe adverse health effects in workers exposed to aerosols of MWF that contain mineral oils. Therefore, the Committee decided to evaluate these studies in order to recommend a health-based occupational exposure limit for working with MWF that contain mineral oils. The mineral oils used in these fluids belong to the group of the other lubricant base oils or, at least in principle, to the group of the highly refined base oils.

11.1 General aspects of mineral oils

Mineral base oils are not sufficiently volatile to present a vapour inhalation hazard under normal operating conditions. Mineral base-oil hydrocarbons have (extremely) low vapour pressures and boil at temperatures of 300-600°C at atmospheric pressure. At elevated temperatures, however, vapour formation may become significant. These vapours may subsequently condense and form aerosols when cooling down. These aerosols have caused irritation of the respiratory tract, and prolonged or repeated inhalation of high concentrations of condensed oils may lead to basal lung fibrosis.

The carcinogenic potential of mineral base oils has appeared to be related to their PAC content. PAH are major constituents of PAC. In 2006, the Health Council of the Netherlands published health-based occupational cancer risk values for PAH, corresponding to predefined excess cancer mortality rates after 40 years of occupational exposure.[57] In addition, a skin notation was recommended for PAH because direct skin contact may cause skin cancer. These health-based occupational cancer risk values for PAH, including the skin notation, apply to PAH-containing mineral base oils and derived products.

There has been general concern on the formation of PAH when mineral oils are used at high temperatures. Used steel-hardening oils appeared to contain significant more PAH than unused oils, and in *S. typhimurium* assays, used crankcase oils and steel-hardening oils showed mutagenic activity whereas unused oils were negative.[61] In addition, clastogenic effects have been observed in a group of workers in a glass industry where mineral oils were used to cool hot (600-800°C) glass surfaces.[112] Overall, the available data indicate that the use of mineral oils at high temperatures is associated with the formation of PAH and that these *used* oils may have acquired mutagenic and clastogenic activities.

11.2 Unrefined or mildly refined mineral base oils

Unrefined or mildly refined mineral base oils are subject to further refining. These oils are (largely) kept and processed in closed systems during the refining process and aerosol formation is unlikely to occur.

11.2.1 Carcinogenicity

In the European Union, the unrefined and mildly refined mineral base oils are classified as carcinogen in category 1A: substances known to have carcinogenic potential for humans ('CLP' Regulation).

The unrefined and mildly refined base oils contain aromatics including (alkylated) PAC. Studies dating back to the early 1920's showed that exposure to unrefined and mildly refined mineral base oils was associated with skin cancer in humans and that these cancers were caused by the PAC present in these oils.

Animal data are in line with the observations on carcinogenicity of mildly refined mineral oils. Many studies have shown that mildly refined mineral lubricant base oils, when applied to the skin, cause skin papillomas and carcinomas in various animal species. With respect to PAC, existing cancer risk values for PAH – including the skin notation attached to PAH – apply to unrefined and mildly refined mineral base oils.

11.3 Highly refined mineral base oils

Case reports show that lipid pneumonia and lipid granulomas may develop after inhalation or aspiration of white oils and petrolatums. These oils do not produce necrosis and are taken up by macrophages in the lungs. No human data on the reproduction toxicity, immunological effects, or neurological effects of highly refined mineral oil mists are available.

11.3.1 Carcinogenicity in animals

No increase in incidence of any tumour was observed after inhalation, oral administration, dermal administration, or subcutaneous injections of highly refined base oils in animal species.

11.3.2 Non-carcinogenic effects in animals

Animal studies show that chronic inhalation exposure to highly refined mineral oils may cause the formation and accumulation of oil-filled lung macrophages and increased lung weights. Significant oil deposition and lipid microgranuloma formation occurred in dogs after 12 months of inhalation exposure to 100 mg/m^3.[114,129] At 5 mg/m^3, few oil-filled macrophages without other tissue response were found in the lungs and the hilar lymph nodes in dogs, rats and gerbils after one year of exposure.[114,129]

The few animal studies available did not show evidence for reproduction toxicity of highly refined white mineral oils after oral administration. Overall, the data on reproduction toxicity are limited.

11.3.3 Recommendation

No epidemiological studies exist with reliable quantitative exposure-response data for highly refined mineral base oils. Animal studies show that these oils do not have carcinogenic potential. Long-term inhalation studies in animals show that oil-filled macrophages accumulate in the lungs and that microgranulomas occur at exposure levels of 100 mg/m^3. Few oil-filled macrophages with no other tissue response were found in the lungs in several animal species, including dogs and rodent species, at chronic (12-24 months) exposure levels of 5 mg/m^3. According to the Committee, the occurrence of oil-filled macrophages is a normal physiological reaction and not an adverse health effect. The formation of microgranulomas, however, is an adverse effect as the inhaled oil droplets cannot completely be removed anymore by the macrophages and reduce an organism's ability to respond to an additional challenge. Therefore, the Committee considers the occurrence of microgranulomas as the critical effect and concludes that 5 mg/m^3 is the no-observed-adverse-effect-level (NOAEL) for this effect.

For extrapolation to a health-based recommended occupational exposure limit (HBROEL), several aspects are taken into account: the difference between experimental conditions and the exposure pattern of a worker, and the interspecies and intraspecies variation. A factor correcting for exposure duration is not deemed necessary as the exposure time in the studies of Wagner *et al.* (1964)[129] and Stula and Kwon (1978)[114] was up to 24 months and is considered sufficient for long-term exposure. An interspecies factor is not needed as the occurrence of microgranulomas in the lungs is a local effect. For intraspecies variation, the default value of 3 is taken.

Applying this assessment factor of 3 yields a HBROEL of 1.6 mg/m^3 inhalable particulate mass, as an 8-hour time-weighted average. This value exclusively applies to aerosols of highly refined mineral base oils, used without additives and only once (not recycled).

A skin notation is indicated if occupational skin exposure adds for 10% or more to systemic toxicity, or if skin exposure may induce skin cancer. Insufficient data are available on the systemic toxicity of highly refined mineral base oils, but the available studies indicate that the systemic toxicity is small. In addition, skin exposure to highly refined base oils does not induce skin tumours. For these reasons, the Committee considers a skin notation not needed.

In its recently published recommendation, the SCOEL subscribes the hazard assessment made by the Committee, *i.e.*, the NOAEL of 5 mg/m^3 based on the occurrence of microgranulomas in two animal species. In contrast to the Committee, the SCOEL does not apply an assessment factor for intraspecies variation.[40]

11.4 Other lubricant base oils and their use in metalworking fluids

Nowadays, the vast majority of the mineral base oils in the European Union contains less than 3% (w/w) DMSO-extractable material as measured by the IP 346 method, and falls in the product group of the *other lubricant base oils*. These oils are severely solvent-refined and/or hydrotreated. These refining processes remove or substantially reduce the amount of PAC present in the unrefined base oils. Based on numerous skin-painting assays in animals, the oils with less than 3% (w/w) DMSO-extractable material lack carcinogenic potential. In addition, these oils appeared to have no mutagenicity in the Modified Ames test.[79] In the European Union, other lubricant base oils that contain less than 3% (w/w) DMSO extractable material as measured by method IP 346 have no classification in any of the carcinogenic categories ('GLP' Regulation) (see Chapter 2.4). When these unspecified lubricant base oils contain a DMSO extractable fraction equal to or greater than 3% (w/w), they are classified in carcinogenicity category 1B: substances presumed to have carcinogenic potential for humans.[41]

The mineral base oils used in oil products and MWF belong to the group of the other lubricant base oils and contain less than 3% (w/w) DMSO extractable material. Other lubricant base oils with a DMSO extractable fraction of 3% (w/w) or more are not used anymore in lubricant products nor in MWF. In the past, however, less refined base oils have been used in oil products and MWF.

MWF are usually divided into four groups: the *straight oil* fluids, the *soluble oil* fluids, the *semi-synthetic* fluids and the *synthetic* fluids. The straight-oil

MWF do not contain water, the synthetic fluids do not contain mineral oil. Also, some MWF contain synthetic oils in addition to or instead of mineral oils. Chemically, the hydrocarbons in synthetic oils are similar to the hydrocarbons in mineral oils: the synthetic oils are mostly short-chain highly branched alkanes, whereas the mineral oils consist of cyclic and non-cyclic longer-chain paraffins. The physical properties of synthetic and mineral oils, however, differ because of the differences in chain lengths of the hydrocarbons.

11.4.1 Strength of the available research data on metalworking fluids

Several epidemiological studies of good methodological quality exist that describe adverse health effects in workers exposed to mineral-oil-containing MWF, *i.e.*, fluids that may contain water, additives, and contaminants, in addition to mineral oil. Several factors hamper the evaluation of these studies. Main factors include co-exposure to non-mineral oil components, differences in the methods used to monitor occupational exposure, and variable composition of, in particular, the water-containing MWF.

Mixed exposure in the past. In many studies, past exposure was not exclusively to straight oil MWF. In other words, mixed exposure to different types of fluids, including the fluids that contained both mineral oil and water, has likely occurred. Overall, it is evident that in many studies mixed exposure has occurred and that this may have resulted in adverse health effects of non-mineral oil components superimposed on those associated with straight mineral oil exposure. This introduces uncertainty in straight mineral oil as the causative agent of the observed adverse health effects.

Monitoring occupational exposure: particulate fraction. The Committee notes that aerosol samples have been collected with different devices and that exposures have been measured in different ways, sometimes as the thoracic mass fraction[36,50,72], sometimes as the inhalable mass fraction[35,74], and other times as the total mass fraction.[3,71,81,111] For the risk assessment, the Committee recalculated the thoracic mass fraction to inhalable mass fraction by multiplying the thoracic mass fraction with a factor of 1.4, as proposed by Woskie *et al.* (2003)[134], and the total mass to inhalable mass fraction by multiplying the total mass fraction with a factor of 2, as recommended by Werner *et al.* (1996)[131].

Monitoring occupational exposure: analysis method. Measurements of aerosol concentrations have included gravimetry with or without extraction by a suitable solvent system, and light scatter. It is likely that the difference in methods used to monitor aerosol mass concentrations has introduced bias in the reported mass concentrations.

Composition of MWF. The type of MWF used has changed during the last decades. Originally, straight mineral oil was used in metalworking. Water-based fluids have become increasingly popular since the 1950s and, nowadays, the majority of MWF used in Europe is prepared from water-miscible cutting-fluid concentrates from which the end-users prepare their water-based MWF. The chemicals added to enhance performance and inhibit growth of microorganisms have regularly changed across calendar time and job title. From the available studies, however, it does not become clear to what extent non-mineral oil components have contributed to the adverse health effects observed.

Contamination of MWF during use. During metalworking, fines and metal ions are introduced in MWF, and at high temperatures thermo-degradation may occur. In water-based MWF, microorganisms have been detected. A few studies[74,111] have determined the amount of micro-organisms and endotoxin present, but in most studies microbial contamination was unknown. With respect to carcinogenicity, PAH levels have been shown to increase in straight mineral oils after prolonged use at high temperatures, compared to non-used oils. In addition, nitrosamines and formaldehyde have occasionally been found in used aqueous MWF.

Notwithstanding the uncertainties described here, it is the Committee's opinion that none of these preclude a judgement of the adverse health effects of occupational exposure to MWF that contain mineral oils. Because of the complexity and diversity of MWF (including their contamination during recycling at the work site), however, the Committee cannot identify the component(s) responsible for the reported adverse health effects. Therefore, the Committee concludes that the observed effects are associated with the use of MWF.

11.4.2 Carcinogenicity of working with metalworking fluids

In a large cohort of metal workers in the car industry, hired between 1917 and 1981, a weak but positive association was found between cumulative occupational exposure to straight oil MWF and cancer of the larynx and rectum. This was reported in 1992[38] and confirmed in an extended follow-up to 1994[34], and in several case-control studies from this same cohort. No other cohort studies with quantitative exposure-response data on cancer have been published since.

It is plausible that certain known carcinogenic substances, such as PAC present in the mineral base oils used in the past, may have been responsible for the carcinogenic potential of MWF. At present, the mineral base oils used in

MWF contain low amounts of PAC. These base oils did not show tumour formation in mouse skin painting assays.

No data are available on the formation of PAH in oil-containing MWF when the oils come into contact with metal surfaces that have become hot during cutting and grinding. By analogy to their formation in oils used at hot temperatures, the Committee expects that these aromatic hydrocarbons may be formed when the mineral oils in MWF come into contact with hot metallic surfaces during cutting or grinding.

Occasionally, genotoxic compounds like N-nitrosodiethanolamine and formaldehyde have been found in water-based MWF. In a human study, the mean number of DNA strand breaks in mononuclear blood cells appeared to be significantly elevated in workers exposed to airborne synthetic MWF that contained N-nitrosodiethanolamine. Such effects are not related to mineral oil exposure but to exposure to genotoxic products formed from additives in MWF.

Recommendation for classification. According to the Committee, the present MWF – as supplied to the end-user – can be considered not to contain mutagenic or carcinogenic compounds, as such additives are not allowed. However, during re-use the composition of MWF changes and MWF become contaminated.

The Committee has consulted the Subcommittee on the Classification of Carcinogenic Substances for the assessment of carcinogenic properties of working with MWF. The Subcommittee's conclusions and recommendations are described in Annex H.

In summary, the Subcommittee concludes that there is a lack of carcinogenic and genotoxic data on *unused* MWF. Therefore, the Subcommittee recommends not to classify *unused* MWF.

In addition, the Subcommittee concludes that *working with MWF* has been insufficiently investigated. While the available data do not warrant a classification as known or presumed to be carcinogenic to man, they indicate that there is cause for concern**.** Therefore, the Subcommittee recommends classifying *working with MWF* as suspected to be carcinogenic to man. This recommendation is comparable to classification in EU category 2 ('GLP' Regulation).

11.4.3 Non-carcinogenic adverse health effects of metalworking fluids

From the available data, the Committee concludes that the major sites affected by occupational exposure to MWF are the skin and the respiratory system.

Skin effects. Skin effects that may be observed after repeated exposure to straight oil MWF include folliculitis, oil acne, and keratosis. The soluble and semi-synthetic MWF (*i.e.*, the water-based emulsions) primarily cause irritant and occasionally allergic contact dermatitis. It is not clear to what extent additives and contaminants of MWF contributed to the observed irritant and allergic skin effects.

Effects on the respiratory system. Respiratory effects that have been observed after exposure to mists of mineral-oil-containing MWF include hypersensitivity pneumonitis, asthma, bronchitis, and respiratory symptoms (wheezing, cough, phlegm), sometimes accompanied by decreases of pulmonary function (baseline and cross-shift).

Outbreaks of hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis) have occurred in workers exposed to water-containing MWF. Both *Mycobacterium* and *Pseudomonas* species have been implicated in the aetiology but other species (*e.g.*, *Acinetobacter*) may be involved, too. According to the Committee, the evidence indicates that the observed hypersensitivity pneumonitis after exposure to MWF is associated with exposure to water-containing fluids and not to mineral oils *per se*.

A summary of the main findings of the epidemiological studies on non-carcinogenic adverse effects of inhalation exposure to MWF is given in Table 11.1. Kriebel *et al.* (1997)[74] showed that machinists with soluble MWF exposure at a level of 0.22 mg/m^3 (arithmetic mean; inhalable mass) had approximately 115 ml lower pre-shift FEV_1 (significant difference at p=0.05) than non-machinists. This is about 3% of the average value of the FEV_1 in this population. Kennedy *et al.* (1989)[72] showed an increased number of workers with 5% cross-shift ΔFEV_1 on Fridays (but not on Mondays) in the exposure category of 0.20-0.55 mg/m^3 ($p<0.05$) as the thoracic particulate fraction (any MWF) which corresponds to approximately 0.3-0.8 mg/m^3 as inhalable mass. In addition, Kennedy *et al.* (1999)[71] observed a decreased FVC at follow-up (p=0.03) at mean arithmetic aerosol mass levels of 0.46 mg/m^3, however without an effect on FEV_1. In their logistic regression model, a predictor of bronchial hyperresponsiveness was the exposure to synthetic MWF, and not the exposure to soluble or straight MWF. The other two studies (Ameille *et al.* 1995[3]; Massin *et al.* 1996[81]) that included the methacholine challenge test found a slightly increased bronchial hyperresponsiveness at higher levels of soluble MWF mist exposure.

From these data, the Committee concludes that adverse health effects on lung function have been found after occupational exposure to mineral-oil-containing

MWF aerosols, and that these effects start to occur at levels of approximately 0.2 mg/m^3.

Recommendation. According to the Committee, the occupational hazard associated with *other lubricant base oils* is apparent from the adverse effects on the respiratory system, including a decrease of the lung function, after occupational exposure to MWF. However, the Committee cannot separate the effects of mineral oil from the effects of other MWF components, including contaminants formed during the use of these fluids. Therefore, the Committee concludes that the observed effects are associated with the *use of* MWF resulting in exposure to mineral oil, its additives, and contaminants. In addition, it appears that a similar hazard is associated with the exposure to MWF that do not contain mineral oil. The consequence of this for the applicability of the recommended exposure limit is described in the section 'Additional considerations'.

The mineral base oils used in MWF, nowadays, are refined to such a degree that they contain trace amounts of PAC and do not carry a carcinogenic potential as based on mouse skin-painting studies.

Several epidemiological studies with quantitative exposure-response data exist that describe adverse health effects in workers exposed to MWF that contain mineral oil (Table 11.1). These studies show that adverse effects on the respiratory system are of major concern. Adverse effects include a decrease of the lung function. These effects started to occur at exposure levels of approximately 0.2 mg/m^3 (arithmetic mean) total weight of inhalable particulate mass, originating from MWF. Because of the small effect size, the Committee considers the level of 0.2 mg/m^3 the lowest level at which adverse health effects may start to occur. This small effect size also justifies a small factor to extrapolate this lowest-observed-adverse-effect-level into a no-adverse-effect-level. For this, the Committee applies a factor of 2 and calculates a no-adverse-effect-level of 0.1 mg/m^3 (arithmetic mean) total weight of inhalable particulate mass, originating from the use of MWF.

The Committee assumes that in the epidemiological studies sensitive workers were likely included. This makes a factor for interindividual variability in sensitivity unnecessary. Therefore, the Committee concludes that the value of 0.1 mg/m^3 represents the health-based occupational exposure limit, as an 8-hour time-weighted average.

In conclusion, to protect against non-carcinogenic adverse health effects the Committee recommends a health-based occupational exposure limit of 0.1 mg/m^3 total weight of inhalable particulate mass including its contaminants, as an eight-hour time-weighted average, applying to working with MWF that contain mineral oil. The Committee remarks that reliably monitoring the health-based

occupational exposure limit might be hampered by the detection limit of the available NIOSH method 5524.

No data on systemic toxic effects are available for the exposure to *unused* MWF. During (re-)use, however, MWF become contaminated and the contaminants cause concern for carcinogenicity and, consequently, systemic toxicity. As a skin notation is indicated if occupational skin exposure adds for 10% or more to systemic toxicity or if skin exposure may induce skin cancer, a skin notation might be indicated for used MWF. However, the Committee is not able to evaluate the need as such, as the contaminants in used MWF are diverse and largely unknown. Nevertheless, the need for a skin notation should be evaluated for each individual component that may be formed in MWF and that might be responsible for adverse systemic effects. A recent study indicates that for a component of MWF dermal uptake is important.[18] The Committee does not exclude the possibility of more MWF-components with a potential for dermal uptake.

The Committee recognizes that MWF may contain many different components in addition to mineral base oils. Therefore, in addition to the derived HBROEL, also other occupational exposure limits (including cancer risk values for carcinogenic substances) and skin notations if attached apply to working with MWF if these (carcinogenic) substances occur in these fluids, either by origin or by formation during their use.

11.5 Groups at extra risk

Atopics, asthmatics, and workers with decreased lung function may be at increased risk to develop adverse respiratory effects due to occupational exposure to MWF.

11.6 Conclusions and health-based recommended occupational exposure limits

The occupational exposure limits that the Dutch Expert Committee on Occupational Safety has derived are not the only limits to be applied. For specific substances in mineral base oils, including substances that are newly formed during the use of these oils, existing occupational exposure limits (including skin notations if attached) are to be applied as well. This includes the occupational cancer risk values and the skin notation of PAH.

Table 11-1 Adverse effects of occupational exposure to aerosols of mineral-oil-containing MWF in order of increasing level of exposure.[a]

reference	exposure		particulate	effect parameter	c	MWF/oil type	arithmetic
	current (mg/m^3)	cumulative ($mg/m^3 \cdot yrs$)	fraction / sampler[b]			RR (95%CI), p-value	mean inhalable mass (mg/m^3)
Kriebel *et al.* 1997[74] cross-sectional 216 machinists 170 controls	0.08 (mean 0.04)		inhalable 7-hole	5% cross-shift ΔFEV_1	-	straight, soluble	0.04
Kriebel *et al.* 1997[74] cross-sectional 216 machinists 170 controls	0.08-0.15 (mean 0.12)		inhalable 7-hole	5% cross-shift ΔFEV_1	-	straight, soluble, 2.3 (1.0-5.0)	0.12
Robins *et al.* 1997[95] cross-sectional (repeated measures) 83 machinists 34 controls	0.14		thoracic 2-stage	 10% cross-shift ΔFEV_1 10% cross-shift ΔFVC; 10% cross-shift ΔFEV_1 10% cross-shift ΔFVC	 - - - -	soluble; non-obstructed subjects; obstructed subjects	0.2
Lillienberg *et al.* 2008, 2010[76,77] cross-sectional metal workers: 923 men, 125 women controls: 374 men, 77 women	0.21 (AM) range 0.04-0.57 0.19 (GM), range 0.04-0.57 approx. 67% MWF (extracted)		inhalable PAS-6 sampler	flu-like symptoms,	+	mostly synthetic	0.21
Kriebel *et al.* 1997[74] cross-sectional 216 machinists 170 controls	0.22 (AM)		inhalable 7-hole	pre-shift FEV_1 (% predicted)	+	soluble p=0.05	0.22
Kriebel *et al.* 1997[74] cross-sectional 216 machinists 170 controls	0.24 and 0.22 (AM)		inhalable 7-hole	cross-shift ΔFEV_1	-	straight, soluble	0.22
Jaakkola *et al.* 2009[65] cross-sectional 726 machinists 84 controls	0.12 (0.001-3.00) median, breathing zone 0.17 (0.007-0.67) median, general air 0.15 (GM) (SD, 2.41)		total light scatter	nasal symptoms throat symptoms eye symptoms cough phlegm production wheezing breathlessness fever chronic bronchitis current asthma ever asthma	+ + - + + + + - + - -	all types, approx 87% soluble, semi-synthetic, synthetic	0.24 (median)

reference	exposure		particulate	effect parameter	c	MWF/oil type;	arithmetic
	current (mg/m^3)	cumulative ($mg/m^3 \cdot yrs$)	fraction / sampler[b]			RR (95%CI), p-value	mean inhalable mass (mg/m^3)
Oudyk *et al.* 2003[89]	0.13		total	chronic respiratory		soluble,	0.26
cross-sectional				symptoms	-	semi-synthetic	
1,334 machinists			light scatter	chronic wheezing	+		
Kriebel *et al.* 1997[74]	0.15 (mean,		inhalable	5% cross-shift ΔFEV_1	+	straight,	0.31
cross-sectional	0.31)					soluble	
216 machinists			7-hole			3.2 (1.2-8.7)	
170 controls							
Kennedy *et al.* 1989[72]	<0.20		thoracic	5% cross-shift ΔFEV_1	-	straight, soluble or	0.3
cross-sectional			2-stage			synthetic	
89 machinists							
42 controls							
Kennedy *et al.* 1989[72]	0.20-0.55		thoracic	5% cross-shift ΔFEV_1	+	straight, soluble or	0.3-0.9
cross-sectional			2-stage			synthetic	
89 machinists							
42 controls							
Lillienberg *et al.* 2008, 2010[76,77]	0.21 (AM) range		Inhalable	chronic bronchitis,	+	mostly soluble	0.42
				chronic rhinitis	+		
Cross-sectional	0.04-0.57		PAS-6				
Metal workers: 923	0.19 (GM),		sampler	wheeze,	+	mostly	
men, 125 women	range			chronic bronchitis,	+	synthetic	
Controls: 374 men,	0.04-0.57			eye irritation	+		
77 women	approx. 67%						
	MWF			symptoms mentioned	-	straight	
	(extracted)			above			
Sprince *et al.* 1997[111]	0.31		total	chronic respiratory		soluble,	0.6
cross-sectional	(mean of 3rd			symptoms:		semi-synthetic	
183 machinists	quartile)		light scatter	- usual cough	-		
66 controls				- usual phlegm	+		
				post-shift resp. symptoms:			
				- throat irritation	+		
				- cough	-		
Sprince *et al.* 1997[111]	0.33 (GM)		total	pre-shift FEV_1 and FVC;	-	soluble,	-
cross-sectional				5% post-shift ΔFEV_1 &	-	semi-synthetic	
183 machinists			light scatter	ΔFVC;			
66 controls				chronic respiratory symptoms:			
				- usual cough	+		
				- usual phlegm	+		
Robins *et al.* 1997[95]	0.34		thoracic			soluble;	0.5
cross-sectional				10% cross-shift ΔFEV_1	-	non-obstructed	
(repeated measures)			2-stage	10% cross-shift ΔFVC	-	subjects;	
83 machinists							
34 controls				10% cross-shift ΔFEV_1	+	obstructed	
				10% cross-shift ΔFVC	+	subjects	

reference	exposure		particulate	effect parameter	c	MWF/oil type;	arithmetic
	current (mg/m^3)	cumulative ($mg/m^3 \cdot yrs$)	fraction / sampler[b]			RR (95%CI), p-value	mean inhalable mass (mg/m^3)
Eisen *et al.* 1997[35] cross-sectional (cohort approach); 1,788 with 112 asthmatic of which 29 (26%) post-hired)	0.60		inhalable no data on collection device	new-onset asthma	+	mean exposure level of 6 cases (range 0.4-0.9)	0.6
Oudyk *et al.* 2003[89] cross-sectional 1,334 machinists	0.32		total light scatter	chronic respiratory symptoms	+	soluble, semi-synthetic	0.6
Eisen *et al.* 2001[36] cross-sectional 1,020 725 controls	0.4-0.6		thoracic 2-stage	FEV_1 FVC	- -	straight, soluble, synthetic isolated finding	0.6-0.9
Greaves *et al.* 1997[50] cross-sectional 1,042 769 controls	0.4-0.6		thoracic 2-stage	current respiratory symptoms; physician-confirmed asthma	+ -	straight synthetic	0.6-0.9
Kennedy *et al.* 1989[72] cross-sectional 89 machinists 42 controls	> 0.55		thoracic 2-stage	5% cross-shift ΔFEV_1	+	straight, soluble, synthetic	0.8
Kennedy *et al.* 1999[71] prospective (2-y) 82 machinists; 157 controls	0.46 (AM)		total 0.8-µm membrane filter	BHR, FEV_1, FVC at baseline BHR, FEV_1 at follow-up FVC at follow-up Δ metacholine slope after 2 yrs	- - + +	straight, soluble, synthetic only for soluble, synthetic exposures	0.9
Massin *et al*. 1996[81] cross-sectional 114 55 controls	0.65-2.20 (GM)		total extractable fibre filter	BHR DRS	- +	soluble	1.3-4.4 (GM)
Sprince *et al*.1997[111] cross-sectional 183 machinists 66 controls	0.90 (mean of 4th quartile)		total light scatter	chronic respiratory sympt.: - usual cough - usual phlegm post-shift resp. symptoms: - throat irritation - cough	 + + + +	soluble, semi-synthetic	1.8
Ameille *et al.* 1995[3] cross-sectional 230 78 controls	2.6 (AM)		total extractable fibre filter	chronic cough/phlegm FEV_1, FVC BHR reanalysis by Wild-Ameille1997: DRS in 1997	+ - - +	straight	5.2 (AM)

reference	exposure		particulate	effect parameter	c	MWF/oil type;	arithmetic
	current (mg/m^3)	cumulative ($mg/m^3 \cdot yrs$)	fraction / sampler[b]			RR (95%CI), p-value	mean inhalable mass (mg/m^3)
Eisen *et al*. 2001[36] cross-sectional 1,020 725 controls		4.7	thoracic 2-stage	FVC (in non-transferred only)	+	straight	
Eisen *et al*. 2001[36] cross-sectional 1,020 725 controls		5	thoracic 2-stage	FEV_1 FVC	- -	soluble, synthetic	

a Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GM, geometric mean; AM, arithmetic mean; BHR, bronchial hyperreactivity; DRS, normalised dose-response slope = 1/(methacholine slope + 2.5).

b Sampler type: 7-hole, 7-hole inlet sampler matching the ACGIH/ISO criteria for inhalable fraction; 2-stage, 2-stage (Marple) cascade impactor (cut-points of 3.5 and 9.8 µm) with the thoracic fraction defined as the sum of the 2 smaller size fractions (*i.e.*, <3.5 µm + 3.5-9.8 µm); fibre filter, collection on 37-mm glass fibre filter, extraction with C_2Cl_2, and analysis by gravimetry; 0.8-µm membrane filter, 37-mm cellulose ester membrane with 0.8-µm pore size, and analysis by gravimetry.

c Effect size: -, no significant difference compared to controls; +, significant difference compared to controls ($p<0.05$).

11.6.1 *Aerosols of **exclusively** highly refined mineral base oils*

The Dutch Expert Committee on Occupational Safety recommends a health-based occupational exposure limit of 1.6 mg/m^3 inhalable particulate mass, as an 8-hour time-weighted average, applying exclusively to aerosols of highly refined mineral base oils, used without additives and only once (not recycled). The Committee recognizes that in some applications, *e.g.*, in MWF, even highly-refined mineral base oils may end up as suspected human carcinogens, comparable to EU category 2 ('GLP' Regulation).

Insufficient data are available on the systemic toxicity of highly refined mineral base oils, but the available studies indicate that the systemic toxicity is small. In addition, skin exposure to highly refined base oils does not induce skin tumours. For these reasons, the Committee considers a skin notation not needed.

11.6.2 *Carcinogenic classification of **unused** metalworking fluids*

The Subcommittee on Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety concludes that there is a lack of carcinogenic and genotoxic data on unused MWF. Therefore, the Subcommittee recommends not to classify unused MWF.

11.6.3 *Carcinogenic classification of **working with** metalworking fluids*

The Subcommittee on Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety is of the opinion is that working with MWF has been insufficiently investigated. While the available data do not warrant a classification as known or presumed to be carcinogenic to man, they indicate that there is cause for concern. Therefore, the Subcommittee recommends classifying working with MWF as suspected to be carcinogenic to man. carcinogenic. This recommendation is comparable to the EU classification in category 2 ('GLP' Regulation).

11.6.4 *Aerosols formed during **working with** mineral-oil-containing metalworking fluids*

The Dutch Expert Committee on Occupational Safety recognizes that there is cause for concern that carcinogenic substances might be formed during the (re-)use of mineral-oil-containing MWF. For specific carcinogenic substances being formed, existing occupational exposure limits, cancer risk values, and skin notations if attached, automatically apply.

In addition to existing exposure limits for specific substances, the Dutch Expert Committee on Occupational Safety recommends a health-based occupational exposure limit of 0.1 mg/m^3 total weight of inhalable particulate mass including its contaminants, as an 8-hour time-weighted average. This value applies to aerosols formed during working with mineral-oil-containing MWF and should be respected next to other occupational exposure limits that exist for specific (carcinogenic) substances occurring in MWF.

The Committee is not able to evaluate the need for a skin notation as the contaminants formed by the use of MWF are diverse and largely unknown. Nevertheless, the need for a skin notation should be evaluated for each individual component that may be formed in MWF and that might be responsible for adverse systemic effects.

11.7 Additional considerations

The results of the epidemiological studies show that working with any of the 4 types of MWF, including the fluids that do not contain mineral oils, is associated with adverse effects on the respiratory system at comparable exposure levels. In addition, the Dutch Expert Committee on Occupational Safety expects that

working with synthetic-oil-based MWF is similarly associated with adverse effects on the respiratory system at comparable exposure levels because of the similarity of synthetic oil hydrocarbons and mineral oil hydrocarbons.

Consequently, it is the opinion of the Dutch Expert Committee on Occupational Safety that – in order to protect against adverse effects on the respiratory system – the HBROEL of 0.1 mg/m^3 for the total weight of inhalable particulate mass including its contaminants, as an 8-hour time-weighted average, is also applicable to working with MWF that do not contain mineral oil or that contain synthetic oil instead of mineral oil.

References

1 Agalliu I, Kriebel D, Quinn MM, Wegman DH, Eisen EA. Prostate cancer incidence in relation to time windows of exposure to metalworking fluids in the auto industry. Epidemiology 2005; 16(5): 664-671.

2 Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for total petroleum hydrocarbons (TPH). Atlanta, GA (USA): U.S.Department of Health and Human Services; 1999.

3 Ameille J, Wild P, Choudat D, Ohl G, Vaucouleur JF, Chanut JC *et al.* Respiratory symptoms, ventilatory impairment, and bronchial reactivity in oil mist-exposed automobile workers. Am J Ind Med 1995; 27(2): 247-256.

4 American Conference of Governmental Industrial Hygienists (ACGIH). Mineral oil, excluding metal working fluids. TLV Chemical Substances 7th Edition Documentation ACGIH 2010.

5 Bakke B, Ulvestad B, Stewart P, Lund MB, Eduard W. Effects of blasting fumes on exposure and short-term lung function changes in tunnel construction workers. Scand J Work Environ Health 2001; 27(4): 250-257.

6 Baldwin MK, Berry PH, Esdaile DJ, Linnett SL, Martin JG, Peristianis GC *et al.* Feeding studies in rats with mineral hydrocarbon food grade white oils. Toxicol Pathol 1992; 20(3 Pt 1): 426-435.

7 Bardin JA, Eisen EA, Tolbert PE, Hallock MF, Hammond SK, Woskie SR *et al.* Mortality studies of machining fluid exposure in the automobile industry. V: A case-control study of pancreatic cancer. Am J Ind Med 1997; 32(3): 240-247.

8 Bardin JA, Gore RJ, Wegman DH, Kriebel D, Woskie SR, Eisen EA. Registry-based case-control studies of liver cancer and cancers of the biliary tract nested in a cohort of autoworkers exposed to metalworking fluids. Scand J Work Environ Health 2005; 31(3): 205-211.

9 Bartels T, Bock W, Braun J, Busch C, Busch W, Dresel W *et al.* Ullman's Encyclopedia of Industrial Chemistry. Lubricants and lubrication. 6th[20], 1-202. 2005. Weinheim Wiley-VCH Verlag GmbH.

10 Beckett W, Kallay M, Sood A, Zuo Z, Milton D. Hypersensitivity pneumonitis associated with environmental mycobacteria. Environ Health Perspect 2005; 113(6): 767-770.

11 Bertazzi PA, Pesatori AC, Zocchetti C, Latocca R. Mortality study of cancer risk among oil refinery workers. Int Arch Occup Environ Health 1989; 61(4): 261-270.

12 Boers D, Zeegers MP, Swaen GM, Kant I, van den Brandt PA. The influence of occupational exposure to pesticides, polycyclic aromatic hydrocarbons, diesel exhaust, metal dust, metal fumes, and mineral oil on prostate cancer: a prospective cohort study. Occup Environ Med 2005; 62(8): 531-537.

13 Boylstein LA, Luo J, Stock MF, Alarie Y. An attempt to define a just detectable effect for airborne chemicals on the respiratory tract in mice. Arch Toxicol 1996; 70(9): 567-578.

14 Bracker A, Storey E, Yang C, Hodgson MJ. An outbreak of hypersensitivity pneumonitis at a metalworking plant: a longitudinal assessment of intervention effectiveness. Appl Occup Environ Hyg 2003; 18(2): 96-108.

15 Bukowski JA. Review of respiratory morbidity from occupational exposure to oil mists. Appl Occup Environ Hyg 2003; 18(11): 828-837.

16 Calvert GM, Ward E, Schnorr TM, Fine LJ. Cancer risks among workers exposed to metalworking fluids: a systematic review. Am J Ind Med 1998; 33(3): 282-292.

17 Carlton WW, Boitnott JK, Dungworth DL, Ernst H, Hayashi Y, Mohr U *et al.* Assessment of the morphology and significance of the lymph nodal and hepatic lesions produced in rats by the feeding of certain mineral oils and waxes. Proceedings of a pathology workshop held at the Fraunhofer Institute of Toxicology and Aerosol Research Hannover, Germany, May 7-9, 2001. Exp Toxicol Pathol 2001; 53(4): 247-255.

18 Cherrie JW, Semple S. Dermal exposure to metalworking fluids and medium-chain chlorinated paraffin (MCCP). Ann Occup Hyg 2010; 54(2): 228-235.

19 Cohen H, White EM. Metalworking fluid mist occupational exposure limits: a discussion of alternative methods. J Occup Environ Hyg 2006; 3(9): 501-507.

20 CONCAWE's Petroleum Products and Health Managements Groups. Lubricating oil basestocks. Brussels: CONCAWE; 1997: Product Dossier No. 97/108. Internet: http://www.concawe.be/ consulted: 10-1-2007.

21 Costa DL, Amdur MO. Effect of oil mists on the irritancy of sulfur dioxide. I. Mineral oils and light lubricating oil. Am Ind Hyg Assoc J 1979; 40(8): 680-685.

22 Costa DL, Amdur MO. Respiratory response of guinea pigs to oil mists. Am Ind Hyg Assoc J 1979; 40(8): 673-679.

23 Cullen MR, Balmes JR, Robins JM, Smith GJ. Lipoid pneumonia caused by oil mist exposure from a steel rolling tandem mill. Am J Ind Med 1981; 2(1): 51-58.

24 Dalbey W, Osimitz T, Kommineni C, Roy T, Feuston M, Yang J. Four-week inhalation exposures of rats to aerosols of three lubricant base oils. J Appl Toxicol 1991; 11(4): 297-302.

25 Dalbey WE. Subchronic inhalation exposures to aerosols of three petroleum lubricants. AIHAJ 2001; 62(1): 49-56.
26 Dalbey WE, Biles RW. Respiratory toxicology of mineral oils in laboratory animals. Appl Occup Environ Hyg 2003; 18(11): 921-929.
27 Dawkins P, Robertson A, Robertson W, Moore V, Reynolds J, Langman G *et al.* An outbreak of extrinsic alveolitis at a car engine plant. Occup Med (Lond) 2006; 56(8): 559-565.
28 Decoufle P. Cancer mortality among workers exposed to cutting-oil mist. Ann N Y Acad Sci 1976; 271: 94-101.
29 Decoufle P. Further analysis of cancer mortality patterns among workers exposed to cutting oil mists. J Natl Cancer Inst 1978; 61(4): 1025-1030.
30 Drasche H, Finzel L, Martschei H, Meyer R. [Industrial-medical investigations of persons exposed to oil mists]. Zentralbl Arbeitsmed 1974; 24(10): 305-312.
31 Ducos P, Gaudin R. N-nitrosodiethanolamine urinary excretion in workers exposed to aqueous metalworking fluids. Int Arch Occup Environ Health 2003; 76(8): 591-597.
32 Ducos P, Gaudin R, Francin JM. Determination of N-nitrosodiethanolamine in urine by gas chromatography thermal energy analysis: application in workers exposed to aqueous metalworking fluids. Int Arch Occup Environ Health 1999; 72(4): 215-222.
33 Eide I. A review of exposure conditions and possible health effects associated with aerosol and vapour from low-aromatic oil-based drilling fluids. Ann Occup Hyg 1990; 34(2): 149-157.
34 Eisen EA, Bardin J, Gore R, Woskie SR, Hallock MF, Monson RR. Exposure-response models based on extended follow-up of a cohort mortality study in the automobile industry. Scand J Work Environ Health 2001; 27(4): 240-249.
35 Eisen EA, Holcroft CA, Greaves IA, Wegman DH, Woskie SR, Monson RR. A strategy to reduce healthy worker effect in a cross-sectional study of asthma and metalworking fluids. Am J Ind Med 1997; 31(6): 671-677.
36 Eisen EA, Smith TJ, Kriebel D, Woskie SR, Myers DJ, Kennedy SM *et al.* Respiratory health of automobile workers and exposures to metal-working fluid aerosols: lung spirometry. Am J Ind Med 2001; 39(5): 443-453.
37 Eisen EA, Tolbert PE, Hallock MF, Monson RR, Smith TJ, Woskie SR. Mortality studies of machining fluid exposure in the automobile industry. III: A case-control study of larynx cancer. Am J Ind Med 1994; 26(2): 185-202.
38 Eisen EA, Tolbert PE, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry I: A standardized mortality ratio analysis. Am J Ind Med 1992; 22(6): 809-824.
39 Ely TS, Pedley SF, Hearne FT, Stille WT. A study of mortality, symptoms, and respiratory function in humans occupationally exposed to oil mist. J Occup Med 1970; 12(7): 253-261.
40 European Commission: Employment, Social Affairs and Inclusion. Recommendation from the Scientific Committee on Occupational Exposure Limits for aerosols of severely refined mineral oils. 2011.

41 European Parliament and the Council of the European Union. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union 2008 , (L353) 1-1355. 31-12-2008. Internet: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF consulted 2009.

42 Fox J, Anderson H, Moen T, Gruetzmacher G, Hanrahan L, Fink J. Metal working fluid-associated hypersensitivity pneumonitis: an outbreak investigation and case-control study. Am J Ind Med 1999; 35(1): 58-67.

43 Friesen MC, Costello S, Eisen EA. Quantitative exposure to metalworking fluids and bladder cancer incidence in a cohort of autoworkers. Am J Epidemiol 2009; 169(12): 1471-1478.

44 Fuchs J, Burg J, Hengstler JG, Bolm-Audorff U, Oesch F. DNA damage in mononuclear blood cells of metal workers exposed to N-nitrosodiethanolamine in synthetic cutting fluids. Mutat Res 1995; 342(1-2): 95-102.

45 Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids: results of the research project "FaSt". Int Arch Occup Environ Health 2004; 77(8): 543-551.

46 Goldstein DH, Benoit JN, Tyroler HA. An epidemiologic study of an oil mist exposure. Arch Environ Health 1970; 21(5): 600-603.

47 Gordon T, Galdanes K. Factors contributing to the acute and subchronic adverse respiratory effects of machining fluid aerosols in guinea pigs. Toxicol Sci 1999; 49(1): 86-92.

48 Gordon T, Harkema JR. Mucous cell metaplasia in the airways of rats exposed to machining fluids. Fundam Appl Toxicol 1995; 28(2): 274-282.

49 Gordon T, Nadziejko C, Galdanes K, Lewis D, Donnelly K. Mycobacterium immunogenum causes hypersensitivity pneumonitis-like pathology in mice. Inhal Toxicol 2006; 18(6): 449-456.

50 Greaves IA, Eisen EA, Smith TJ, Pothier LJ, Kriebel D, Woskie SR *et al.* Respiratory health of automobile workers exposed to metal-working fluid aerosols: Respiratory symptoms. Am J Ind Med 1997; 32(5): 450-459.

51 Gupta A, Rosenman KD. Hypersensitivity pneumonitis due to metal working fluids: Sporadic or under reported? Am J Ind Med 2006; 49(6): 423-433.

52 Hallock MF, Smith TJ, Woskie SR, Hammond SK. Estimation of historical exposures to machining fluids in the automotive industry. Am J Ind Med 1994; 26(5): 621-634.

53 Hashimoto DM, Kelsey KT, Seitz T, Feldman HA, Yakes B, Christiani DC. The presence of urinary cellular sediment and albuminuria in newspaper pressworkers exposed to solvents. J Occup Med 1991; 33(4): 516-526.

54 Health and Safety Executive (HSE). EH40/2005: Workplace Exposure Limits. Sudbury, UK: HSE Books; 2005.

55 Health and Safety Laboratory. Measurement of oil mist from mineral oil-based metalworking fluids MDHS84. HSE Books; 1997.

56 Health and Safety Laboratory. Measurement of personal exposure of metalworking machine operators to airborne water-mix metalworking fluids MDHS95/2. HSE Books; 2003.
57 Health Council of the Netherlands. BaP and PAH from coal-derived sources. Health-based calculated occupational cancer risk values of benzo[a]pyrene and unsubstituted non-heterocyclic polycyclic aromatic hydrocarbons from coal-derived sources. The Hague: Health Council of the Netherlands; 2006: 2006/01OSH. Internet: www.gr.nl.
58 Hodgson G. Cutaneous hazards of lubricants. Occup Health Rev 1971; 22(1): 16-25.
59 Hodgson MJ, Bracker A, Yang C, Storey E, Jarvis BJ, Milton D *et al.* Hypersensitivity pneumonitis in a metal-working environment. Am J Ind Med 2001; 39(6): 616-628.
60 Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA). Kühlschmierstoffe 7750. In: BIA-Arbeitsmappe 19. Erich Schmidt Verlag GmbH & Co. KG, Berlin; 1997:
61 International Agency for Research on Cancer (IARC). Mineral oils (lubricant base oils and derived products). IARC Monogr Eval Carcinog Risk Chem Hum 1984; 33: 87-168.
62 International Agency for Research on Cancer (IARC). Mineral oils. IARC Monogr Eval Carcinog Risk Hum 1987;(Suppl. 6): 403.
63 International Agency for Research on Cancer (IARC). Mineral oils: untreated and mildly-treated oils (Group1); highly refined oils (Group 3). IARC Monographs 1987;(Suppl. 7): 252-254.
64 Irander K, Hellquist HB, Edling C, Odkvist LM. Upper airway problems in industrial workers exposed to oil mist. Acta Otolaryngol 1980; 90(5-6): 452-459.
65 Jaakkola MS, Suuronen K, Luukkonen R, Jarvela M, Tuomi T, Alanko K *et al.* Respiratory symptoms and conditions related to occupational exposures in machine shops. Scand J Work Environ Health 2009; 35(1): 64-73.
66 Jarvholm B. Cutting oil mist and bronchitis. Eur J Respir Dis Suppl 1982; 118: 79-83.
67 Jarvholm B, Bake B, Lavenius B, Thiringer G, Vokmann R. Respiratory symptoms and lung function in oil mist-exposed workers. J Occup Med 1982; 24(6): 473-479.
68 Jarvholm B, Lavenius B. Mortality and cancer morbidity in workers exposed to cutting fluids. Arch Environ Health 1987; 42(6): 361-366.
69 Jarvholm B, Lillienberg L, Sallsten G, Thiringer G, Axelson O. Cancer morbidity among men exposed to oil mist in the metal industry. J Occup Med 1981; 23(5): 333-337.
70 Kazerouni N, Thomas TL, Petralia SA, Hayes RB. Mortality among workers exposed to cutting oil mist: update of previous reports. Am J Ind Med 2000; 38(4): 410-416.
71 Kennedy SM, Chan-Yeung M, Teschke K, Karlen B. Change in airway responsiveness among apprentices exposed to metalworking fluids. Am J Respir Crit Care Med 1999; 159(1): 87-93.
72 Kennedy SM, Greaves IA, Kriebel D, Eisen EA, Smith TJ, Woskie SR. Acute pulmonary responses among automobile workers exposed to aerosols of machining fluids. Am J Ind Med 1989; 15(6): 627-641.
73 Kreiss K, Cox-Ganser J. Metalworking fluid-associated hypersensitivity pneumonitis: a workshop summary. Am J Ind Med 1997; 32(4): 423-432.

74 Kriebel D, Sama SR, Woskie S, Christiani DC, Eisen EA, Hammond SK *et al.* A field investigation of the acute respiratory effects of metal working fluids. 1: Effects of aerosol exposures. Am J Ind Med 1997; 31(6): 756-766.

75 Krzesniak L, Kowalski J, Droszcz W. Respiratory abnormalities in workers exposed ot oil mist. Eur J Resp Dis 1981; 118(Suppl 113): 88-89.

76 Lillienberg L, Andersson EM, Jarvholm B, Toren K. Respiratory symptoms and exposure-response relations in workers exposed to metalworking fluid aerosols. Ann Occup Hyg 2010; 54(4): 403-411.

77 Lillienberg L, Burdorf A, Mathiasson L, Thorneby L. Exposure to metalworking fluid aerosols and determinants of exposure. Ann Occup Hyg 2008; 52(7): 597-605.

78 Lushbaugh CC, Green JW, Redemann CE. Effects of prolonged inhalation of oil fogs on experimental animals. Arch Ind Hyg Occup Med 1950; 1(2): 237-247.

79 Mackerer CR, Griffis LC, Grabowski Jr JS, Reitman FA. Petroleum mineral oil refining and evaluation of cancer hazard. Appl Occup Environ Hyg 2003; 18(11): 890-901.

80 Malloy EJ, Miller KL, Eisen EA. Rectal cancer and exposure to metalworking fluids in the automobile manufacturing industry. Occup Environ Med 2007; 64(4): 244-249.

81 Massin N, Bohadana AB, Wild P, Goutet P, Kirstetter H, Toamain JP. Airway responsiveness, respiratory symptoms, and exposures to soluble oil mist in mechanical workers. Occup Environ Med 1996; 53(11): 748-752.

82 Ministery of Social Affairs and Employment (SZW). Wijziging Arbeidsomstandighedenregeling. Staatscourant 2006;(252): 23-27.

83 Monarca S, Pasquini R, Scassellati SG, Savino A, Viola V. Mutagenic/carcinogenic hazards in a cold-rolling steel plant exposed to mineral oils: environmental monitoring phase. Int Arch Occup Environ Health 1984; 54(4): 345-354.

84 National Institute for Occupational Safety and Health. Oil mist, mineral Method 5026. http://ww.cdc.gov/niosh/docs/2003-154/pdfs/5026

85 National Institute for Occupational Safety and Health. Metalworking fluids (MWF) all categories Method 5524. http://www.cdc.gov/niosh/docs/2003-154/pdfs/5524

86 National Institute of Occupational Safety and Health (NIOSH). Criteria for a Recommended Standard. Occupational Exposure to Metalworking Fluids. Cincinnati, OH: NIOSH; 1998: DHHS (NIOSH) Publication No. 98-102.

87 O'Brien DM. Aerosol mapping of a facility with multiple cases of hypersensitivity pneumonitis: demonstration of mist reduction and a possible dose/response relationship. Appl Occup Environ Hyg 2003; 18(11): 947-952.

88 Occupational Safety and Health Administration (OSHA). Final report of the OSHA Metalworking Fluids Standards Advisory Committee. Washington, DC USA: OSHA; 1999.

89 Oudyk J, Haines AT, D'Arcy J. Investigating respiratory responses to metalworking fluid exposure. Appl Occup Environ Hyg 2003; 18(11): 939-946.

90 Oxhoj H, Andreasen H, Henius UM. Respiratory symptoms and ventilatory lung function in machine shop workers exposed to coolant-lubricants. Eur J Respir Dis Suppl 1982; 118: 85-89.

91 Pasternack B, Ehrlich L. Occupational exposure to an oil mist atmosphere. A 12-year mortality study. Arch Environ Health 1972; 25(4): 286-294.

92 Penes MC, Vallon JJ, Sabot JF, Vallon C. GC/MS detection of paraffins in a case of lipoid pneumonia following occupational exposure to oil spray. J Anal Toxicol 1990; 14(6): 372-374.

93 Perol M, Vallon C, Vallon JJ, Guerin JC. [Lipid pneumopathy caused by occupational exposure to cutting oil]. Rev Mal Respir 1989; 6(3): 271-274.

94 Robertson W, Robertson AS, Burge CB, Moore VC, Jaakkola MS, Dawkins PA *et al.* Clinical investigation of an outbreak of alveolitis and asthma in a car engine manufacturing plant. Thorax 2007; 62(11): 981-990.

95 Robins T, Seixas N, Franzblau A, Abrams L, Minick S, Burge H *et al.* Acute respiratory effects on workers exposed to metalworking fluid aerosols in an automotive transmission plant. Am J Ind Med 1997; 31(5): 510-524.

96 Robinson C, Waxweiler RJ, McCammon CS. Pattern and model makers, proportionate mortality 1972-1978. Am J Ind Med 1980; 1(2): 159-165.

97 Ronneberg A, Andersen A, Skyberg K. Mortality and incidence of cancer among oil exposed workers in a Norwegian cable manufacturing company. Part 2. Mortality and cancer incidence 1953-84. Br J Ind Med 1988; 45(9): 595-601.

98 Rosenman KD, Reilly MJ, Kalinowski D. Work-related asthma and respiratory symptoms among workers exposed to metal-working fluids. Am J Ind Med 1997; 32(4): 325-331.

99 Roy TA, Johnson SW, Blackburn GR, Mackerer CR. Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content. Fundam Appl Toxicol 1988; 10(3): 466-476.

100 Schaper M, Detwiler K. Evaluation of the acute respiratory effects of aerosolized machining fluids in mice. Fundam Appl Toxicol 1991; 16(2): 309-319.

101 Selgrade MK, Hatch GE, Grose EC, Illing JW, Stead AG, Miller FJ *et al.* Pulmonary effects due to short-term exposure to oil fog. J Toxicol Environ Health 1987; 21(1-2): 173-185.

102 Selgrade MK, Hatch GE, Grose EC, Stead AG, Miller FJ, Graham JA *et al.* Pulmonary effects due to subchronic exposure to oil fog. Toxicol Ind Health 1990; 6(1): 123-143.

103 Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Deutsche Forschungsgemeinschaft (DFG). MAK- und BAT-Werte-Liste 2007. Weinheim, Federal Republic of Germany: Wiley-VCH; 2007.

104 Shoda T, Toyoda K, Uneyama C, Takada K, Takahashi M. Lack of carcinogenicity of medium-viscosity liquid paraffin given in the diet to F344 rats. Food Chem Toxicol 1997; 35(12): 1181-1190.

105 Shoshkes M, Banfield WG, Rosenbaum SJ. Distribution, effect, and fate of oil aerosol particles retained in the lungs of mice. Arch Ind Hyg Occup Med 1950; 1(1): 20-35.

106 Silverstein M, Park R, Marmor M, Maizlish N, Mirer F. Mortality among bearing plant workers exposed to metalworking fluids and abrasives. J Occup Med 1988; 30(9): 706-714.

107 Skyberg K, Ronneberg A, Christensen CC, Naess-Andresen CF, Borgersen A, Refsum HE. Lung function and radiographic signs of pulmonary fibrosis in oil exposed workers in a cable manufacturing company: a follow up study. Br J Ind Med 1992; 49(5): 309-315.

108 Skyberg K, Ronneberg A, Kamoy JI, Dale K, Borgersen A. Pulmonary fibrosis in cable plant workers exposed to mist and vapor of petroleum distillates. Environ Res 1986; 40(2): 261-273.

109 Skyberg K, Skaug V, Gylseth B, Pedersen JR, Iversen OH. Subacute inhalation toxicity of mineral oils, C15-C20 alkylbenzenes, and polybutene in male rats. Environ Res 1990; 53(1): 48-61.

110 Smith JD. Health aspects of lubricants. Den Haag: CONCAWE; 1987: Report 5/87.

111 Sprince NL, Thorne PS, Popendorf W, Zwerling C, Miller ER, DeKoster JA. Respiratory symptoms and lung function abnormalities among machine operators in automobile production. Am J Ind Med 1997; 31(4): 403-413.

112 Sram RJ, Hola N, Kotesovec F, Novakova A. Cytogenetic analysis of peripheral blood lymphocytes in glass workers occupationally exposed to mineral oils. Mutat Res 1985; 144(4): 277-280.

113 Stear MA. Controlling health risks from workplace exposure to metalworking fluids in the United Kingdom engineering industry. Appl Occup Environ Hyg 2003; 18(11): 877-882.

114 Stula EF, Kwon BK. Pulmonary pathology from inhalation of a complex mineral oil mist in dogs, rats, mice and gerbils. Am Ind Hyg Assoc J 1978; 39(5): 393-399.

115 Sullivan PA, Eisen EA, Kriebel D, Woskie SR, Wegman DH. A nested case-control studt of stomach cancer mortality among automobile machinists exposed to metalworking fluids. AEP 10[7], 480-481. 2000.

116 Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH, Hallock MF et al. Mortality studies of metalworking fluid exposure in the automobile industry: VI. A case-control study of esophageal cancer. Am J Ind Med 1998; 34(1): 36-48.

117 Suuronen K, Aalto-Korte K, Piipari R, Tuomi T, Jolanki R. Occupational dermatitis and allergic respiratory diseases in Finnish metalworking machinists. Occup Med (Lond) 2007; 57(4): 277-283.

118 Svendsen K, Hilt B. Exposure to mineral oil mist and respiratory symptoms in marine engineers. Am J Ind Med 1997; 32(1): 84-89.

119 Svendsen K, Hilt B. Lung function disturbances and chest X-ray abnormalities among marine engineers. Am J Ind Med 1999; 35(6): 590-594.

120 Teschke K, Chow Y, van Netten C, Varughese S, Kennedy SM, Brauer M. Exposures to atmospheric effects in the entertainment industry. J Occup Environ Hyg 2005; 2(5): 277-284.

121 Thompson D, Kriebel D, Quinn MM, Wegman DH, Eisen EA. Occupational exposure to metalworking fluids and risk of breast cancer among female autoworkers. Am J Ind Med 2005; 47(2): 153-160.

122 Thorne PS, mcakova-Dodd A, Kelly KM, O'neill ME, Duchaine C. Metalworking fluid with mycobacteria and endotoxin induces hypersensitivity pneumonitis in mice. Am J Respir Crit Care Med 2006; 173(7): 759-768.

---

123 Tolbert PE, Eisen EA, Pothier LJ, Monson RR, Hallock MF, Smith TJ. Mortality studies of machining-fluid exposure in the automobile industry. II. Risks associated with specific fluid types. Scand J Work Environ Health 1992; 18(6): 351-360.

124 Trimmer GW, Freeman JJ, Priston RA, Urbanus J. Results of chronic dietary toxicity studies of high viscosity (P70H and P100H) white mineral oils in Fischer 344 rats. Toxicol Pathol 2004; 32(4): 439-447.

125 Urbanus JH, Lobo RC, Riley AJ. European hazard classification advice for crude oil-derived lubricant base oils compared with the proposed mineral oil mist TLV. Appl Occup Environ Hyg 2003; 18(11): 815-817.

126 Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. Am J Ind Med 2005; 47(5): 411-418.

127 Verma DK. Relationships between inhalable, thoracic, and respirable aerosols of metalworking fluids. J Occup Environ Hyg 2007; 4(4): 266-271.

128 Vineis P, Di Prima S. Cutting oils and bladder cancer. Scand J Work Environ Health 1983; 9(5): 449-450.

129 Wagner WD, Wright PG, Stokinger HE. Inhalation toxicology of oil mists. I. Chronic effects of white mineral oil. Am Ind Hyg Assoc J 1964; 25: 158-168.

130 Wang JD, Wegman DH, Smith TJ. Cancer risks in the optical manufacturing industry. Br J Ind Med 1983; 40(2): 177-181.

131 Werner MA, Spear TM, Vincent JH. Investigation into the impact of introducing workplace aerosol standards based on the inhalable fraction. Analyst 1996; 121(9): 1207-1214.

132 Wild P, Ameille J. Bronchial reactivity in oil-mist exposed automobile workers revisited. Am J Ind Med 1997; 32(4): 421-422.

133 World Health Organization (WHO). Selected petroleum products. Environmental Health Criteria 1982; 20: 1-139.

134 Woskie SR, Virji MA, Hallock M, Smith TJ, Hammond SK. Summary of the findings from the exposure assessments for metalworking fluid mortality and morbidity studies. Appl Occup Environ Hyg 2003; 18(11): 855-864.

135 Zeka A, Eisen EA, Kriebel D, Gore R, Wegman DH. Risk of upper aerodigestive tract cancers in a case-cohort study of autoworkers exposed to metalworking fluids. Occup Environ Med 2004; 61(5): 426-431.

A	Request for advice
B	The Committee
C	Comments on the public review draft
D	Identity of mineral oils
E	Human data
F	Animal data
G	IARC and EU carcinogenic classifications of various mineral base oils
H	Advice of the Subcommittee on Carcinogenic Classification of Substances
I	Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures (‘GLP’ Regulation)
J	Carcinogenic Classification of Substances by the Subcommittee

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 at 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 at 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

- G.J. Mulder, *chairman*
  Emeritus Professor of Toxicology, Leiden University, Leiden
- P.J. Boogaard
  Toxicologist, Shell International BV, The Hague
- J.J.A.M. Brokamp, *advisor*
  Social and Economic Council, The Hague
- D.J.J. Heederik,
  Professor of Risk Assessment in Occupational Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R. Houba
  Occupational Hygienist, The Netherlands Expertise Centre for Occupational Respiratory Disorders, Utrecht
- H. van Loveren
  Professor of Immunotoxicology, Maastricht University, Maastricht, and National Institute for Public Health and the Environment, Bilthoven
- T.M. Pal
  Occupational Physician, Netherlands Center for Occupational Diseases, Amsterdam
- A.H. Piersma
  Professor of Reproductive Toxicology, Utrecht University, Utrecht and National Institute for Public Health and the Environment, Bilthoven

- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam, Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- H. Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, The Hague
- G.M.H. Swaen,
  Epidemiologist, Dow Benelux N.V., Terneuzen
- R.C.H. Vermeulen
  Epidemiologist/Environmental Hygienist, Institute for Risk Assessment Sciences, Utrecht University, Utrecht
- R.A. Woutersen
  Professor of Translational Toxicology, Wageningen University, Wageningen, and TNO Quality of Life, Zeist
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- E.J.M. Pennings, *scientific secretary (until January 1, 2009)*
  Health Council of the Netherlands, The Hague
- C.A. Bouwman, *scientific secretary (until January 1, 2011)*
  Health Council of the Netherlands, The Hague
- J.T.J. Stouten, *scientific secretary*
  Health Council of the Netherlands, The Hague

The first draft of this report was prepared by S. Dekkers, E.L.J.P. Tielemans, J.H.E. Arts, and C. de Heer of the Toxicology Division of TNO Quality of Life, Zeist, The Netherlands.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the

Committee’s work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other’s possible interests.

Annex **C**

Comments on the public review draft

A draft of the present report was released in 2009 for public review. The following organizations and persons have commented on the draft:

- Dutch Lubricants Association, Den Haag, the Netherlands
- FME-CWM, Zoetermeer; Koninklijke Metaalunie, Nieuwegein, the Netherlands
- V. Gálvez Pérez, Ministerio de Trabajo e Inmigración, Madrid, Spain
- G. Minsavage, CONCAWE, Brussels, Belgium
- K. Wise, American Petroleum Institute, Washington DC, USA; J. Skowronski, Canadian Petroleum Products Institute, Ottawa, Canada
- R. Zumwalde, National Institute for Occupational Safety and Health, Cincinnati OH, USA.

Annex **D**

Identity of mineral oils

Table D-1 Important mineral oil refinery streams as defined by the TSCA and EINECS inventory.[a]

substance	EINECS	CAS number	carbon number distribution	viscosity at 40°C (mm^2/sec)	boiling range (°C)	remarks
unrefined or mildly refined base oils (acid-treated, chemically neutralized)						
crude oil distillation streams						
light paraffinic distillates (petroleum)	265-051-5	64741-50-0	C15-C30	<19	-	contains a large proportion of saturated aliphatic hydrocarbons
heavy paraffinic distillates (petroleum)	265-052-0	64741-51-1	C20-C50	≥19	-	contains a large proportion of saturated aliphatic hydrocarbons
light naphthenic distillates (petroleum)	265-053-6	64741-52-2	C15-C30	< 9	-	contains few normal paraffins
heavy naphthenic distillates (petroleum)	265-054-1	64741-53-3	C20-C50	≥19	-	contains few normal paraffins
vacuum residuum		64741-49-7	C11-C25	-	205-400	
acid-treating streams						
acid-treated light paraffinic distillates (petroleum)	265-121-5	64742-21-8	C15-C30	<19	-	predominantly saturated hydrocarbons

acid-treated heavy paraffinic distillates (petroleum)	265-119-4	64742-20-7	C20-C50	≥19	-	predominantly saturated hydrocarbons
acid-treated light naphthenic distillates (petroleum)	265-118-9	64742-19-4	C15-C30	<19	-	contains relatively few normal paraffins
acid-treated heavy naphthenic distillates (petroleum)	265-117-3	64742-18-3	C20-C50	≥19	-	contains relatively few normal paraffins
acid-treated residual oil		64742-17-2	>C25	-	>400	
chemically neutralized streams						
chemically neutralized light paraffinic distillates (petroleum)	265-128-3	64742-28-5	C15-C30	<19	-	
chemically neutralized heavy paraffinic distillates (petroleum)	265-127-8	64742-27-4	C20-C50	≥19	-	contains a relatively large proportion of aliphatic hydrocarbons
chemically neutralized light naphthenic distillates (petroleum)	265-136-7	64742-35-4	C15-C30	<19	-	contains relatively few normal paraffins
chemically neutralized heavy naphthenic distillates (petroleum)	265-135-1	64742-34-3	C20-C50	≥19	-	contains relatively few normal paraffins
highly refined base oils						
white mineral oil						
white mineral oil (petroleum)	232-455-8	8042-47-5	C15-C50	-	-	obtained by intensive treatment with sulphuric acid and oleum, or by hydrogenation
light white mineral oil (petroleum)	295-550-3	92062-35-6	>C12			
severely hydrotreated oil						
hydrotreated bright stock-based lubricating oil (petroleum)	276-735-8	72623-83-7	>C25	-	-	
hydrotreated bright stock-based lubricating oil (petroleum)	295-425-3	92045-44-8	>C50	-	-	
hydrotreated solvent-refined bright stock-based lubricating oil (petroleum)	295-426-9	92045-45-9	>C40	-	-	

other lubricant base oils (unspecified refining severity)

clay-treating streams						
clay-treated light paraffinic distillates (petroleum)	265-138-8	64742-37-6	C15-C30	< 19	-	contains a relatively large proportion of saturated hydrocarbons
clay-treated heavy paraffinic distillates (petroleum)	265-137-2	64742-36-5	C20-C50	≥ 19	-	contains a relatively large proportion of saturated hydrocarbons
clay-treated light naphthenic distillates (petroleum)	265-147-7	64742-45-6	C15-C30	< 19	-	contains relatively few normal paraffins
clay-treated heavy naphthenic distillates (petroleum)	265-146-1	64742-44-5	C20-C50	≥ 19	-	contains relatively few normal paraffins
clay-treated residual oil (petroleum)	265-143-5	64742-41-2	>C25	-	>400	
solvent-refining streams						
solvent-refined light paraffinic distillates (petroleum)	265-091-3	64741-89-5	C15-C30	< 19	-	predominantly saturated hydrocarbons
solvent-refined heavy paraffinic distillates (petroleum)	265-090-8	64741-88-4	C20-C50	≥19	-	predominantly saturated hydrocarbons
solvent-refined light naphthenic distillates (petroleum)	265-098-1	64741-97-5	C15-C30	<19	-	contains few normal paraffins
solvent-refined heavy naphthenic distillates (petroleum)	265-097-6	64741-96-4	C20-C50	≥19	-	contains few normal paraffins
solvent-refined residual oil (petroleum)	265-101-6	64742-01-4	>C25	-	>400	obtained as the solvent-insoluble fraction from solvent refining of a residuum using a polar organic solvent such as phenol or furfural
solvent-deasphalted residual oil (petroleum)	265-096-0	64741-95-3	>C25	-	>400	obtained as the solvent-soluble fraction from C3-C4 solvent deasphalting of a residuum
hydrotreating streams						
hydrotreated light paraffinic distillates (petroleum)	265-158-7	64742-55-8	C15-C30	<19	-	contains a relatively large proportion of saturated hydrocarbons

hydrotreated heavy paraffinic distillates (petroleum)	265-157-1	64742-54-7	C20-C50	≥19	-	contains a relatively large proportion of saturated hydrocarbons
hydrotreated light naphthenic distillates (petroleum)	265-156-6	64742-53-6	C15-C30	<19	-	contains relatively few normal paraffins
hydrotreated heavy naphthenic distillates (petroleum)	265-155-0	64742-52-5	C20-C50	≥19	-	contains relatively few normal paraffins
hydrotreated residual oil (petroleum)	265-160-8	64742-57-0	>C25	-	>400	
petrolatum		8009-03-8	>C25			predominantly saturated crystalline and liquid hydrocarbons
complex-dewaxing streams						
complex-dewaxing light naphthenic distillates (petroleum)	265-180-7	64742-76-3	C15-C30	-	-	contains relatively few normal paraffins
complex-dewaxing heavy naphthenic distillates (petroleum)	265-179-1	64742-75-2	C20-C50	-	-	contains relatively few normal paraffins
extracts						
light paraffinic distillates solvent extract (petroleum)	265-104-2	64742-05-8	C15-C30	-	-	predominantly aromatic hydrocarbons
heavy paraffinic distillates solvent extract (petroleum)	265-103-7	64742-04-7	C20-C50	-	-	predominantly aromatic hydrocarbons
light naphthenic distillates solvent extract (petroleum)	265-102-1	64742-03-6	C15-C30	-	-	predominantly aromatic hydrocarbons
heavy naphthenic distillates solvent extract (petroleum)	265-111-0	64742-11-6	C20-C50	-	-	predominantly aromatic hydrocarbons
residual oil solvent extract (petroleum)	265-110-5	64742-10-5	>C25	-	-	predominantly aromatic hydrocarbons
solvent-dewaxing streams						
solvent-dewaxed light paraffinic distillates (petroleum)	265-159-2	64742-56-9	C15-C30	<19	-	obtained by removal of normal paraffins
solvent-dewaxed heavy paraffinic distillates (petroleum)	265-169-7	64742-65-0	C20-C50	≥19	-	obtained by removal of normal paraffins

solvent-dewaxed light naphthenic distillates (petroleum)	265-168-1	64742-64-9	C15-C30	<19	-	obtained by removal of normal paraffins
solvent-dewaxed heavy naphthenic distillates (petroleum)	265-167-6	64742-63-8	C20-C50	≥19	-	obtained by removal of normal paraffins
solvent-dewaxed residual oil (petroleum)	265-166-0	64742-62-7	>C25	-	>400	obtained by removal of normal paraffins
catalytic-dewaxing streams						
catalytic-dewaxed light paraffinic distillates (petroleum)	265-176-5	64742-71-8	C15-C30	<19	-	
catalytic-dewaxed heavy paraffinic distillates (petroleum)	265-174-4	64742-70-7	C20-C50	≥19	-	
catalytic-dewaxed light naphthenic distillates (petroleum)	265-173-9	64742-69-4	C15-C30	<19	-	contains relatively few normal paraffins
catalytic-dewaxed heavy naphthenic distillates (petroleum)	265-172-3	64742-68-3	C20-C50	≥19	-	contains relatively few normal paraffins
hydrocracked stream						
heavy hydrocracked distillates (petroleum)	265-077-7	64741-76-0	C15-C39		260-600	

[a] Modified from IARC[61] and CONCAWE[20].

Table D2 Physico-chemical properties of several mineral base oils.[a]

base oil description (CAS registry number)	kinematic viscosity (mm^2/s) at:		flash point	pour point	density	average molecular weight
	40°C	100°C	(°C)	(°C)	(kg/L)	
base/process oils						
light, paraffinic	18.9	3.9	196	-12	0.82	-
heavy, paraffinic	650	34.8	307	-9	0.85	-
light, naphthenic	7.9	2.2	150	-42	0.84	-
heavy, naphthenic	492	16.4	250	-9	0.95	-
light, high aromatic	65	6.0	212	3	1.02	-
heavy, high aromatic	1080	25.1	247	26	1.00	-
distillates, solvent-dewaxed, light paraffinic (64742-56-9)	8.4	2.4	157	-18	0.85	280
distillates, solvent-dewaxed, heavy paraffinic (64742-65-0)	25.1	4.8	204	-12	0.86	390
distillates, hydrotreated, light paraffinic (64742-55-8)	17.0	3.7	190	-18	0.86	360
distillates, hydrotreated, heavy paraffinic (64742-54-7)	73.9	9.1	232	-9	0.88	500
distillates, hydrotreated, light naphthenic (64742-53-6)	8.5	2.2	145	-60	0.87	290
distillates, hydrotreated, heavy naphthenic (64742-52-5)	145	10.5	220	-24	0.91	440
residual oils, solvent-dewaxed (64742-62-7)	1300	50	285	-6	0.95	700
white oils						
white mineral oil (8042-47-5)	27.3	5.0	217	-15	0.86	400
medicinal white oil, light paraffinic	14.8	3.4	208	-12	0.84	-
medicinal white oil, heavy paraffinic	66.7	7.8	228	-6	0.88	-
medicinal white oil, light naphthenic	14.2	3.1	-	-49	0.87	-
medicinal white oil, heavy naphthenic	68.7	7.8	-	-23	0.89	-
technical white oil, light paraffinic	15.4	3.5	195	-15	0.84	-
technical white oil, heavy paraffinic	67.0	7.5	230	-14	0.89	-

[a] Modified from IARC[61] and CONCAWE[20].

Annex **E**

Human data

Table E-1 Characteristics of epidemiological studies on respiratory effects of mineral oil exposure; only studies with quantitative exposure assessment included.

reference **study design** **study population**	**exposure** **sampling, analysis, levels**	**effect assessment**	**statistical analysis**	**risk estimate (PR, OR, RR or regression coefficient)**	**notes**
Lillienberg *et al.* 2008, 2010[76,77] cross-sectional machine workers response rate: 67% (1499/2294) number of exposed: 1048 (923 men, 125 women) number of controls/ non-exposed: 451 (374 men, 77 women)	straight, soluble, synthetic MWF aerosols; 104 personal full-shift air samples at 5 machine shops; PAS-6 samplers with 25 mm polytetra-fluoroethylene filters with 3 µm pore size; sampling 6-8 h; airflow 2 L/min; gravimetric analysis and/or supercritical fluid extraction combined with GC to extract MWF past exposure	respiratory symptoms; self-administered questionnaire	comparing prevalences by chi-square tests or Fishers exact test; log-binomial regression models on male data only, adjusted for age, smoking	PR (95% CI)	exposure categories ‘straight’, ‘mostly emulsion’, ‘mostly synthetic’; grinding or non-grinding operations; current exposure estimated based on use of compressed air and machine enclosure

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Jaakkola *et al.* 2009[65] cross-sectional machine workers, men response rate: 79% (757/961) number of exposed: 726 number of controls/ non-exposed: 84	soluble, semi-synthetic, synthetic MWF aerosols; 380 breathing-zone measurements, 57 general air measurements at 60 companies; hand-held real-time aerosol photometer, DataRAM; sampling 1-5 min (breathing zone), 0.5-2 h (general air); size range 0.1-10 µm; light scattering	respiratory symptoms; computer-assisted telephone interview by trained interviewer	proportional odds model, multivariate regression analyses, adjusted for age, smoking, atopy in childhood	OR (95% CI)	87% of MWF water miscible; median general air measurements twofold higher in medium-sized machine shops compared to small and large shops
Oudyk *et al.* 2003[89] cross-sectional: automotive machining workers response rate: 81% (2368/2935) number of exposed: 1034 number of controls/ non-exposed: -	soluble or semi-synthetic MWF aerosol; area samples with direct reading instrument (MEI RAM-1); 3 spot measurements at all "I"-beams for 20 seconds at each location; particle size not reported; self-administered exposure questionnaire	respiratory symptoms; self-administered respiratory symptom-screening questionnaire	regression of MWF exposure, years in the plant, smoking status on presence or absence of respiratory symptoms, symptom groupings; linear trend analysis (chi-square) for the relation between exposure levels and symptoms	OR (95% CI)	type of MWF not measured; endotoxine, bacteria, biocide, amines not measured; 44% (1034/2368) excluded from analysis because of impossibility to assign exposure values; excluded had 75% of symptom response rate of included; exposure data available for 59% (37/63) of the working units, involving 56% of respondents; no personal exposure sampling; authors: direct reading measurements comparable (91-125%) to gravimetric measurements; personal exposure value at lower end of exposure range estimated from mapped areas (n=20)

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Bakke *et al.* 2001[5] tunnel construction workers cross-sectional, 2-week follow-up response rate: 65% (31/48) number of exposed: 31 number of controls/ non-exposed: 20	blasting fumes including oil mist, oil vapour, total, respirable dust, VOC, alpha-quartz, formaldehyde, carbon monoxide, nitrogen dioxide; personal sampling of oil exposure for 2-4 h with closed-face cassettes with glass fiber filters and cellulose acetate back-up filter; sampling for 2-4 h; analysis by FTIR; oil vapours with charcoal tubes measured by GC-FID; defined by job cycle: 10 days off - 6 days on - 1 day off - 5 days on	short-term changes in lung function spirometry at start (after 10 days off) and after 11 days (+1 day off) of work	Ln-transformation of exposure data; Kruskal Wallis tests; Mann-Whitney tests; one-way ANOVA with bonferroni post-hoc tests for changes in lung function by job category; analysis of confounding (age, height, smoking status, atopy) by multiple linear regression	-	co-exposure to dust, quartz, volatile organic compounds, NO_2, CO; the authors concluded that the most likely explanation for the observed lung function changes was peak exposures to NO_2
Eisen *et al.* 2001[36] car manufacturing workers*, male cross-sectional response rate: initial participation 86% (n=1882) number of exposed: 1020 (352 straight oil, 443 soluble oil, 225 synthetic oil) number of controls/ non-exposed: 725	straight, soluble, synthetic MWF aerosol; thoracic fraction by summing two smaller sized fractions of 2-stage Marple cascade impactor (3.5 and 9.8 µm cut-points); current exposure from workers' department/job at time of testing; cumulative exposure from workers' job records, past hygiene measurements, and records of operations and productions	loss of baseline pulmonary function spirometry	graphical analysis to assess validity of underlying assumptions; non-parametric smoothing to assess linearity; linear regression for exposure-response relationships (FEV_1, FVC), adjusting for age, height, race, smoking (pack-years), grinding, plant, exposure; analysis of healthy worker effect	regression coefficients	confounders and possible bias discussed, including transfer status

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Svendsen/Hilt, 1999[119] marine engineers, male prospective cohort of 492 seamen response rate: - number of exposed: chest films: 68 exposed/ 101 controls; number of controls/ non-exposed: spirometry: 44 exposed/71 controls	see Svendsen/Hilt, 1997	lung abnormalities X-ray by 2 certified B-readers (blind to exposure); pulmonary function spirometry	spirometry values standardized for age and height; *t*-test for differences in mean; prevalences adjusted for age and smoking (direct method); multivariate regression analysis for significant differences of spirometry results and ILO classification to explore confounding by 'smoking habits' and 'self-reported former exposure to asbestos'	RR (95% CI) for X-ray abnormalities; p-value for differences in spirometry results	crude estimate of oil mist exposure; small study size
Kennedy *et al.* 1999[71] first-year apprentice machinists at technology school prospective cohort (2-y follow-up) response rate: 83-91% number of exposed: 82 number of controls/ non-exposed: 157	straight, soluble, synthetic MWF, not subdivided by type; 68 personal 'total aerosol mass samples' at 13 different shops with plastic cassette with a 0.8-µm pore size, 37-mm membrane filter (Nucleopore), airflow 2 L/min, full-shift, gravimetric analysis; estimation by machinists during questioning	pulmonary function spirometry; asthma-like symptoms questionnaire by trained interviewer; airway responsiveness methacholine challenge (PC20) at baseline and follow-up; cut-off 8 mg/mL; PC20: methacholine concentration with 20% drop in FEV_1, determined by inter/ extrapolation	comparisons of means and rates by *t*-test, chi-square, Fisher exact; multiple linear regression analysis with log-transformed methacholine slope as the dependent variable and smoking, age, race, sex, asthma, atopy, pulmonary function, exposure variables as the predictor variables; logistic regression for predictors of BHR at base-line and follow-up	regression coefficients (SE); OR for predictors	straight oils used in combination with soluble and synthetic oils in all shops tested; measurements restricted to machine shops with employer approval; analysis of included and excluded subjects

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Svendsen/Hilt 1997[118] cross-sectional: marine engineers, male response rate: 70% (492/700) number of exposed: 197 (169 current and 28 former) number of controls/ non-exposed: 295	lubricating (bp 300-700°C) and fuel oil (bp 175-300°C) mist; area sampling in engine rooms of 19 ferries; sampler type not reported; sampling on Nucleopore 37-mm glass fiber filter for 60-120 min; air flow 2 L/min; analysis and particle size not reported; area measurements supplemented with optical aerosol monitor (Casella AMS950) data for specific tasks and estimation of actual exposure levels as time-weighted average concentrations; self-reported questionnaire (work history and past exposure to oil mist, asbestos, welding fumes, irritating gases/fumes)	respiratory symptoms; self-administered questionnaire	bivariate analysis with prevalences standardized for age, smoking (direct method, based on distributions); multivariate analysis by logistic regression with independent variables (self-reported exposures of asbestos (thought to be partly responsible) irritating gases/ fumes, welding fumes, oil mist; age, smoking, currently being marine engineer, number of years worked as a marine engineer	PR (95% CI); OR (95% CI)	co-exposure to engine exhaust and past exposure to asbestos; *'crude estimate'* .... of oil mist exposure

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Sprince *et al.* 1997[111] cross-sectional: car transmission plant, male and female response rate: participation 80% number of exposed: 183 number of controls/ non-exposed: 66 matched controles	soluble and semi-synthetic MWF aerosol; short-term passive area sampling with real-time light-scattering device (MIE MiniRAM PDM-3); aerosol concentrations referred to as total aerosol; interview on work history; culturable micro-organisms area air samples with two-stage Anderson microbial sampler (AMS) 28.3 L/min for 0.5-3 min total micro-organisms area sampling with open-face sampler using Nuclepore Filtration/Elution (NFE) method, 2 L/min, 300 min endotoxins area air samples with closed-face samplers on mixed cellulose ester filters	respiratory symptoms; modified ATS-DLD questionnaire and pre- and post-shift self-administered questionnaires; interview on work-relatedness of respiratory symptoms; baseline, cross-shift pulmonary function spirometry	logistic regression analyses, adjusting for age, gender, race, current smoking status; multivariate analysis	OR (95% CI)	MiniRAMs factory-calibrated to gravimetric samples of road dust and most sensitive in the 01-10 µm size range; no measurements of mineral oil concentrations in total aerosol; *'large number of analyses.... individual p-values should be interpreted with caution'*
Rosenman *et al.* 1997[98] surveillance program in 45 facilities using MWF (1988-1994) response rate: - number of exposed: 755 number of controls/ non-exposed: -	straight, soluble, semi-synthetic, synthetic MWF, grouped by type; area samples of 22 facilities; sampler type, analysis, particle size not reported; questionnaire, interviews	respiratory symptoms, chronic bronchitis, new-onset physician-diagnosed asthma; questionnaire, interview; asthma case finding from reports of physicians, hospitals, filed claims (1988-1994)	pearson chi-square for differences between companies; reanalysis of data by smoking category (current, ex-smoking, non-smoking)	prevalences	physician-diagnosed asthma; exclusion of pre-hired onset asthma; no BHR; area samples not representative

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Robins *et al.* 1997[95] cross-sectional (with repeated measures): automotive transmission plant response rate: initial response 84% (185/220) number of exposed: 83 number of controls/ non-exposed: 46	soluble MWF aerosol only; thoracic fraction by personal 2-stage sampler (<10 µm) with 37-mm Nucleopore polycarbonate membrane filter, airflow 2 L/min; sampling for >5½ hours; questionnaire thoracic bacteria; endotoxin (June 1992, January 1993, June 1993)	respiratory symptoms, chronic bronchitis, asthma; questionnaire interview, cross-shift pulmonary function pre-/ post-shift spirometry (June 1992, January 1993, June 1993)	multivariable linear, logistic models; regression models with variables for smoking (status, pack-years), amount of bacteria, baseline obstruction, exposure x baseline obstruction, department	regression coefficients, comparative OR for ≥10% cross-shift decrease of pulmonary function	age, race generally not associated with outcomes of interest; oil vapour, nicotine also measured, but not corrected for; selection bias, high rate of non-participation during the 3 years of the study; no BHR
Kriebel *et al.* 1997[74] cross-sectional with case-control sampling: automotive parts machining plant, male and female response rate: - number of exposed: 216 (87% of day-shift workers with consistent exposure) number of controls/ non-exposed: 170	straight, soluble MWF aerosol personal sampling with 7-hole inlet sampler with 0.4-µm polycarbonate filter, airflow 2 L/min, full shift, gravimetric analysis; personal sampling endotoxins personal sampling with 7-hole inlet sampler, airflow 2 L/min, full shift; limulus amebocyte lysate (LAL) analysis culturable bacteria area sampling with culturable microbial impactor, 5-25 min	respiratory symptoms; standardized (ATS) questionnaire, pulmonary function spirometry	initial univariate, bivariate analysis; analysis of confounders, effect modifiers including age, duration of exposure, race, asthma status, smoking status; linear regression; logistic regression for the nested case-control data of endotoxin	RR (95% CI) OR (95% CI)	discussion of different sampler, exposure levels in the study by Kennedy *et al.* (1998)

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Greaves *et al.* 1997[50] cross-sectional: 3 car manufacturing plants*, male response rate: - number of exposed: 1042 number of controls/ non-exposed: 769	straight, soluble , synthetic MWF aerosol current exposure: 475 personal samples with 2-stage Marple personal cascade impactor (size-selective cut points: 9.8 and 3.5 µm), airflow 2 L/min, full shift, taken between 1985 and 1986; past exposure: 394 personal and area air samples by variety of methods (1958-1984) personnel records, interview	respiratory symptoms, chronic bronchitis, asthma; questionnaire administered by trained technicians; interview; self-reported information on physician-confirmed asthma, chronic bronchitis	logistic regression to adjust for age, race, current smoking, factory, grinding	OR (95% CI)	analysis based on thoracic aerosol fraction, *i.e.*, sum of the 2 smallest size fractions; grinding distinguished from other machining operations in the analyses; transfer bias analysed, discussed; no attempt to identify specific causative agents in the MWF; physician-diagnosed asthma, no BHR
Eisen *et al.* 1997[35] cross-sectional, cohort approach car manufacturing workers*, male response rate: >85% participation number of exposed: 1788;112 asthmatics: 29 post-hired (26%) number of controls/ non-exposed: -	straight, soluble, synthetic MWF aerosol; quantitative exposure data only for (semi)synthetic MWF aerosol as inhalable particulates; complete exposure history from current measurements, industrial records, interviews; exposure defined at the time of asthma onset to evaluate transfer bias	post-hired physician-diagnosed asthma questionnaire by trained technician: complete exposure history, onset date of asthma	regression adjusting for age, smoking status, time since hire; cohort approach; analysis of job transfer bias (healthy worker effect)	RR (ratios of incidences)	reanalysis of Greaves' study data adjusting for transfer bias (healthy-worker effect); year of hire appeared to act as a confounder; evidence for transfer bias in the original study by Greaves (Monson *et al.* 1993); pre-hired asthmatics excluded; BHR not measured

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Massin *et al.* 1996[81] cross-sectional: ball-bearing manufacturing plant response rate: - number of exposed: 114 (male) number of controls/ non-exposed: 55 (male)	soluble oil aerosol only; area sampling on 37-mm glass fibre filters (Whatman GF/C), air flow 1 L/min, for 2-3 h; gravimetric analysis after extraction with dichloromethane; working hours, occupational history (not stated how this information was obtained); cumulative exposure by multiplication of area values (GM) by number of working months in that area	respiratory symptoms, chronic bronchitis, asthma; questionnaire, expert interviewer; lung function, spirometry; airway responsiveness, methacholine challenge	multivariate analysis; multiple logistic regression analysis; adjusted for smoking status, age for effect of exposure on symptoms; multiple linear regression analysis for effect of exposure on spirometry outcomes	OR for symptoms; p-value for BHR; regression coefficients for baseline FEV_1, age, cumulative exposure	according to authors, '*values measured in this study can only be considered as an indicator of the exposure as <10% of the mist is soluble in dichloromethane*'; asthma positive if yes to: have you ever been diagnosed as having bronchial asthma? BHR measured
Ameille *et al.* 1995[3]; Wild/Ameille 1997[132] cross-sectional: car manufacturing plant response rate: - number of exposed: 230 number of controls/ non-exposed: 78	straight, soluble mineral oil mist area sampling on 37-mm glass fibre filter (Whatman GF/A), airflow 2 L/min for 8 h; gravimetric analysis after extraction with dichloromethane questionnaire by trained interviewers	respiratory symptoms, bronchitis, asthma; questionnaire by trained interviewers; pulmonary function, spirometry; airway responsiveness, methacholine challenge(PD_{15}, PD_{20})	chi-square; logistic regression, linear modelling/regres-sion; adjusted for smoking, spirometry technician	OR	asthma not confirmed by physician; all area measurements in the straight cutting oil areas only; BHR measured

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Skyberg *et al.* 1992[107] cable impregnation workers cohort at follow-up in 1990 response rate: - number of exposed: 25 number of controls/ non-exposed: 25 matched controls	mineral oil mist from kerosene-like oils, kerosene; area, personal sampling; sampler type not reported; sampling on glass fibre filters, mixed cellulose ester membrane filters analysed by infrared spectroscopy after extraction with tetrachloroethylene; company's personnel records	respiratory symptoms; questionnaire interviews; pulmonary function, spirometry; arterial pH, pO_2, pCO_2; fibrosis X-ray	Wilcoxon's matched pairs signed rank test on median values	-	cohort of Skyberg *et al.* (1986); matched for age, heights, smoking; exposure to mineral oil vapours (50-100 mg/m^3) and aerosols (0.5-1.5 mg/m^3); no correction for co-exposure to asbestos, dust; underestimation of actual levels; likely survivors
Kennedy *et al.* 1989[72] cross-sectional survey: automotive parts machinists, males response rate: participation rate 86% number of exposed: 89 number of controls/ non-exposed: 42 controls	straight, soluble, synthetic MWF aerosol; personal air samples with a 2-stage (<3.5 and 9.8 µm) Marple impactor; airflow 2 L/min; sampling for 6-8 h; gravimetric analysis; inhalable aerosol defined as particulates ≤9.8 µm (sum of the 2 smallest particle fractions)	acute effects on pulmonary function, spirometry	logistic regression analysis; adjusted for race, childhood asthma, smoking	OR (95% CI)	exposure-response analysis included; selection bias suggested by authors as the non-participant (no cross-shift assessment of lung function available) exposed had substantially worse lung function than the participant exposed; FEV_1 decreased irrespective of MWF type, suggestive of multiple components/agents as the cause

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Skyberg *et al.* 1986[108] cross-sectional: man ≥5 y of employment at July 1st, 1980 oil impregnation and metal sheathing workers, male response rate: - number of exposed: 25 number of controls/ non-exposed: 25 matched controls (matched pair study design)	mineral oil mist from kerosene-like oils, kerosene; area, personal sampling on 37-mm glass fibre filters (Whatman GF/A), airflow 2 L/min, 8 h, analysed by infrared spectroscopy after extraction with tetrachloroethylene; interviews, company records for all subjects	respiratory symptoms questionnaire, interviews; pulmonary function, spirometry; fibrosis X-ray	student's *t* and McNemar's test	-	matched for age, height, smoking habits; no correction for co-exposure to asbestos, dust; underestimation of actual exposure levels; short-term vapour exposure levels of up to 4000 mg/m^3; possibly survivors, but unlikely according to authors
Oxhoj *et al.* 1982[90] cross-sectional: machine shop workers of 27 industries, male and female response rate: - number of exposed: 375 number of controls/ non-exposed: -	straight, soluble, semi-synthetic, synthetic oil; area samples, sampler type, analysis, particle size not reported	respiratory symptoms questionnaire; pulmonary function, spirometry	chi-square analysis of smoking, tobacco consumption, prevalence of cough, phlegm; anova of lung function after correction for age, height from reference equations	-	germ count, nitrites, amines, oil vapour measured but not reported
Jarvholm *et al.* 1982a[66] Swedish bearing ring manufacture workers prospective cohort (employed in 1978, followed up until 1981) response rate: - number of exposed: 64 number of controls/ non-exposed: 31	same as Jarvholm *et al.* 1982	respiratory symptoms questionnaire; pulmonary function spirometry	analysis by smoking category	-	preliminary data; prevalence rate ratio for number of men with chronic bronchitis

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Jarvholm *et al.* 1982[67] cross-sectional: Swedish Bearing ring manufacture workers (March 1978) response rate: - number of exposed: 323 number of controls/ non-exposed: 323-164	straight and soluble oil; area sampling, sampler type not reported, sampling on glass-wool filter for 2-4 h, analysis not reported; particle size was determined with a Royco-225 light scattering device	respiratory symptoms questionnaire; pulmonary function, spirometry; radiographic findings X-ray	t-test and multivariate analysis with linear model for age, height and exposure; analysis by smoking category	-	spirometry values expressed as percent of predicted
Krzesniak *et al.* 1981[75] tractor parts manufacturing workers response rate: - number of exposed: 531 (403 males, 128 females) number of controls/ non-exposed: 245	oil mist, not further defined; sampler type, analysis, and particle size not reported	respiratory symptoms questionnaire; pulmonary function, spirometry	-	-	smoking in exposed not different from smoking in controls; normalisation of spirometry values; oil mist varied between 5-99.5 mg/m^3
Irander *et al.* 1980[64] cross-sectional pilot study: Swedish lathe operators, male response rate: - number of exposed: 6 number of controls/ non-exposed: 7 matched controls	non-synthetic cutting oil, not further defined; sampler type, analysis and particle size not reported	nasal symptoms interview nasal effect clinical examination	matched for age, smoking	-	small number of subjects

reference study design study population	exposure sampling, analysis, levels	effect assessment	statistical analysis	risk estimate (PR, OR, RR or regression coefficient)	notes
Drasche *et al.* 1974[30] cross-sectional: various workers response rate: - number of exposed: 443 (of which 170 non-smoking) number of controls/ non-exposed: 398	oil mist and vapour in 17 different companies sampling, analysis and particle size not reported	respiratory symptoms; questionnaire	analysis by smoking category	-	84% of subjects between 40-150 mg/m^3
Goldstein *et al.* 1970[46] newspaper plant pressmen prospective cohort response rate: - number of exposed: about 460 number of controls/ non-exposed: about 700	mineral oil mist sampler type, analysis not reported; particle size determined with Casella cascade impactor	respiratory absence rate (≥8 days); reported morbidity between 1960-1964		-	no correction for confounding due to co-exposures and smoking (‘no smoking histories obtained’)
Ely *et al.* 1970[39] cross-sectional, prevalence study: machine shop WORKERS response rate: - number of exposed: >1700 number of controls/ non-exposed: -	mainly mineral oil area air samples (n=68) with unspecified high volume air sampler with BM-2133 filter; sampling for >1 h; gravimetric analysis	respiratory symptoms, lung function; self-administrated questionnaire, spirometry	multiple linear regression analysis with predictors height, age, cigarette years, smoking years, smoking history, job years, disease history	-	

abbreviations:
BHR, bronchial hyperreactivity; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FTIR, Fourier transform infrared spectrum; FVC, forced vital capacity; GC-FID, gas chromatography with flame ionisation detector; MWF, metalworking fluids; OR, odds ratio; PC_{20}, concentration in inhaled aerosol associated with a 20% drop in FEV_1; PD_{20}, PD_{15}, dose in inhaled aerosol associated with a 20 and 15% drop in FEV_1; PR, prevalence ratio; RR, relative risk or rate ratio; VOC, volatile organic compounds

* The Greaves (1997), Eisen (1997), and Eisen (2001) studies largely used the same study population.

Table E-2 Exposure-response data for asthma.[a]

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls	exposed	risk ratio / conclusion (95% CI)
Ameille *et al.* 1995 (correction published in Wild/Ameille, 1997)[3,132]	MWF aerosol	GM (extracted total particulate):			no significant differences between the 4 groups in prevalence of bronchial hyperresponsiveness (PD15 ≤1500 µg or PD20 ≤1500 µg) and not in the dose-response slopes (slope = % fall in FEV_1/total dose of µmol methacholine)
	controls (C)		6.4		
	straight (St)	2.19 (GSD 1.9)		7.7	
	soluble (So)	(not measured)		6.0	
	both (St&So)			5.0	
	St + St&So			5.6	
	So + St&So			5.3	
	C + So		6.2		
	C + St		6.8		
Massin *et al.* 1996[81]	aerosol (soluble mineral oil)	GM (extracted total particulate): cutting area 1989: 1.49 (GSD 1.22) machining area 1979-1989: 2.2 (GSD 1.55) machining area 1990-1993: 0.65 (GSD 1.29)	4	5	
		prevalence of bronchial hyperresponsiveness (FEV_1 fall ≥20%)	8 (4/55)	9 (10/114)	not statistically significant
		mean of dose-response slope (1/(slope +2.5) (SD)	0.30 (0.07)	0.27 (0.08)	p<0.03 based on linear model after adjusting for baseline FEV_1, age; multiregression of normalised dose-response slope yielded regression coefficient of -0.0099 for cumulative exposure (10 y • mg/m^3)
Rosenman *et al.* 1997[98] (no BHR) data)		range (sampler type not indicated):	new and symptomatic		
	mineral oil	<0.1-3.57	-	9.8	
	soluble oil			23.5	
	semi-synthetic			28.6	
	synthetic			25.0	
	total			21.0	
Robins *et al.* 1997 (no BHR data)[95]	aerosol of soluble MWF assembly	mean (thoracic particulate) 0.13	3		
	valve and case	0.32 and 0.56		5	

Kriebel *et al.* 1997 (no BHR data)[74]	MWF aerosol non-machining: classroom workers assembly workers machining: straight soluble	GM (inhalable particulate): 0.02 (GSD: 2.89, range: 0-0.1) 0.07 (GSD: 1.75, range: 0-0.3) 0.18 0.19 (GSD: 0.27, range: 0.1-2.0) 0.17 (GSD: 0.25, range: 0.05-2.8)	7	8 12	soluble MWF machinists versus non-machinists: PR: 1.8 (0.8-3.9) post-hire PR: 3.2 (0.8-13.7) pre-hire PR: 1.4 (0.7-2.8)
Greaves *et al.* 1997 (no BHR data)[50]	MWF aerosol assembly workers: never machinist previously machinist machinist: straight soluble synthetic	current mean exposure (thoracic particulate) 0.11 (SD 0.02) 0.12 (SD 0.02) 0.43 (SD 0.26) 0.55 (SD 0.17) 0.41 (SD 0.08) individual straight MWF exposure estimate past mean exposure (thoracic particulate, $mg/m^3 \bullet y$) 5.10 (SD 11.0) 5.28 (SD 9.11) 1.14 (SD 3.16) individual straight MWF exposure estimate	5.9 7.1	5.8 5.5 5.8 5.8 5.5 5.8	OR 1.38 0.63 0.96 1.46 1.03 1.02 1.01 0.99 adjusted for age, race, smoking, current/past grinding, factory
Eisen *et al.* 1997 (no BHR data)[35]	MWF aerosol synthetic soluble straight	average exposure in 2 years prior to onset (thoracic particulate): 0.6 (range: 0.36-0.91) (post-hired asthmatics)			RR post-hire (adjusted for year of hire and age) 3.2 (1.2-8.3) 0.5 (0.2-1.1) 2.0 (0.9-4.6)

Jaakkola *et al.* 2009[65]	MWF aerosol machine workers mixture of soluble, semi-synthetic, synthetic	median exposure breathing zone: 0.12 (range 0.001-3.00) mg/m^3; mean 0.12 (SD 4.07) mg/m^3 median exposure general air machine shops: 0.17 (range 0.007-0.67) mg/m^3; mean 0.15 (SD 2.41) mg/m^3	current: 1.2 ever: 4.8	1.7 5.0	OR current: 2.2 (0.3-17.7), adjusted for age, smoking, atopic disorders during childhood or school age 3.6 (0.6-19.9), for machine workers with exposure $\geq$0.17 mg/m^3; adjusted OR ever: 1.3 (0.4-4.0), adjusted 1.7 (0.6-5.1), for machine workers with exposure $\geq$0.17 mg/m^3; adjusted
Lillienberg *et al.* 2010[76]	MWF aerosols machine workers mixture(s) of soluble, synthetic, straight	AM: 0.21 mg/m^3; GM: 0.19 mg/m^3 (GSD: 1.62 mg/m^3); range: 0.04-0.57 mg/m^3	current: men: 6.2 women: 5.2 ever: men: 7.5 women: 6.5	7.4 8.0 8.3 10.4	PR: men: all exposed: 1.20 (0.71-2.03) mostly emulsion: 1.01 mostly synthetic: 1.02 straight oil: 1.18

[a] Abbreviations: AM, arithmetic mean; BHR, bronchial hyper responiveness; CI, confidence interval; FEV1, forced expiratory volume in 1 second; GM, geometric mean; GSD, geometric standard deviation; MWF, metalworking fluids; PD20, PD15, dose in inhaled aerosol associated with a 20 and 15% drop in FEV1; PR, prevalence ratio; OR, odds ratio; RR, rate ratio; SD, standard deviation

Table E-3 Exposure-response data for bronchitis.[a]

reference	exposure group (oil type)	exposure concentration (mg/m^3)	prevalence (%) controls	exposed	risk ratio / conclusion (95% CI)
Jarvholm 1982[66]	aerosol (straight and emulsified oil)	median exposure (sampler not indicated, GM particle size 2 µm) 1-4.5 (different exposure groups; range: 0.3-18.0)			RR 1.8 (1.1-2.9)
Ameille *et al.* 1995; Wild/ Ameille 1997[3,132]	MWF aerosol controls (C) straight (St) soluble (So) both (St&So) St + St&So So + St&So C + So C + St	GM (extracted total particulate): 2.19 (GSD 1.9) (not measured)	 2.6 2.3 4.2	 7.5 2.0 3.5 4.5 3.1 	
Massin *et al.* 1996[81]	aerosol (soluble mineral oil)	GM (extracted total particulate): cutting area 1989: 1.49 (GSD 1.22) machining area 1979-1989: 2.2 (GSD 1.55) machining area 1990-1993: 0.65 (GSD 1.29)	2	8	
Rosenman *et al.* 1997[98]	 mineral oil soluble oil semi-synthetic synthetic	range (sampler type not indicated): <0.1-3.57	-	 10.4 15.7 7.1 19.8	
Robins *et al.* 1997[95]	soluble MWF aerosol machinists assembly (controls) valve case	mean (thoracic particulate): 0.41 0.13 0.32 0.56	 3 	 13 19	OR 6.8 ($p<0.05$)
Svendsen/Hilt 1997[118]	oil mist (lubricating oil and fuel oil)	AM (sampler type not indicated): engine rooms: 0.2 (SD 0.13) during tasks: 1.3 (SD 0.6) estimated TWA concentration: 0.45 (range: 0.12-0.74)	10.6	13.2	PR 1.24 (0.7-2.1)

reference	exposure group (oil type)	exposure concentration (mg/m^3)	prevalence (%) controls	exposed	risk ratio / conclusion (95% CI)
Greaves *et al.* 1997[50]	MWF aerosol assembly workers:	current mean exposure (thoracic particulate)			OR
	never machinist	0.11 (SD 0.02)	8.4		
	previous machinist	0.12 (SD 0.02)	8.9		
	machinist:				
	straight	0.43 (SD 0.26)		11.5	1.35
	soluble	0.55 (SD 0.17)		11.5	0.80
	synthetic	0.41 (SD 0.08)		16.8	3.50 ($p<0.05$)
		individual straight MWF exposure estimate			1.19
		past mean exposure (thoracic particulate, $mg/m^3 \bullet y$)			
	straight	5.10 (SD 11.0)		11.5	1.01
	soluble	5.28 (SD 9.11)		11.5	1.01
	synthetic	1.14 (SD 3.16)		16.8	0.89 ($p<0.10$)
		individual straight MWF exposure estimate			0.99 adjusted for age, race, smoking, current/past grinding, factory
Jaakkola *et al.* 2009[65]	MWF aerosol machine workers mixture of soluble, semi-synthetic, synthetic	median exposure breathing zone: 0.12 (range 0.001-3.00) mg/m^3 mean 0.12 (SD 4.07) mg/m^3 median exposure general air machine shops: 0.17 (range 0.007-0.67) mg/m^3 mean 0.15 (SD 2.41) mg/m^3	3.6	4.3	OR: 1.0 (0.3-3.5) adjusted for age, smoking, atopic disorders during childhood or school age 2.8 (1.0-7.5) for machine workers with exposure $\geq$0.17 mg/m^3; adjusted
Lillienberg *et al.* 2010[76]	MWF aerosols machine workers mixture(s) of soluble, synthetic, straight	AM: 0.21 mg/m^3 GM: 0.19 mg/m^3 (GSD: 1.62 mg/m^3) range: 0.04-0.57 mg/m^3	men: 2.4 women: 2.6	4.5 1.6	PR: men: all exposed: 2.00 (0.97-4.10) mostly emulsion: 2.20 (1.01-4.78) mostly synthetic: 3.05 (1.16-8.01) straight oil: 0.72 (0.16-3.34)

[a] Abbreviations: AM, arithmetic mean; CI, confidence interval; GM, geometric mean; GSD, geometric standard deviation; MWF, metalworking fluids; PR, prevalence ratio; OR, odds ratio; RR, rate ratio; SD, standard deviation; TWA, time-weighted average.

Table E-4 Exposure-response data for cough.[a]

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls -	exposed	risk ratio or conclusion (confidence interval)
Ely *et al.* 1970[39]	oil mist non-smokers ex-smokers current smokers	mean (sampler type not reported): 5.2 (range: 0.07-110)		 2.0 13.2 23.4	
Kzesniak *et al.* 1981[75]	oil mist	range (sampler type not reported): 5-99.5	17.9	38.8	($p<0.05$)
Jarvholm 1982[66]	aerosol (straight and emulsified oil)	median exposure (sampler type not indicated, GM particle size 2 µm): 1-4.5 (different exposure groups) (range: 0.3-18.0)			RR 2.8 (1.3-2.6), adjusted for age, smoking
Oxhoj *et al.* 1982[90]	 oil aerosols controls mineral oil soluble semi-synthetic synthetic	median (sampler type not indicated): 0.35 (range: 0.1-2.0) Range for controls: 0.0-0.1	 18	 32 18 15 25 17	($p<0.05$)
Ameille *et al.* 1995; Wild/Ameille 1997[3,132]	MWF aerosol controls (C) straight (St) soluble (So) both (St&So) St + St&So So + St&So C + So C + St	GM (extracted total particulate): 2.19 (GSD 1.9) (not measured)	cough and/or phlegm 17.9 16.3 20.3	 25.0 13.7 25.9 25.7 22.6	chronic cough OR 2.2 (95% CI, 1.01-4.85) (>15 y of exposure, trend with exposure duration) ($p<0.05$)
Massin *et al.* 1996[81]	aerosol (soluble mineral oil)	GM (extracted total particulate): cutting area 1989: 1.49 (GSD 1.22) machining area 1979-1989: 2.2 (GSD 1.55) machining area 1990-1993: 0.65 (GSD 1.29)	cough or phlegm 11	 32	OR: 4.9 ($p<0.002$), adjusted for age, smoking
Rosenman *et al.* 1997[98]	 mineral oil soluble oil semi-synthetic synthetic	range (sampler type not indicated): <0.1-3.57	 -	 14.8 18.3 28.6 21.4	

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls -	exposed	risk ratio or conclusion (confidence interval)
Robins *et al.* 1997[95]	soluble MWF aerosol	mean (thoracic particulate):	cough		
	assembly	0.13	35		
	valve	0.32		50	
	case	0.56		46	
			chronic cough		
	assembly	0.13	15		
	valve	0.32		17	
	case	0.56		31	
Sprince *et al.* 1997[111]	soluble, semi-synthetic MWF aerosol	GM (total particulate, direct reading):			OR
	machine operators	0.33 (range 0.04-1.44)			3.1 (1.4-6.9)
	assemblers (controls)	0.08 (range 0.02-0.20)			
	total aerosol exposure				1.8 (1.1-2.8)
	2 vs 1 quartile	0.20 (vs 0.07)			1.6 (0.6-4.3)
	3 vs 1 quartile	0.31 (vs 0.07)			2.2 (0.8-5.8)
	4 vs 1 quartile	0.90 (vs 0.07)			3.0 (1.2-8.0)
	semi-synthetic versus assemblers				2.1 (1.0-4.2) post-shift
	total aerosol exposure				2.1 (1.1-3.9)
	2 vs1 quartile	0.20 (vs 0.07)			1.7 (0.4-8.0)
	3 vs 1 quartile	0.31 (vs 0.07)			3.4 (0.8-13.6)
	4 vs 1 quartile	0.90 (vs 0.07)			5.3 (1.3-21.8) adjusted for smoking, age, race, gender association with total culturable bacteria
Kriebel *et al.* 1997[74]	MWF aerosol	GM (inhalable particulate):			chronic cough
	non-machining:		10		PR
	classroom	0.02 (GSD 2.9, range 0-0.1)			
	assembly	0.07 (GSD 1.8, range 0-0.3)			
	machining:				
	straight	0.19 (GSD 1.8) (0.08-2.02)		19	2.2 (1.1-4.6)
	soluble	0.17 (GSD 1.8) (0.05-2.76)		6	
Svendsen/Hilt 1997[118]	oil mist (lubricating oil and fuel oil)	estimated TWA concentration (sampler type not reported): 0.45 (range 0.12-0.74)	cough or wheezing 24.4	24.2	

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls -	exposed	risk ratio or conclusion (confidence interval)
Greaves *et al.* 1997[50]	assembly workers:	current mean (thoracic particulate):			OR
	never machinist	0.11 (SD 0.02)	20.9		
	previously machinist	0.12 (SD 0.02)	19.8		
	machinist:				
	straight	0.43 (SD 0.26)		26.4	1.60
	soluble	0.55 (SD 0.17)		21.2	1.37
	synthetic	0.41 (SD 0.08)		33.6	4.82 ($p<0.01$)
		individual straight MWF exposure estimate			1.46
		past mean (thoracic particulate, $mg/m^3 \bullet y$)			
	straight	5.10 (SD 11.0)			1.02
	soluble	5.28 (SD 9.11)			0.99
	synthetic	1.14 (SD 3.16)			0.93
		individual straight MWF exposure estimate			0.99 adjusted for age, race, smoking, current/past grinding, factory
Eisen *et al.* 1997[35]	MWF aerosol	current mean (thoracic particulate):			
	synthetic				
	post-hire asthmatics	0.6 (range 0.36-0.91) (post-hired asthmatics)		44.8	
	pre-hire astmatics			20.5	
	non-asthmatics			20.3	
	total cohort (straight, soluble, synthetic MWF)			20.7	
Oudyk *et al.* 2003[89]	soluble, semi-synthetic MWF aerosol	range of departmental averages (total particulate, direct reading):			OR
	average exposure	0.02-0.84			
	current smoker				1.72 (1.2-2.4)
	peak exposure groups:	average of departmental 95th percentile (total particulate, direct reading):			
	peak (control)	0.06 (range 0.02-0.09)			
	peak low	0.15 (range 0.10-0.19)			0.98 (0.7-1.4)
	peak medium	0.27 (range 0.20-0.47)			1.72 (1.2-2.5)
	peak high	1.37 (range 0.59-2.85)			1.54 (0.9-2.7)
	current smoker				1.68 (1.2-2.3)

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls	exposed	risk ratio or conclusion (confidence interval)
Jaakkola *et al.* 2009[65]	MWF aerosol machine workers mixture of soluble, semi-synthetic, synthetic	median exposure breathing zone: 0.12 (range 0.001-3.00) mg/m^3; mean 0.12 (SD 4.07) mg/m^3 median exposure general air machine shops: 0.17 (range 0.007-0.67) mg/m^3; mean 0.15 (SD 2.41) mg/m^3	3.6	9.1	OR: 2.5 (0.8-8.1), adjusted for age, smoking, atopic disorders during childhood or school age 3.1 (1.5-6.4) for machine workers with exposure $\geq$0.17 mg/m^3; adjusted
Lillienberg *et al.* 2010[76]	MWF aerosols machine workers mixture(s) of soluble, synthetic, straight	AM: 0.21 mg/m^3; GM: 0.19 mg/m^3 (GSD: 1.62 mg/m^3); range: 0.04-0.57 mg/m^3	cough with plegm men: 14.9 women: 18.4	 21.2 26.8	

[a] Abbreviations: AM, arithmetic mean; CI, confidence interval; GM, geometric mean; GSD, geometric standard deviation; MWF, metalworking fluids; OR, odds ratio; RR, rate ratio; SD, standard deviation; TWA, time-weighted average.

Table E-5 Exposure-response data for phlegm.[a]

reference	exposure group	exposure concentration (mg/m^3)	prevalence (%) controls	exposed	risk ratio / conclusion (confidence interval)
Ely *et al.* 1970[39]	oil mist	mean (sampler type not			
	non-smokers	reported):		12.2	
	ex-smokers	5.2 (range: 0.07-110)		10.5	
	current smokers			26.0	
Jarvholm *et al.* 1982[66]	oil mist	median exposure (sampler type			RR
	non-smokers	not indicated, GM particle size			2.3 (1.2-3.9),
	smoker	2 µm):			adjusted for age and
	ex-smokers	1-4.5 (different exposure			smoking
	(straight and emulsified	groups)			
	oil)	(range: 0.3-18.0)			
Oxhoj *et al.* 1982[90]		median (sampler type not indicated):			
	oil aerosols	0.35 (range: 0.1-2.0)		25	(p<0.05)
	controls	range for controls: 0.0-0.1	11		
	mineral oil			17	
	emulsion			11	
	semi-synthetic			19	
	synthetic			14	
Ameille *et al.* 1995; Wild/Ameille 1997[3,132]	MWF aerosol	GM (extracted total particulate):	cough and/or phlegm		
	controls (C)	2.19 (GSD 1.9)	17.9	25.0	
	straight (St)	(not measured)		13.7	
	soluble (So)			25.9	
	both (St&So)			25.7	(p<0.05)
	St + St&So			22.6	
	So + St&So				
	C + So		16.3		
	C + St		20.3		
Massin *et al.* 1996[81]	aerosol (soluble mineral oil)	GM (extracted total particulate):	cough or phlegm		chronic cough or phlegm
		cutting area 1989: 1.49 (GSD 1.22) machining area 1979-1989: 2.2 (GSD 1.55) machining area 1990-1993: 0.65 (GSD 1.29)	11	32	OR: 4.90 (p<0.002) adjusted for smoking, age
Robins *et al.* 1997[95]	MWF aerosol	mean (thoracic particulate):	phlegm		
	machinists	0.41			OR: 3.1 (p<0.05)
	assembly	0.13	26		
	valve	0.32		60	
	case	0.56		48	

			chronic phlegma		
	assembly	0.13	15		
	valve	0.32		27	
	case	0.56		25	
Sprince *et al.* 1997[111]	soluble , semi-synthetic MWF aerosol	GM (total particulate, direct reading)			OR
	machine operators	0.33 (range 0.04-1.44)			3.1 (1.6-6.1)
	assemblers (control)	0.08 (range 0.02-0.20)			
	total aerosol exposure				1.7(1.2-2.6)
	2 vs 1 quartile	0.20 (vs 0.07)			1.4 (0.6-3.4)
	3 vs 1 quartile	0.31 (vs 0.07)			2.8 (1.2-6.5)
	4 vs 1 quartile	0.90 (vs 0.07)			3.8 (1.7-8.8)
					adjusted for smoking, age, race, gender; also association with endotoxin, total culturable bacteria, total organisms
Kriebel *et al.* 1997[74]	MWF aerosol	GM (inhalable particulate):			
	non-machining:		8		
	classroom	0.02 (GSD 2.9, range 0-0.1)			
	assembly	0.07 (GSD 1.8, range 0-0.3)			
	machining:				
	straight	0.19 (GSD 1.8) (0.08-2.02)		11	
	soluble	0.17 (GSD 1.8) (0.05-2.76)		8	
Greaves *et al.* 1997[50]	assembly workers:	Current mean (thoracic particulate):			OR
	never machinist	0.11 (SD 0.02)	17.2		
	previously machinist	0.12 (SD 0.02)	18.6		
	machinist:				
	straight	0.43 (SD 0.26)		24.5	2.22 ($p<0.05$)
	soluble	0.55 (SD 0.17)		22.3	1.19
	synthetic	0.41 (SD 0.08)		35.0	7.32 ($p<0.001$)
		Individual straight MWF exposure estimate			2.80 ($p<0.05$)
		past mean exposure (thoracic particulate, $mg/m^3 \bullet y$):			
	straight	5.10 (SD 11.0)		24.5	1.03 ($p < 0.10$)
	soluble	5.28 (SD 9.11)		22.3	1.01
	synthetic	1.14 (SD 3.16)		35.0	0.85 ($p<0.05$)
		individual straight MWF exposure estimate			0.96 ($p<0.05$) adjusted for age, race, smoking, current/past grinding, factory

Oudyk *et al.* 2003[89]	aerosol of soluble and semi-synthetic MWF average exposure groups: average (control) average medium average high current smoker peak exposure groups: peak (control) peak low peak medium peak high current smoker	average of departmental averages (total particulate, direct reading): 0.06 (range 0.02-0.09) 0.12 (range 0.10-0.16) 0.37 (range 0.25-0.84) average of departmental 95th percentile (total particulate, direct reading): 0.06 (range 0.02-0.09) 0.15 (range 0.10-0.19) 0.27 (range 0.20-0.47) 1.37 (range 0.59-2.85)			OR 1 1.24 (0.96-1.61) 1.58 (0.99-2.51) 1.51 (1.11-2.04) 1 1.05 (0.75-1.46) 1.56 (1.09-2.22) 1.78 (1.04-3.06) 1.49 (1.10-2.02)
Jaakkola *et al.* 2009[65]	MWF aerosol machine workers mixture of soluble, semi-synthetic, synthetic	median exposure breathing zone: 0.12 (range 0.001-3.00) mg/m^3; mean 0.12 (SD 4.07) mg/m^3 median exposure general air machine shops: 0.17 (range 0.007-0.67) mg/m^3; mean 0.15 (SD 2.41) mg/m^3	8.3	12.4	OR: 1.4 (0.6-3.3) adjusted for age, smoking, atopic disorders during childhood or school age 1.9 (1.0-3.5) for machine workers with exposure $\geq$0.17 mg/m^3; adjusted

[a] Abbreviations: GM, geometric mean; GSD, geometric standard deviation; MWF, metalworking fluids; OR, odds ratio; RR, rate ratio or relative risk; SD, standard deviation.

Table E-6 Exposure-response data for pulmonary function.[a]

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Ely *et al.* 1970[39]	aerosol	mean (sampler type not reported): 5.2 (range: 0.07-110)	FEV_1, FVC			no statistical significant association
Kzesniak *et al.* 1981[75]	oil mist	range (sampler type not reported): 5-99.5	prevalence of: decreased FEV_1%FVC (%)	11.4	35.6	differences were statistically significant ($p<0.05$)
			decreased FEF_{25-75} (%)	18.4	33.3	
			$FEF_{200-1200}$ (%) (compared to normal values from literature)	2.8	15.8	
Jarvholm *et al.* 1982[67]	oil mist (straight, emulsified oil)	median exposure (sampler type not indicated, GM particle size 2µm): 1-4.5 (different exposure groups) (range: 0.3-18.0)	FEV_1(% predicted) (SD)		107 (14)	no statistical difference in FEV1 or FVC among non smoking and all subjects
			VC (% predicted) (SD) (among non-smoking (n=25))		98 (13)	
Jarvholm *et al.* 1982[67]	oil mist (straight, emulsified oil)	median exposure (sampler type not indicated, GM particle size 2µm): 1-4.5 (different exposure groups) (range: 0.3-18.0)	difference FEV_1 between 1978 and 1981 (litres) (SD)	0.05 (0.2)	-0.03 (0.3)	no statistically significant differences
			difference FVC between 1978 and 1981 (litres) (SD)	0.02 (0.3)	-0.04 (0.3)	
Oxhoj *et al.* 1982[90]		median (sampler type not indicated): 0.35 (range: 0.1-2.0) Range for controls: 0.0-0.1	FEV_1 (litre)			no differences in FEV_1, FVC, FEV_1%, MEF_{50}, or MEF_{25} after adjusting for smoking, age and height
	control never-smokers:					
	mineral oil				4.00	
	emulsion				4.14	
	semi-synthetic				4.27	
	synthetic				4.25	
	ex-smokers:					
	mineral oil				3.33	
	emulsion				4.05	
	semi-synthetic				3.79	
	synthetic				4.45	
	smokers:					
	mineral oil				3.91	
	emulsion				3.75	
	semi-synthetic				3.73	
	synthetic				3.59	

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Skyberg *et al.* 1986[108]	aerosol	TWA (extracted total particulate):	VC (% predicted) (SD)	91.9 (19)	91.6 (15)	p<0.05
		0.15-0.30 (with short term vapour exposure up to 4000)	FEV_1 (% predicted) (SD)	84.2 (24)	87.5 (20)	p<0.05 both exposed and non-exposed workers had significant lower VC and FEV_1 values (matched for age, not corrected for co-exposure to asbestos, dust, compared to local reference values)
Kennedy *et al.* 1989[72]	aerosol	range (total particulate):				only statistically significant differences between non-participant and participant machinists in follow-up study
	machinists	0.16-2.03				
	controls	0.07-0.44				
	participant		FEV_1 (%predicted)	98.7	99.0	
	non-participant			99.1	90.2	
	participant		FVC (%predicted)	100	100.3	
	non-participant			98.4	92.4	
Skyberg *et al.* 1992[107]	oil mist, vapour	estimated TWA(extracted total particulate):	median FEV_1 (litre) (25-75 %tile)	3.52 (3.2-4.4)	3.41 (2.7-4.2)	no statistical difference in FEV1 or VC, but a significant decrease in CO transfer.
		50-100 (vapour) 0.5-1.5 (mist)	median VC (litre) (25-75 %tile)	4.46 (4.0-5.3)	4.46 (3.8-5.9)	
Ameille *et al.* 1995; Wild/Ameille 1997[3,132]	MWF aerosol	GM (extracted total particulate):	FEV_1 (% predicted) (SD)			significant association between duration of exposure to straight oils and FEV_1, FEF_{25-75}, V_{50}, V_{25} (after adjustment for technician, smoking)
	controls (C)	2.19 (GSD 1.9)		101 (14)		
	straight (St)	(not measured)			100 (13)	
	soluble (So)				106 (13)	
	both (St&So)				101 (15)	
	St + St&So				101 (15)	
	So + St&So				102 (15)	
	C + So			103 (14)		
	C + St			101 (14)		
	controls (C)		FVC	102 (14)		
	straight (St)		(% predicted) (SD)		104 (15)	
	soluble (So)				108 (13)	
	both (St&So)				103 (13)	
	St + St&So				104 (14)	
	So + St&So				105 (13)	
	C + So			104 (14)		
	C + St			103 (14)		

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Massin *et al.* 1996[81]	aerosol (soluble mineral oil)	GM (extracted total particulate): cutting area 1989: 1.49 (GSD 1.22) machining area 1979-1989: 2.2 (GSD 1.55) machining area 1990-1993: 0.65 (GSD 1.29)	FEV_1 mean standardized residuals (SD)	0.22 (0.98)	0.38 (1.08)	p=0.06
			FVC mean standardized residuals (SD)	0.47 (0.91)	0.37 (0.92)	p=0.14
			FVC/ FEV_1 mean standardized residuals (SD)	0.14 (0.78)	0.20 (0.79)	p=0.30
			FEF_{25-75} mean standardized residuals (SD)	-0.26 (0.95)	-0.13 (1.11)	p=0.11
			V_{max50} mean standardized residuals (SD)	0.04 (1.04)	0.10 (1.28)	p=0.24
			V_{max25} mean standardized residuals (SD)	-0.40 (0.84)	-0.45 (0.94)	p=0.54, not statistically significant after adjustment for smoking
Sprince *et al.* 1997[111]	soluble, semi-synthetic MWF aerosol	GM (total particulate, direct reading): 0.33 (range				no statistically significant differences (decrease associated
	machine operators	0.04-1.44)	FEV_1		92(13)	with total culturable
		0.08 (range	(% predicted) (SD)			bacteria)
	assemblers (controls)	0.02-0.20)		93 (13)		
	machine operators	0.33 (range 0.04-1.44)	FCV (% predicted) (SD)		97 (13)	
	assemblers (controls)	0.08 (range 0.02-0.20)		97 (13)		
Kriebel *et al.* 1997[74]	MWF aerosol	GM (inhalable particulate):				FEV_1 machinists soluble approx. 115 mL lower than FEV_1 non-machinists
	straight	0.19 (GSD 1.8) (0.08-2.02)	FEV_1 (litre) (SD)	3.58 (0.7)	3.88 (0.7)	
	soluble	0.17 (GSD 1.8) (0.05-2.76)			3.66 (0.8)	
	straight	0.19 (GSD 1.8) (0.08-2.02)	FEV_1 (% predicted) (SD)	98 (14)	100 (13)	p=0.05, adjusted for age, height, gender, race, smoking
	soluble	0.17 (GSD 1.8) (0.05-2.76)			96 (15)	

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
	straight	0.19 (GSD 1.8) (0.08-2.02)	FVC (litre) (SD)	4.57 (0.9)	4.95 (0.9)	
	soluble	0.17 (GSD 1.8) (0.05-2.76)			4.70 (1.0)	
	straight	0.19 (GSD 1.8) (0.08-2.02)	FVC (% predicted) (SD)	101 (13)	103 (13)	
	soluble	0.17 (GSD 1.8) (0.05-2.76)			100 (13)	
Kennedy *et al.* 1999[71]	MWF aerosol (straight, soluble, synthetic MWF)	GM (total particulate): 0.31 (GSD 2.4, range <0.7-3.65)	FEV_1 (% predicted) (SD)			
			baseline	102.3 (10)	100.2 (11)	no statistically
			follow-up	100.8 (11)	98.5 (11)	significant
			difference (mL/y) (SD)	-65.3 (105)	-61.9 (87.3)	differences
			FVC (% predicted) (SD)			
			baseline	106.1 (10)	103.4 (11)	p=0.06
			follow-up	106.0 (10)	103.0 (10)	p=0.03
			FEV_1/FVC% (SD)			
			baseline	80.6 (6)	80.9 (6)	no statistically
			follow-up	79.2 (6)	79.7 (6)	significant differences
			methacholine slope (SD) (mL/mg)			
			baseline	-19.7 (32.4)	-18.4 (31.1)	no statistically significant difference
			follow-up	-18.5 (28.4)	-35.4 (87.7)	p=0.09
						linear regression: bronchial responsiveness at follow-up associated with soluble and synthetic MWF exposure; logistic regression: OR: 1.44 (1.1-1.9) for synthetic MWF exposure only, as predictor of BHR

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Svendsen/ Hilt 1999[119]	aerosol	estimated TWA (sampler type not				
	all	reported):	FEV_1 (litre) (SD)	3.9 (0.6)	3.9 (0.6)	
	current and	0.45		3.8 (0.5)	3.8 (0.6)	
	ex-smokers	(range 0.12-0.74)	FEV_1 (%predicted)	86.6 (8.0)	82.8 (11)	$p<0.05$ also after
	all		(SD)	86.4 (7.8)	82.4 (11)	adjustment for
	current and		FVC (litre) (SD)	4.5 (0.7)	4.7 (0.7)	potential confounding
	ex-smokers			4.4 (0.6)	4.7 (0.8)	
	all					
	current and					
	ex-smokers					
	(lubricating and fuel oil)					
Eisen *et al.* 2001[36]	MWF aerosol	current mean				no statistically
	assembly workers:	(thoracic particulate)				significant association between
	never machinist	0.11 (SD 0.02)	FEV_1 (liter)(SD)	3.83 (0.7)		FVC or FEV_1 and
	previously machinist	0.11 (SD 0.02)		3.65 (0.8)		current exposure to
	machinist:					any type of MWF;
	straight	0.43 (SD 0.26)			3.65 (0.8)	statistical significant
	soluble	0.55 (SD 0.17)			3.58 (0.8)	association between
	synthetic	0.41 (SD 0.08)			3.86 (0.8)	cumulative exposure
	never machinist		FEV_1	95.5 (14)		to straight oil and
	previously machinist		(% predicted) (SD)	96.1 (14)		FVC
	machinist:					(after adjustment for
	straight				94.7 (15)	transfer bias, age,
	soluble				95.1 (15)	height, race,
	synthetic				94.4 (14)	smoking)
	never machinist		FVC (liter)(SD)	4.82 (0.9)		
	previously machinist			4.57 (0.9)		
	machinist:					
	straight				4.64 (0.9)	
	soluble				4.52 (0.9)	
	synthetic				4.86 (0.8)	
	never machinist		FVC	97.7 (13)		
	previously machinist		(% predicted)(SD)	97.5 (12)		
	machinist:					
	straight				96.4 (12)	
	soluble				97.1 (12)	
	synthetic				96.5 (12)	

reference	exposure (oil type)	exposure concentration (mg/m³)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Bakke *et al.* 2001[5]	aerosol	GM (total particulate, infrared spectroscopy)				
	outdoor workers (controls)	0.12 (GSD 2.2)	FEV_1 before work (litre)	4.1 (0.7)		changes were reversible within 10 d
	ANFO workers	0.27 (GSD 1.7)			3.9 (0.7)	
	SSE workers	0.18 (GSD 1.3)			3.8 (0.7)	
	outdoor workers	0.12 (GSD 2.2)	FEV_1 change (%)	<1		p<0.001
	ANFO workers	0.27 (GSD 1.7)			7	
	SSE workers	0.18 (GSD 1.3)			-2	
	outdoor workers	0.12 (GSD 2.2)	FVC before work	5.4 (0.8)		
	ANFO workers	0.27 (GSD 1.7)	(litre)		5.3 (0.9)	(p<0.05)
	SSE workers	0.18 (GSD 1.3)			5.0 (0.8)	
	outdoor workers	0.12 (GSD 2.2)	FVC change (%)	2		
	ANFO workers	0.27 (GSD 1.7)			3	
	SSE workers	0.18 (GSD 1.3)			<-1	
	outdoor workers	0.12 (GSD 2.2)	FEF_{25-75} (litre/sec)	3.6 (0.9)		
	ANFO workers	0.27 (GSD 1.7)	(SD)		3.2 (0.9)	
	SSE workers	0.18 (GSD 1.3)			3.7 (1.0)	
	outdoor workers	0.12 (GSD 2.2)	FEF_{25-75} change	-3		
	ANFO workers	0.27 (GSD 1.7)	(%)		8	(p<0.01);
	SSE workers	0.18 (GSD 1.3)			1	authors concluded that the effects were most likely caused by peak exposures to nitrogen dioxide

[a] ANFO, ammonium nitrate fuel oil; BHR, bronchial hyperresponsiveness; $FEF_{200-1200}$, forced expiratory flow rate from 200 to 1200 mL; FEF_{25-75}, forced expiratory flow rate from 25 to 75% of the FVC; FEV_1, forced expiratory volume in 1 second; FEV1%, FEV_1 expressed as percent of FVC; FVC, forced vital capacity; GM, geometric mean; GSD, geometric standard deviation; MEF_{50}, MEF_{25}, maximal expiratory flow at 50 and 20% of the FVC; MWF: metalworking fluids; OR, odds ratio; SD, standard deviation; SSE, size-sensitized emulsion; TWA, time-weighted average; V_{75},V_{50},V_{25}, maximal flow rate at 75, 50, and 25% of exhaled FVC; VC, vital capacity.

Table E-7 Exposure-response data for cross shift pulmonary function.[a]

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter controls	exposed	risk ratio / conclusion
Kennedy *et al.* 1989[72]	MWF aerosol	range (total particulate):	prevalence of cross-shift decrement in FEV_1	9.5	23.6	RR: 2.5 p<0.05
	machinists	0.16-2.03	(decrease ≥5%, on Mondays)			
	controls	0.07-0.44				
		mean (thoracic particulate):	prevalence of cross-shift decrement in FEV_1			OR (95% CI):
	straight oil	0.28 (range 0.10-0.59)	(decline ≥5%, on Mondays)			5.8 (1.1-29)
	soluble oil	0.27 (range 0.07-0.86)				
	synthetic	0.23 (range 0.07-0.44)				4.4 (1.0-20)
	controls A	0.05 (range 0.02-0.15)				
	controls B	0.03 (range 0.01-0.08)				6.9 (1.4-35), adjusted for race, asthma, and smoking
Robins *et al.* 1997[95]	non-obstructed	mean (thoracic particulate):	incidence of cross-shift decrement in FEV_1 (decline ≥10%)			OR:
	non-smoker				2.9%	
	current smoker				8.8%	
	obstructed					
	non-smoker				8.0%	
	current smoker				25.4%	
	non-obstructed		incidence of cross-shift decrement in FCV (decline ≥10%)			
	non-smoker				1.2%	
	current smoker				3.9%	
	obstructed					
	non-smoker				8.0%	
	current smoker				15.3%	
	other subjects	0.14	OR (95% CI) for cross-shift ΔFEV_1 (decline ≥10%)			1.0
	obstructed	0.14				2.75 (0.9-8.4)
	other subjects	0.34				0.91 (0.6-1.4)
	obstructed	0.34				4.6 (1.8-11.7)
	other subjects	0.57				0.86 (0.4-2.0)
	obstructed	0.57				6.2 (2.2-17.8)
	other subjects	0.14	OR (95% CI) for cross-shift ΔFVC (decline ≥10%)			1.0
	obstructed	0.14				1.19 (0.2-6.1)
	other subjects	0.34				0.73 (0.4-1.4)
	obstructed	0.34				4.09 (1.1-15.3)
	other subjects	0.57				0.61 (0.2-2.0)
	obstructed	0.57				8.43 (2.1-34.4)

reference	exposure (oil type)	exposure concentration (mg/m^3)	effect parameter (description and unit)	value of effect parameter		risk ratio / conclusion
				controls	exposed	
Sprince *et al.* 1997[111]	aerosol	GM (total particulate, direct reading): 0.33 (range 0.04-1.44)	incidence of cross-shift decrement in FEV_1 (decline≥5%)	12	16	no statistically significant differences
	machine operators	0.08 (range 0.02-0.20)	incidence of cross-shift decrement in FCV (decline≥5%)	9	14	
	assemblers (controls):		cross-shift decrement in FEV_1 (% change) (SD)	-0.5 (5.2)	-1.5 (6.6)	
			cross-shift decrement in FCV (% change) (SD)	-0.6 (4.8)	-0.9 (5.1)	
Kriebel *et al.* 1997[74]	aerosol (straight and soluble oil) exposure categories	mean (inhalable particulate):	incidence of cross-shift decrement in FEV_1 (decline≥5%)			RR:
	low (≤0.08 mg/m^3)	0.04		10.3	0	1
	medium (0.08-0.15 mg/m^3)	0.12		21.7	8.8	2.3 (1.0-5.0)
	high (≥0.15 mg/m^3)	0.31		33.3	11.2	3.2 (1.2-8.7)
	machining versus non machining all exposure categories	0.16		14.2	9.7	0.4 (0.2-0.8) (adjusted for machining status)

[a] GM, geometric mean, GSD, geometric standard deviation; SD, standard deviation; FEV_1, forced expiratory volume during one second; FVC, forced vital capacity; RR, relative risk; OR, odds ratio.

Table E-8 Carcinogenicity of mineral oil mists: epidemiological studies on metal workers.(ACGIH 2010[4]; IARC 1984[61]; Calvert *et al.* 1998[16])

study population (number of subjects)	**employment criteria (exposure)**	**observed effects (number with cancer)**	**rate ratio (95%CI or P-value)**	**reference (comments)**
Cohort studies				
white male workers at a heavy industrial plant in the USA (n=5189, followed up until 1967)	employed between 1936-1967 (spend ≥1 y in metal-machining jobs)	deaths from: cancer of the digestive system; cancer at all other sites combined	exposed/expected: 58/60.3 46/51.5	Decoufle 1976[28]
white male workers at a heavy industrial plant in the USA (n=2485, followed up until 1968)	employed between 1936-1967, for ≥5 y (spend ≥5 y in metal-machining (oil-mist-exposed) jobs prior to 1938)	death from: cancer of the stomach and large intestinal combined rectal cancer (4) pancreatic cancer (1) bladder and lower urinary tract cancer (2) stomach cancer (11) oesophageal cancer (1)	exposed/expected: 15/7.6 (p<0.05) heavy exposed/expected: 7/3.6 (ns) SMR: 1.29 (ns) SMR: 1.29 (ns) SMR: 0.8 (ns) SMR: 1.67 (ns) SMR: 0.59 (ns)	Decoufle 1978 [29]
automotive workers (n=11838, followed up until 1980)	worked at least 1 month in building B	death from: liver-biliary tract cancer testicular cancers lung cancer hodgkin's disease stomach cancer asthma; emphysema	SMR (heavy exposed): 1.68 (1.02-2.59) 2.57 (1.11-5.06) 1.22 (1.05-1.40) 2.14 (1.17-3.60) 1.08 (0.76-1.50) 2.09 (1.10-3.39) 1.47 (1.11-1.19)	Kazerouni *et al.* 2000[70](update from decoufle, 1976;1978) (smoking not taken into account, more specific information on presence of contaminants and additives needed)
workers in a packing department in Sweden employed between 1954-1957 (n=98, 78 women, 20 men) (followed up to 1973)	(exposed to anti-rust oil, acid refined)	cancer (total)	observed/expected: women: 12/3.9 (p<0.005) men: 0	Jarvholm/ Lavenius 1981 (cited in IARC 1984[61])
workers in a metalworking plant in Sweden (n=792, 22 lost to follow-up)	(exposed to oil mist for ≥5 y)	death from: cancer (total) scrotal cancer stomach cancer cancer of the digestive tract	observed/expected: 43/52.9 turners: 4/0 grinders: 7/3.7 (ns) 16/11.2	Jarvholm *et al.* 1981[69]

turning department workers employed at bearing-ring manufacturing plant in Sweden (follow-up 1960-1980) (682 white men)	employed any time between 1960-1980	squamous cell cancer of the skin (5)	SIR: 16.6 (p<0.001)	Jarvhorm *et al.* 1985 (cited in NIOSH 1998[86])
grinding and turning department workers employed at a bearing-ring manufacturing plant in Sweden (792 white men)	exposed ≥5 y and employed at any time between 1950-1966	scrotal cancer (7) bladder cancer (7) stomach cancer (9) oesophageal cancer (2)	too few to make reliable risk estimate SIR: 1.04 (0.4-2.2) SIR: 1.11 (0.5-2.1) SIR: 1.25 (0.2-4.5)	Jarvholm/ Lavenium 1987[68]
workers in 3 car manufacturing plants (in the manufacturing of steering gears) (26,726 white and 6488 black men)	employed ≥3 y between 1939-1984 (MWF)	cancer: leukaemia: plant I (65) larynx: plant II (15) lung: plant II (213) pancreas: plant I (21) (black male only) liver: plant III (9)	SMR: 1.57 (1.21-2.00) 1.85 (1.03-3.05) 1.16 (1.01-1.32) 1.70 (1.05-2.61) 2.77 (1.26-5.25)	Eisen *et al.* 1992[38] plant I, predominantly straight, soluble oil; plant II, straight, soluble, synthetic oil; plant III, straight oil.
workers in 2 car manufacturing plants (in the production of axles, gears and transmissions) (17,743 white, 5641 black men)	employed >3 y before 1985 (MWF) straight oil soluble oil synthetic oil straight oil soluble oil synthetic oil straight oil soluble oil synthetic oil straight oil soluble oil synthetic oil	cancer: larynx: white (23) black (1) white (30) black (6) white (8) rectum: white (37) black (1) white (51) black (3) white (9) pancreas: white (34) black (8) white (61) black (19) white (19) stomach: white (49) black (9) white (99) black (17) white (21)	SMR: 1.98 (1.26-2.98) 0.5 (0.01-2.78) 1.41 (0.95-2.01) 1.46 (0.53-3.19) 1.57 (0.68-3.09) 1.47 (1.04-2.03) 0.45 (0.01-2.53) 1.09 (0.81-1.43) 0.68 (0.14-1.99) 0.92 (0.42-1.74) 0.8 (0.55-1.11) 1.40 (0.60-2.77) 0.77 (0.59-1.00) 1.62 (0.98-2.54) 1.03 (0.62-1.61) 1.12 (0.83-1.48) 1.05 (0.48-1.99) 1.19 (0.97-1.45) 1.01 (0.59-1.62) 1.28 (0.79-1.96)	Tolbert *et al.* 1992[123]

		oesophagus:		
	straight oil	white (22)	1.18 (0.74-1.79)	
		black (5)	0.76 (0.24-1.77)	
	soluble oil	white (35)	1.03 (0.72-1.43)	
		black (10)	0.72 (0.34-1.32)	
	synthetic oil	white (8)	0.99 (0.43-1.94)	
		leukaemia:		
	straight oil	white (38)	1.25 (0.88-1.71)	
		black (2)	0.77 (0.09-2.78)	
	soluble oil	white (75)	1.33 (1.05-1.67)	
		black (4)	0.74 (0.20-1.90)	
	synthetic oil	white (16)	1.22 (0.70-1.98)	
Hourly workers at Michigan car manufacturing plants (15,069 white, 3796 black men, 3134 men of unknown race)	employed for a minimum of 3 y before January 1, 1985 and alive on January 1, 1994; followed from 1985 through 2004	cancer, 20-y lag:	hazard ratio	Friesen *et al.* 2009[43]
		bladder:		
	straight oil	>0->0.15 mg/m³•y	1.40 (0.82-2.38)	
		0.15-<0.52 mg/m³•y	1.22 (0.71-2,09)	
		0.52-<1.86 mg/m³•yr	1.13 (0.67-1.90)	
		1.86-<8.98 mg/m³•y	1.51 (0.88-2.61)	
		≥8.98 mg/m³•y	2.07 (1.19-3.62)	
	soluble oil	>0-1.04 mg/m³•y	1.20 (0.69-2.08)	
		1.04-<2.84 mg/m³•y	1.08 (0.61-1.89)	
		2.84-<6.69 mg/m³•y	0.90 (0.52-1.57)	
		6.69-<17.1 mg/m³•y	0.89 (0.50-1.60)	
		≥17.1 mg/m³•y	1.02 (0.56-1.88)	
	synthetic oil	>0-<0.07 mg/m³•y	1.14 (0.56-2.31)	
		0.07-<0.19 mg/m³•y	1.08 (0.52-2.23)	
		0.19-<0.45 mg/m³•y	1.18 (0.57-2.42)	
		0.45-<2.08 mg/m³•y	0.61 (0.29-1.26)	
		≥2.08 mg/m³•y	0.78 (0.38-1.61)	
		lung:		
	straight	>0-<0.18 mg/m³•y	0.82 (0.59-1.13)	
		0.18-<0.49 mg/m³•y	0.95 (0.69-1.30)	
		0.49-<1.34 mg/m³•y	0.80 (0.58-1.11)	
		1.34-<5.15 mg/m³•y	0.86 (0.62-1.20)	
		≤5.15 mg/m³•y	0.88 (0.64-1.21)	
	soluble oil	>0-<1.34 mg/m³•y	0.94 (0.69-1.27)	
		1.34-<4.00 mg/m³•y	0.80 (0.59-1.09)	
		4.00-<9.13 mg/m³•y	0.76 (0.55-1.04)	
		9.13-<20.0 mg/m³•y	0.91 (0.66-1.26)	
		≥20.0 mg/m³•y	1.08 (0.76-1.51)	
	synthetic oil	>0-<0.11 mg/m³•y	0.90 (0.59-1.36)	
		0.11-<0.38 mg/m³•y	0.95 (0.63-1.43)	
		0.38-<0.88 mg/m³•y	1.11 (0.73-1.70)	
		0.88-<2.27 mg/m³•y	1.08 (0.72-1.63)	
		≥2.27 mg/m³•y	0.89 (0.58-1.36)	

hourly workers at Ohio engine manufacturing plants (5331 white, 1180 black men)	employed any time between 1973-1986, also retired and alive as of 1970, no minimum employment	cancer: pancreas white (8) black: (7) stomach white (15) black (2)	SMR: 0.91 (0.39-1.79) 3.03 (1.21-6.24) 2.54 (1.42-4.20) 0.85 (0.1-3.06)	Rotimi *et al.* 1993 (cited in Calvert 1998[16])
white workers at a metalworking facility in Iowa (59% held factory jobs) (n=3630)	hired between 1950-1967 and employed ≥6 months	cancer: pancreas: total work force (11) factory workers (5) stomach: total work force (5) factory workers (2)	SMR: 2.0 (0.9-3.8) 3.6 (1.2-8.3) 1.4 (0.4-3.2) 2.3 (0.3-8.1)	Acquavella *et al.* 1993 (cited in NIOSH 1998[86])
Proportionate mortality studies				
pattern and model makers	wood shop metal shop both wood shop metal shop both	colon cancer (30) (13) (43) brain cancer (7) (5) (12)	PMR: 163 (p<0.01) 183 167 (p<0.002) 175 294 211 (p<0.03)	Robinson *et al.* 1980[96]
union workers at an engine plant (machine and assembly in New York who died between 1970-1980 (follow up 1970-1980)	employed ≥10 y employed >20 y employed ≥10 y employed >20 y employed ≥10 y employed >20 y employed ≥10 y employed >20 y employed ≥10 y employed >20 y	cancer: skin (1) larynx (3) rectum (4) rectum (4) pancreas (11) pancreas (7) bladder (7) bladder (4) stomach (4) stomach (3) oesophagus 3 oesophagus 2	PMR: 0.60 (ns) 1.81 (ns) 1.38 (ns) 2.76 (p<0.05) 1.89 (p<0.05) 2.32 (p<0.05) 2.28 (p<0.05) 2.76 (ns) 0.91 (ns) 1.37 (ns) 1.16 (ns) 1.43 (ns)	Vena *et al.* 1985 (cited in NIOSH 1998[86]) (before 1950 soluble and insoluble MWF used, increased use of synthetic MWF in the mid-1950s)
workers at a diesel engine and construction equipment manufacturer in Illinois (461 eligible deaths among union workers)	employed >10 y, died between 1970-1982	cancer: larynx (2) rectum (2) pancreas white (5) black (5) bladder (2) stomach (6) oesophagus 2	PMR: 1.76 (ns) 0.80 (ns) 1.19 (ns) 3.57 (p<0.05) 0.78 (ns) 1.85 (ns) 1.01 (ns)	Mallin *et al.* 1986 (cited in NIOSH 1998[86])

hourly workers at a ball bearing manufacturing plant in Connecticut (616 white men)	died between 1970-1982 and employed ≥10 y	cancer: skin (4) rectum (11) pancreas (8) bladder (1) stomach (11) oesophagus 6	PMR: 1.88 (0.51-4.80) 3.07 (1.54-5.50) 1.09 (0.55-2.18) 0.24 (0.01-1.31) 1.99 (1.12-3.54) 1.85 (0.68-4.02)	Park *et al.* 1988 (cited in NIOSH 1998[86])
union workers at a ball bearing manufacturing plant in Connecticut (1532 white men)	died between 1950-1982 and employed ≥5 y employed in grinding >10y employed in machining >10y employed in grinding >10 y	cancer: skin (4) rectum (14) pancreas white (24) (9) (5) bladder (14) stomach white (35) (13) oesophagus (13)	 PMR: 0.92 (0.25-2.34) PMR: 1.36 (0.81-2.29) PMR: 1.43 (0.96-2.12) MOR: 3.10 (p=0.05) MOR: 3.71 (p=0.05) PMR: 1.26 (0.75-2.13) PMR: 1.97 (1.43-2.72) PMR: 3.39 PMR: 1.83 (1.07-3.12)	Silverstein *et al.* 1988[106]
workers employed at Detroit area engine plants (1170 white, 613 black men)	employed ≥2 y, active any time between 1966-1987 and died between 1970-1990 plant 1 plant 2 plant 1 plant 2 machining with straight MWF plant 1 plant 2 grinding with straight MWF machining or heat treat employment plant 1 plant 2 cam-/crankshaft depertment (plant 1)	cancer: larynx: white (1) white (4) pancreas: white (10) white (11) (4) bladder: white (6) white (5) (7) (4) stomach: white (8) white (8) (3)	 PMR: 0.69 (0.02-3.83) PMR:1.67 (0.46-4.28) PMR:1.82 (0.87-3.34) PMR:1.23 (0.62-2.21) MOR: 3.61 (1.04-12.6) PMR:2.16 (0.79-4.70) PMR:1.13 (0.37-2.64) MOR: 2.99 (1.15-7.77) MOR: 2.86 (1.14-7.18) PMR: 2.09 (0.90-4.11) PMR: 1.30 (0.56-2.57) MOR: 5.13 (1.56-16.9)	Park/Mirer 1996 (cited in NIOSH 1998[86])

population based studies

scrotal cancer (case-control study)				
cases: man diagnosed in the state between 1935-1973 identified from the connecticut tumour registry (n=45, including 34 deceased and 11 alive) controls: males selected from death registers in Connecticut matched for age at death, year of death, number of jobs (3 for each case) and non-matched males dying in Connecticut at age 35 y and over during 1935-1975 (n=460) and living males selected from the files of the state department of motor vehicles and matched for age, year of birth, number of jobs, town of residence (3 for each case)	workers ever employed as toolmaker, setter, set-up man, hardener, polisher, machinist, or machine operator	squamous cell carcinoma	matched analysis: OR (excluding machinists and machine operator): 4.9 (1.8-15.9, p=0.002) OR (all jobs): 10.5 (4.0-36.9, p<0.001) unmatched analysis: OR (native born): 9.5 OR (foreign born): 7.2	Roush *et al.* 1982 (cited in IARC 1984[61]; NIOSH 1998[86])
laryngeal cancer (case-control studies)				
cases: deceased workers who worked between 1917 and 1981 at 3 car manufacturing plants in the state of Michigan (n=38) and deaths selected from cancer case registries in the city of Detroit and the state of Michigan (death certificates) (n=78) controls: workers at 3 car manufacturing plants in the state of Michigan (USA) (5 to each case)	475 full-shift personal air samples and 394 company exposure measurements collected between 1958-1987 cumulative exposure ≥0.5 (95% CI, 1.01-3.62) mg/m^3•y with a 10 y lag in length of exposure (corresponding to an annual average of 0.025 mg/m^3)	larynx cancer (28)	adjusted OR: 1.91 OR: 2.23 (1.25-3.98) (NIOSH)	Eisen *et al.* 1994[37] (some evidence of confounding by sulphur)
Connecticut	ever worked as machinist ever worked as metal grinder	larynx cancer (22) larynx cancer (17)	2.5 (1.2-5.2) 2.10 (1.0-4.7)	Zagraniski *et al.* 1986 (cited in NIOSH 1998[86])
Texas	ever worked as machinist	larynx cancer (5)	0.53 (0.18-1.58)	Brown *et al.* 1988 (cited in NIOSH 1998[86])

France	ever worked in metalworking as mechanic for at least 15 y	larynx cancer (7)	1.8 (ns)	Haguenoer *et al.* 1990 (cited in NIOSH 1998[86])
hospital based Germany (100 cases and 100 controls)	ever exposed to mineral oil, self-reported	larynx cancer	OR: 2.2 (0.9-5.3)	Ahrens *et al.* 1991 (cited in NIOSH 1998[86])
Washington State	ever employed as grinding, abrading, or buffing operator	larynx cancer	1.8 (0.5-6.2)	Wortley *et al.* 1992 (cited in NIOSH 1998[86])
China	usual occupation of blacksmith, machine-tool operator, electrician or other related worker	larynx cancer (12)	1.2 (0.5-3.1)	Zheng *et al.* 1992 (cited in NIOSH 1998[86])
Connecticut	high machining fluid exposure versus oral cancer controls	larynx cancer (81)	1.48 (1.01-2.16)	Russi *et al.* 1997 (cited in NIOSH 1998[86])
Michigan, USA	UAW/GM cohort: nested case-cohort design in sub-cohort of 3093 males	cancer incidence: larynx (78) stomach (77) oesophagus (37 squamous cell carcinoma, 36 adeno-carcinoma)	1.07 (1.01-1.12) association only for larynx cancer and cumulative straight MWF exposure	Zeka *et al.* (2004)[135] (no associations of other cancers with other MWF)
hepatobiliary cancer (case-control studies)				
Michigan, USA	UAW/GM cohort: nested case-cohort design controls=569	liver cancer (39) biliary tract cancer (24)	no associations with any MWF; 6.2 (1.6-24) for >1 mg/m^3•y of straight MWF exposure occurring >20 y prior to risk date	Bardin *et al.* (2005)[8] (no associations with soluble and synthetic MWF)
Rectal cancer (case-control studies)				
Sweden	ever exposed to cutting oils	rectal cancer (25)	2.1 (1.1-4.0)	Gerhardsson de Verdier *et al.* 1992 (cited in NIOSH 1998[86])
Montreal	ever exposed to cutting oils	rectal cancer (13)	0.7 (90%CI: 0.4-1.0)	Siemiatycki *et al.* 1987 (cited in NIOSH 1998[86])
Michigan, USA	UAW/GM cohort: nested case-cohort	rectal cancer mortality (90) controls=1707	2.7 (1.4-5.3) at >10 mg/m^3•y cumulative straight MWF exposure; no association with soluble and synthetic MWF exposures	Malloy *et al.* (2007)[80] (results indicate latency period of at least 15 years)

pancreatic cancer (population-based study; case-control studies)				
Los Angeles	machinists, white men	pancreatic cancer incidence (21)	1.30	Mack/Paganini 1981 (cited in NIOSH 1998[86])
Michigan, USA	UAW/GM cohort: case-control (n=97; controls=1825)	pancreatic cancer (97)	synthetic: 2.8 (1.1-6.9) at >1.4 mg/m^3•y; grinding synthetic: 3.0 (1.2-7.5) at >1.4 mg/m^3•y	Bardin *et al.* 1997[7] (no associations with straight and soluble MWF)
oesophageal cancer (case-control studies)				
Michigan, USA	UAW/GM cohort: nested case-control (n=53; controls=971)	oesophageal cancer (53)	3.8 (1.0-14) for ever grinding/synthetic; 9.3 (2.1-42) for 12 y of grinding with soluble MWF; 4.1 (1.1-15) for any cumulative exposure to synthetic MWF; 3.1 (0.9-10) for 15 mg/m^3•y grinding/ soluble MWF exposure	Sullivan *et al.* (1998)[116] (no associations with machining operations nor with straight MWF exposures)
breast cancer (case-control)				
Michigan, USA	UAW/GM cohort: nested case-control among female automobile workers	breast cancer (99) controls (626)	no association with straight, synthetic fluids; in last decade before diagnosis: OR: 1.18 (1.02-1.35) for soluble MWF	Thompson *et al.* (2005)[121]
bladder and lower urinary tract cancer (case-control studies)				
United States	machinists	bladder cancer	observed/expected: 4/1 (RR: 4.0)	Dunham *et al.* 1968 (cited in Vineis 1983[128]) (not controlled for smoking)
England	machinists (exposed for ≥20 y)	bladder cancer (13 cases)	observed/expected: 13/4 (RR: 4.8)	Anthony/ Thomas 1970 (cited in Vineis 1983[128]) (not controlled for smoking)
Canada	machinists (ever worked as metal machinists)	bladder cancer	RR: 2.7 (1.1-7.6)	Howe *et al.* 1980 (cited in Vineis, 1983[128]; IARC 1984[61]) (not controlled for smoking)

Finland	machinists	bladder cancer	observed/expected: 5/1 (RR: 5.0)	Tola *et al.* 1980 (cited in Vineis 1983[128]) (not controlled for smoking)
England	machinists	bladder cancer	RR: 1.5 (1.2-1.8) predominantly turners	Cartwright 1982 (cited in Vineis 1983[128]) (not controlled for smoking)
Italy	turners started work before 1945	bladder cancer	observed/expected: 11/4 (RR: 2.7)	Veneis 1982 (cited in Vineis 1983[128]) (not controlled for smoking)
Germany	metal workers	bladder and lower urinary tract cancer ever worked as turner (18) or as metal worker (43)	 2.25 (1.0-5.6) 0.84 (0.54-1.3)	Claude *et al.* 1988 (cited in NIOSH 1998[86])
Britain	ever had an occupation with potential cutting oil exposure	bladder cancer potential exposure (52) potential high exposure (21)	 1.3 (0.9-1.9) 1.5 (0.8-2.8)	Coggon *et al.* 1984 (cited in NIOSH 1998[86])
Spain	metal workers	bladder cancer ever worked as toolmaker for >6 months (31) or as machinery adjuster, assembler or mechanic for >6 months	0.77 (0.5-1.1)	1.86 (1.2-2.8) Gonzalez *et al.* 1989 (cited in NIOSH 1998[86])
Sweden	toolmakers or machinists in 1960	bladder cancer (322)	1.19 ($p<0.01$)	Malker *et al.* 1987 (cited in NIOSH 1998[86])
Belgium	metal workers	bladder cancer all metal workers (34) turners (8)	 2.45 (1.28-4.69) 2.57 (0.92-7.16)	Schifflers *et al.* 1987 (cited in NIOSH 1998[86])
Montreal	ever exposed to cutting oils	bladder cancer (47)	1.2 (90%CI:1.0-1.6)	Siemiatycki *et al.* 1987 (cited in NIOSH 1998[86])
Detroit		bladder and lower urinary tract cancer all machinists (137) tool and die workers (32)	1.1 (0.8-1.5)	1.5 (0.9-2.7) Silverman *et al.* 1983 (cited in NIOSH 1998[86])
USA	ever worked as: machinist >6 months; drill press operator >6 months	bladder cancer (102) (51)	 1.3 (1.0-1.7) 1.1 (0.6-1.9)	Silverman *et al.* 1989 (cited in NIOSH 1998[86])

Ohio	ever worked as: grinding machine operator machinist	bladder and lower urinary tract cancer (11) (45)	 2.00 (ns) 0.69 (p<0.05)	Steenland 1987 (cited in NIOSH 1998[86])
Italy	ever employed in machine tools >6 months	bladder cancer (16)	1.5 (0.7-3.3)	Vineis/Magnani 1985 (cited in NIOSH 1998[86])
prostate cancer (case-control; case-cohort)				
Michigan, USA	UAW/GM cohort: nested case-control (cases: n=872; controls: n=4375)	prostate cancer (872)	RR: 1.12 (1.04-1.20) per 10 mg/m^3•y for straight MWF exposure 25 y before risk age (linear relation); relation with soluble MWF exposure: non-linear with 25 y of latency	Agalliu *et al.* (2005)[1]; (modest association with prostate cancer risk with latency period of at least 25 y)
The Netherlands	prospective case-cohort from 204 municipal cities	prostate cancer (1386) during 9.3 y of follow-up from 1986 till1996	no association with mineral oil exposure	Boers *et al.* (2005)[12]
Stomach cancer (case control / other studies)				
Connecticut, USA	workers ever exposed to soluble oil	stomach cancer (8)	MOR: 6.2 (p=0.05)	Park *et al.* 1988 (cited in NIOSH, 1998[86]) (nested case-control study)
Montreal, Canada	ever exposed to cutting oils	stomach cancer (24)	1.1 (90% CI: 0.8-1.4)	Siemiatycki *et al.* 1987
Workers employed in a tool and die area of an automotive stamping and assembly plant in Ohio	ever employed as tool and die worker	stomach cancer (2)	MOR: 9.55 (2.3-40)	Park 1994 (cited in NIOSH 1998[86])
Michigan, USA	UAW/GM cohort: nested case-control	stomach cancer mortality (140)	4.4 (1.5-13) for grinding/ synthetic with 1.3 mg/m^3•y in last decade of life; 1.9 (1.0-3.6) in highest category of grinding/soluble exposure	Sullivan *et al.* (2000)[115]
toolmakers and machinists in Sweden		stomach cancer (376)	SIR: 1.11 (ns)	Chow *et al.* 1994 (cited in NIOSH, 1998[86])
metal workers in China	 metal grinders, polishers, tool sharpeners, machine-tool operators toolmakers, metal pattern makers, metal workers	stomach cancer (191) (193)	 SIR: 1.41 (p<0.01) SIR: 1.11 (ns)	Kneller *et al.* 1990 (cited in NIOSH 1998[86])

tool and die workers in Ohio	ever employed as tool and die worker	stomach cancer (2)	MOR: 9.55 (2.3-40)	Park 1994 (cited in NIOSH 1998[86])

Abbreviations: CI, confidence interval; MOR, mortality odds ratio; MWF, metalworking fluids; ns, not statistically significant; OR, odds ratio; PMR, proportionate mortality ratio; RR, relative risk; SIR, standardised incidence ratio; SMR, standardised mortality ratio; UAW/GM, United Autoworkers/General Motors.

Table E-9 Carcinogenicity of mineral oil mists: epidemiological studies on printing pressmen.

study population (number of subjects)	**employment criteria (exposure)**	**observed effects (number with cancer)**	**rate ratio (95%CI or P-value)**	**reference (comments)**
cohort studies				
pressroom workers employed between 1947-1962 in a newspaper plant in New York City, USA (n=460) compared with non-exposed compositors (n=700)	oil-mist concentrations ranged from 5-21 mg/m^3 (MMD about 15 µm, 15% of the droplets considered respirable, carbon black 0.1-0.2 µm)	death from: pulmonary carcinoma, cancer of the nasopharynx or paranasal sinuses	Exposed: 3 out of 2797 person-years (crude rate: 1.07 per 1000) non-exposed: 6 out of 5127 person-years (crude rate: 1.17 per 1000) no deaths	Goldstein *et al*. 1970.[46] (no data on: age distribution, degree of completeness of death ascertainment, or classification methods of causes of deaths)
pressroom workers employed between 1958-1969 in a newspaper plant in New York City, USA (n=778) compared with non-exposed compositors (n=1207)	oil-mist concentrations ranged from 5-21 mg/m^3 (MMD about 15 µm, 15% of the droplets considered respirable, carbon black 0.1-0.2 µm)	death from cancers of several sites	no mortality pattern was discernible	Pasternack/Ehrlich 1972[91] (updated and expanded from Goldstein *et al.*, 1970) (small numbers of deaths; follow-up may be to short)
newspaper pressmen, members of the Los Angeles Pressmen's Union for at least 1 y between 1949-1965 (n=1361), followed up to 1979 (91%)		deaths from: kidney cancer leukaemia lung cancer stomach cancer buccal cavity and pharynx cancer colon-rectum cancer	observed/expected: 5/1.6 (p<0.05) 7/2.8 (p<0.05) 22/14.8 (ns) 3/4.3 (ns) 2/2.2 8/8.9	Paganini-Hill *et al.* 1980 (cited in ACGIH, 2010[4]; IARC, 1984[61]) (no mention of nasal cancer made in the report, no presentation of results relating to duration of employment

Proportionate mortality studies			
newspaper workers in London and Manchester, UK, employed between 1952-1966 (3465)	death from: lung cancer	observed/expected: manual printing trade workers: 365/273 ($p<0.01$) (30% excess in London and 40% in Manchester) machine room men in Manchester: 38/18.7 (RR=2.0) ($p<0.01$) in London: 71/57.3 (RR: 1.2) non-manual workers: no significant differences observed	Moss *et al.* 1972 and Moss, 1973 (cited in IARC 1984[61]) (The study included all manual workers in the newspaper printing industry and did not specifically mention printing pressmen)
newspaper printing workers in London who died during 1954-1970	deaths from: all malignancies lung cancer stomach cancer	observed/expected: 195/163.5 ($p<0.02$) 93/70 ($p<0.01$) 29/20.5 ($p<0.10$)	Greenberg 1972 (cited in IARC 1984[61]) (this study addressed partly the same newspaper worker population as Moss *et al.*, 1972, not controlled for smoking)
white male members of a labour union representing printing pressmen in the USA (n=2604)	deaths from: cancer of the buccal cavity and pharynx lung cancer stomach cancer rectal cancern nasal cancer	observed/expected: 9/3.8 ($p<0.05$); confined to men aged 20-54:7/0.7 ($p<0.01$) 41/36.4 (ns) 11/7.1 (ns) 7/4.5 (ns) 2/0.2 (ns)	Lloyd *et al.* 1977 (cited in ACGIH 2010[4]; IARC 1984[61])
male former US government printing Office employees in Washington DC, died between 1948-1977 from cancer	deaths from: leukaemia colon cancer	printing pressmen: 79% increase in relative frequency based on 4 deaths (ns) 58 % increase in the frequency based on 10 deaths (ns)	Greene *et al.* 1979 (cited in ACGIH 2010[4]; IARC 1984[61]) (ascertainment of cancer deaths incomplete, no characterization of the extent to exposure to oil mists)

cross-sectional study				
cases: deaths among white males in Los Angeles County, aged 20-64 y during period 1968-1970 (n=2161) and incident cases from Los Angeles county cancer surveillance program during 1972-1973) (n=1777)		lung cancer pressmen: 10 deaths and 10 incident cases printing, newspaper workers: 30 deaths and 16 incident cases	SMR: 276 (p<0.01) SMR: 98	Menck and Henderson 1976 (cited in IARC 1984[61]) (it is possible that men included in the pressmen category could have worked in setting other than newspaper pressrooms)
cases: newspaper pressroom workers (n=215) Controls: compositors (n=32)	organic solvents (primarily naphtha's) and glycol ethers	leukocyturia albuminuria solvent-related dermatitis	dose-related increased 16% versus 0% High prevalence	Hashimoto *et al.* 1991[53]
case-control study				
cases from the Roswell Park Memorial Institute, USA	jobs entailing exposure to mineral oils or cutting oils	buccal cavity and pharynx cancer	print workers Age-adjusted RR: 2.58 (p=0.04) Smoking-adjusted RR: 2.33 (p=0.04)	Decoufle *et al.* 1977 (cited in IARC 1984[61]) and (the category print workers was not specified)

Abbreviations: MMD, mass media diameter; ns, not statistically significant; RR, relative risk; SMR, standardised mortality ratio.

Table E-10 Carcinogenicity of mineral oil mists: epidemiological studies on jute workers.

study population (number of subjects)	**employment criteria (exposure)**	**observed effects (number with cancer)**	**rate ratio (95%CI or P-value)**	**reference (comments)**
field survey of 3023 workers in seven jute establishments in Dundee, Scotland		pre-malignant skin changes (keratosis) (219)	all jute workers: 7.2% Spinners: 15.9%	Kinnear *et al.* 1955 (cited in ACGIH 2010[4]; IARC 1984[61])

Table E-11 Carcinogenicity of mineral oil mists: epidemiological studies on other workers.

study population (number of subjects)	employment criteria (exposure)	observed effects (number with cancer)	rate ratio (95%CI or P-value)	reference (comments)
pressmen in a wax manufacturing department of an oil refinery in the USA from 1937-1956		all cancers (19) scrotum cancer (11)	rate for men aged 45-64: 806/100,000 in contrast to a rate of 0.15/100,000 for US white males of the same age group	Hendricks *et al.* 1959 (cited in ACGIH 2010[4]; IARC 1984[61])
oil refinery workers (n=1595, Italian)	employed between 1949-1982	death from:	expected deaths	Bertazzi *et al.* 1989[11]
	moving department workers	all cancer (22) lung cancer (11)	11.7 3.6
	production workers	leukaemia (2)	0.61
	maintenance workers	kidney cancer (2)	0.18
cable manufacturing (n=529, Norwegian)	employed for at least one d between 1920 and 1979 >1 y in oil exposed work	deaths from: ischaemic heart disease (26)	observed/expected: 26/16.1	Ronnebert *et al.* 1988[97]
		lung cancer (10)	observed/expected: 10/3.9
optical manufacturing industry		death from: total cancers		Wang *et al.* 1983[130]
		lens workers	observed/expected: 70/48
		gastrointestinal cancers	sMOR:
	medium	lens workers	2.2
	long-term		2.5
	long-term	metal frame workers colorectal cancers	2.9
	medium	lens workers	3.2
	long-term long-term		2.6
		metal frame workers	3.4

Abbreviations: sMOR, standardised mortality odds ratio.

Table E-12 Genotoxicity and mutagenicity.

test system	test substance	results	remarks	reference
In vitro				
S. typhimurium strain TA98 TA100	urine of 17 exposed occupationally to mineral oils & iron oxide particles; Urine of 16 men exposed to mineral oils	+ with aroclor-induced rat-liver metabolic system and glucuronidase	the IARC working group noted the lack of suitable controls	Laires *et al.* 1982 (cited in IARC 1984[61])
chromosome aberration test	blood lymphocytes of pressed glass makers operating an automatic line of press-and-blow machines (mineral oil aerosol levels < 0.5 mg/m^3)	frequency of aberrant cells (%AB.C.) and the value of breaks per cell (B/C) ratio increased statistically significantly compared to controls; higher rate of dicentrics, reciprocal translocations, and cells with pulverisation	findings suggest that these workers might experience increased risk of genetic injury due to exposure to mineral oil	Sram *et al.* 1985[112]

Annex **F**

Animal data

Table F-1 Absorption, distribution, excretion and metabolism.

animal species	doses	test substance	duration	results	reference
inhalation	*(mg/m³)*				
mouse (13 albino)	4,500 4,330 average MMD 2.5 µm	liquid petrolatum SAE no 10	2 h	80% of the oil droplets in the lung had diameter <2.5 µm. Phagocytosis of the oil completed after 48 h	Shoshkes *et al.* 1950[105]
mouse rat rabbit	63	diesel-engine lubricating oil: S.G.F. no 1		oil found in alveolar macrophages in the mediastinal lymph nodes, lymphatic channels of lungs and pleura	Lushbaugh *et al.* 1950[78] (cited in IARC 1984[61])
oral					
rabbit rat guinea-pig	large amounts	liquid petrolatum		small quantities deposited in mesenteric lymph nodes, in several cases in the intestinal mucosa, liver, spleen	Stryker 1941 (cited in IARC 1984[61])

rat (Sprague-Dawley, Holtzman)	0.66 mL/kg bw	tritiated mineral oil (US Pharmacopeia grade liquid petrolatum)		5 h after administration: 1.5% of the dose absorbed unchanged; 1.5% found in the carcasses as non-mineral oil substances; liver, fat, kidney, brain, spleen contained mineral oil; 2 d after administration: 0.3% remained in the animals	Ebert *et al.* 1966 (cited in IARC 1984[61])
intravenous					
rabbit		paraffinic oil	intravenous injection	taken up by liver, bone marrow, lung, endothelial cells of spleen; liver granulomas observed	Gonet *et al.* 1960, Buhrer/Widgren, 1963 (cited in IARC 1984[61])
subcutaneous and intramuscular					
rat (albino, female) squirrel (female) monkey (female)	0.1 mL 0.3 mL	mineral-oil adjuvant emulsions formulated with white oil and spiked with [^{14}C]-*n*-hexadecane.	subcutaneous injection intramuscular injection	recovery 1 w after administration: <2% of the radioactivity in expired CO_2, < 0.01% of the radioactivity in urine, faeces, 85-99% remained at the site of injection; recovery 10 m after administration: 25-30% remained at the site of intramuscular injection	Bollinger 1970 (cited in IARC 1984[61])
intraperitoneal					
rat (Sprague-Dawley, Holtzman)		tritiated mineral oil (US Pharmacopeia grade liquid petrolatum)		8 d after administration: 11% of the dose excreted in faeces	Ebert *et al.* 1966 (cited in IARC 1984[61])

Table F-2 Irritation and sensitization studies.

animal species	doses	test substance	duration	results	reference
rabbit guinea-pig	?	paraffinic base stock (13.1-194 mm^2/sec at 37.8 C) naphthenic base stock (15.7-432 mm^2/sec at 37.8 C)		no eye irritation no dermal sensitization	Beck *et al.* 1982 (cited in IARC 1984[61])
?	?	paraffinic distillate: unrefined, API 84-01 solvent dewaxed, light API 78-9 solvent dewaxed heavy API 78-10, 79-3, 79-4, 79-5	?	 moderate skin irritation; slight eye irritation; no skin sensitization slight skin irritation; no eye irritation, skin sensitisation no skin, eye irritation; no skin sensitization	API 1986c, 1982c-f (cited in CONCAWE 1997[20])
?	?	naphthenic distillate: solvent refined, light API 78-5 solvent refined, heavy API 79-1 hydrotreated, light API 83-12 hydrotreated, heavy API 83-15	?	 slight skin irritation no eye irritation, skin sensitization skin irritation; slight eye irritation; no skin sensitization slight skin, eye irritation; no skin sensitization	API 1982a,g, 1986, 1987 (cited in CONCAWE 1997[20])
?	?	white mineral oil	?	slight skin irritation	Hoekstra/Phillips 1963 (cited in CONCAWE 1997[20])
?	?	White mineral oil: Paraffin oil	?	no eye irritation	Carpenter/Smyth 1946 (cited in CONCAWE 1997[20])
guinea pig	10 100	medicinal grade mineral oil light lubricating oil naphthenic medicinal oil		no irritation after simultaneous exposure with 1 or 10 ppm SO_2 irritation after simultaneous exposure with 50 ppm SO_2	Costa/Amdur 1979[21]

Table F-3 Acute toxicity studies.

animal species	doses	test substance	duration	results	reference
inhalation	mg/m^3				
mouse (albino male)	200	white mineral oil motor oil (SAE 10 and 20)	4 h	mild inflammatory reaction (0-144 h after exposure); maximal macrophage reaction at 96 h	Wagner *et al.* 1961 (cited in ACGIH 2010[4]; WHO 1982[133])
mouse	20-2,000	10 aerosolized machining fluids: synthetic, semi-synthetic, soluble fluids straight fluids	3 h	sensory and pulmonary irritation RD_{50}: 100-1000 mg/m^3 RD_{50}: 100,000 mg/m^3	Schaper/Detwiler 1991[100]
rat	 1 1 10 10	machining fluid used unused used (equivalent to 0.8 µg/m^3 endotoxin) unused (no measurement of endotoxin)	3 d 2 h/d	 increase in the amount of stored intraepithelial mucosubstances (Vs) in nasal septum and intrapulmonary airways and in total cells and neutrophils in lavage fluid increase in Vs in nasal septum	Gordon/Harkema 1995[48]
guinea pig (Hartley) (n=5)	5 50	machining fluid soluble machining unused clean dirty semi-synthetic unused clean dirty	3 h	pulmonary effects	Gordon/Galdanes 1999[47]
mice Swiss webster males	0.17-55	machining fluid G (MFG)	3.75 h	sensory irritation of the upper airways, airflow limitation along the conduction airways, pulmonary irritation at the alveolar level.	Boylstein *et al.* 1996[13]
guinea-pig	10, 40, and >200	medicinal-grade mineral oil laboratory-grade paraffin oil light lubricating oil S-75 multigrade motor oil (SAE10 W-30)	1 h	at 10 and 40 mg/m^3: no alteration in respiratory function at >200 mg/m^3: reduced lung compliance (only after exposure to light lubricating oil)	Costa/Amdur 1979[22]

rat (5 Wistar males)	0.2 mL	mineral oil multigrade motor oil multigrade motor oil (SAE 10W-20W-30)	?	no mortality after 24 h; mortality in one of the 5 animals given SAE motor oil no severe acute pulmonary oedema or haemorrhage characteristic of kerosene and of similar low-viscosity hydrocarbon mixtures	Gerarde 1963 (cited in IARC 1984[61])
?	?	paraffinic distillates: solvent-extracted, dewaxed solvent-extracted, dewaxed solvent-hydrotreated solvent-dewaxed, light	?	 LC_{50} >4 mg/L LC_{50} >4 mg/L LC_{50} >4 mg/L	Whitman *et al*. 1989 (cited in CONCAWE 1997[20])
?	?	naphthenic distillate, hydrotreated, light (API 83-12)	?	LC_{50}: 2.18 mg/L	API 1987 (cited in CONCAWE 1997[20])
dermal					
rabbit	?	paraffinic base stock (13.1-194 mm^2/sec at 37.8 C) Naphthenic base stock (15.7-432 mm^2/sec at 37.8 C)	?	no dermal toxicity	Beck *et al*. 1982 (cited in IARC 1984[61])
?	?	paraffinic distillate: unrefined, API 84-01 solvent dewaxed, light API 78-9 solvent dewaxed, heavy API 78-10, 79-3, 79-4, 79-5	?	 LD_{50} >2 g/kg LD_{50} >5 g/kg LD_{50} >5 g/kg	API 1986c, 1982c-f (cited in CONCAWE 1997[20])
?	?	naphthenic distillate: solvent refined, light API 78-5 solvent refined, heavy API 79-1 hydrotreated, light API 83-12 hydrotreated, heavy API 83-15	?	 LD_{50} >5 g/kg LD_{50} >5 g/kg LD_{50} >2 g/kg LD_{50} >2 g/kg	API 1982a,g, 1986, 1987 (cited in CONCAWE 1997[20])
oral					
?	?	paraffinic distillate: unrefined, API 84-01 solvent dewaxed, light API 78-9 solvent dewaxed heavy API 78-10, 79-3, 79-4, 79-5	?	 LD_{50} >5 g/kg LD_{50} >5 g/kg LD_{50} >5 g/kg	API 1986c, 1982c-f (cited in CONCAWE 1997[20])

?	?	naphthenic distillate: solvent refined, light API 78-5 solvent refined, heavy API 79-1 hydrotreated, light API 83-12 hydrotreated, heavy API 83-15	?	 LD_{50} >5 g/kg LD_{50} >5 g/kg LD_{50} >5 g/kg LD_{50} >5 g/kg	API 1982a,g, 1986, 1987 (cited in CONCAWE 1997[20])
?	?	white mineral oil: Tufflo 6056	?	LD_{50} >5 g/kg	API 1992 (cited in CONCAWE 1997[20])

Table F-4 Short-term toxicity studies.

animal species	**doses**	**test substance**	**duration**	**results**	**reference**
inhalation	mg/m^3				
mouse (13 albino)	4,500 MMD 2.2 µm 4330 MMD 2.7 µm	liquid petrolatum SAE no 10	14 d 4-8 h/d 5 d/w	localised foreign body reactions of modern severity infrequently occurring patches of lipid pneumonia.	Shoshkes *et al.* 1950[105]
rat (Wistar male)	10,000 mmd 0.3-0.5 µm	mineral oil aerosol	?	classic lipid pneumonia oil granuloma formation	Eckert/Kandt 1975 (cited in ACGIH 2010[4])
rat	13, 30 and 60	aerosols of axle and machine lubricating oils	6 m 5 h/d	reversible effects on immune reactivity, electrocardiograms, respiratory function and arterial pressure	Lutov 1974 (cited in ACGIH 2010[4])
rat (males)	1,500 and 300	low aromatic base Oil (no aerosols)	14 d 12 h/d	damage of kidney tubules no histopathological changes in the lungs	NPD 1987a (cited in Eide 1990[33])
rat (males and females)	850	base oil vapour		nephritic effects were only observed in male rats	NPD 1987b (cited in Eide 1990[33])
rat	500 1,500 MMAD: ca.1 µm	oil fog of lightweight lubricating oil	4 w 3.5 h/d 4 d/w	slight accumulation of macrophages in alveolar lumen, increase in total cells in lavage fluid; accumulation of macrophages within alveolar lumen, increase in protein content and total cell content (due to influx of poly-morphonuclear leukocytes) in lavage fluid, increase in lung weight and end-expiratory volume, and pneumonitis.	Selgrade *et al.* 1987[101]

rat	200 500 1,500 MMAD: ca 1 µm	oil fog of lightweight lubricating oil	13 w 3.5 h/d 4 d/w	diffuse accumulation of macrophages in alveoli in all dose groups (concentration dependent); elevated end expiratory volume in males at 1500 mg/m^3, resolved after 4 w of recovery	Selgrade *et al.* 1990[102]
rat (males)	150	low-aromatic drilling fluid vapour (no aerosols)	13 w 6 h/d 5d/w	no nephritic effects no histopathological changes in the lungs	Statoil 1988b) (cited in Eide 1990[33])
rat (Sprague-Dawley)	0 50 150 400-520	cutting oil, gear oil, commercial engine oil	13 w 6/h/d 5d/w	histopathological changes in lung; increased lung weight; pulmonary hydroxyproline; pulmonary function unaffected.	Dalbey 2001[25]
rat	47 and 673 82-97% of the weight < 4.7 µm	two different mineral oil mists	2 w 7 h/d 5 d/w	increased alveolar macrophage vacuolization (one oil) increase in the number of alveolar macrophages (other oil)	Skyberg *et al.* 1990[109]
mouse (80 CF1) mouse (250 strain A) rat (80 albino rats) rabbits (4) monkeys (6 macaca mulatto) (7)	132 63 63	car lubricating oil (SAE No. 10) Diesel lubricating oil (SGE No.1) car lubricating oil diesel lubricating oil	100 d 30 min/h 24h/d up to 1 y 100 d 100 d	no increased incidence of lipid pneumonia compared to controls 2 deaths 6 deaths infectious pneumonitis, pulmonary lipophages, hyperplastic gastritis (probably due to swallowing of inhaled oil)	Lushbaugh *et al.* 1950[78]
rat	50 500 and 1,500 1,500	aerosol of 2 solvent-extracted paraffinic oils: 8 mm^2/s at 40°C 34 mm^2/s at 40°C	9 d (5 d of exposure, 2 d rest, 4 d of exposure)	no effects observed; alterations in food consumption, body and organ weights, dermal irritation, clinical signs of CNS depression; microscopic evidence of inflammation and irritation in pulmonary tissue	Whitman 1989 (cited in CONCAWE 1997[20])
rat	50 210 1,000	aerosol of: solvent-extracted oil (100 SUS oil) hydrotreated, acid washed white oil severely hydrocracked, hydrotreated oil	4 w 6 h/d 5 d/w	lung weight and dry/wet lung weight ratio increased with concentration; accumulation of foamy alveolar macrophages	Dalbey *et al.* 1991[24](cited in CONCAWE 1997[20])

oral	mg/kg bw				
rat (Sprague-Dawley)	5 (gavage)	paraffinic base stock (13.1-194 mm^2/sec at 37.8°C) naphthenic base stock (15.7-432 mm^2/sec at 37.8°C)	14 d	no mortality	Beck *et al.* 1982 (in IARC 1984[61])
dog (beagle) rat (long evens)	300 ppm 1,500 ppm	highly refined mineral oils (food and medicinal grade)	90 d	no toxic effects	Smith *et al.* 1995 (cited in CONCAWE 1997[20])
rat (Fischer 344)	20 to 20,000 ppm	white oils (different viscosities, crude type and refinery history) (low viscosity oils (13-15 mm^2/s at 40C) produced greatest effects, intermediate viscosity oils (~70 mm^2/s at 40°C) lesser effects, high viscosity oils (~100 mm^2/s at 40°C) no effects	subchronic	increased organ weight, microscopic inflammatory changes in liver, mesenteric lymph node; accumulation of saturated mineral hydrocarbons in tissues	Baldwin *et al.* 1992; Smith *et al.* 1995 (cited in CONCAWE 1997[20])
dermal	mg/kg bw				
rabbit	?	paraffinic base stock (13.1-194 mm^2/sec at 37.8°C) naphthenic base stock (15.7-432 mm^2/sec at 37.8°C)	?	no dermal toxicity	Beck *et al.* 1982 (cited in IARC 1984[61])
guinea-pig (albino male)	?	light mineral oils aliphatic hydrocarbons	?	epidermal hypertrophy, hyperplasia, hyperkeratosis, subsequent depilation; skin-damaging effects related to molecular size of the hydrocarbon (C14-19 most active)	Hoekstra/ Phillips 1963 (cited in IARC 1984[61]; WHO 1982[133])
rat (sherman, male)	2	mineral oil	3 m 3 d/w	no toxic effects	Kimbrough *et al.* 1980 (cited in IARC 1984[61])

rabbit (NZW)	2,000 1,000 200	parafinic distillates, unrefined API 84-01	28 d 3 d/w	moderate skin irritation, proliferative changes; marginal body weight decrease slight skin irritation; no systemic effects minimal skin irritation; no systemic effects	API 1986d (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	parafinic distillates, solvent dewaxed, light API 78-9	21 d 4 h/d 3 d/w	skin acanthosis, parakeratosis, chronic dermal inflammation; no systemic effects	API 1982e (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	parafinic distillates, solvent dewaxed, heavy API 78-10	21 d 4 h/d 3 d/w	skin acanthosis, parakeratosis, chronic dermal inflammation; no systemic effects	API 1982f (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	parafinic distillates, solvent dewaxed, heavy API 79-3	21 d 4 h/d 3 d/w	no skin or systemic effects	API 1982c (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	parafinic distillates, solvent dewaxed, heavy API 79-4	21 d 4 h/d 3 d/w	no skin or systemic effects	API 1982b (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	parafinic distillates, solvent dewaxed, heavy API 79-5	21 d 4 h/d 3 d/w	no skin or systemic effects	API 1982d (cited in CONCAWE 1997[20])
rabbit (NZW)	5,000	naphthenic distillates, solvent refined, light API 78-5	21 d 4 h/d 3 d/w	skin: acanthosis, parakeratosis, chronic dermal inflammation; no systemic effects	API 1982g (cited in CONCAWE 1997[20])
rabbit (NZW)	2,000	naphthenic distillates, solvent refined, heavy API 79-1	21 d 4 h/d 3 d/w	no skin or systemic effects	API 1982a (cited in CONCAWE 1997[20])
rabbit (NZW)	2,000 1,000 200	naphthenic distillates, hydrotreated, light API 83-12	28 d 3 d/w	moderate skin irritation; reduced testis weight slight (males) or moderate (females) skin irritation; no systemic effects minimal skin irritation; no systemic effects	API 1986a (cited in CONCAWE 1997[20])

rabbit (NZW)	2,000	naphthenic distillates, hydrotreated, heavy API 83-15	28 d 3 d/w	slight skin irritation, hyperplasia; elevated ALAT, ASAT; decreased body weight, subacute hepatitis, increased relative liver weight in females.	API 1987a (cited in CONCAWE 1997[20])
	1,000			slight skin irritation; elevated ASAT & ALAT.	
	200			minimal skin irritation; no systemic effects.	
rabbit (NZW)	1,000	5 paraffinic base oils	28 d 5 d/w	minor skin irritation; no system effects	Trimmer *et al.* 1989 (cited in CONCAWE 1997[20])
rat	Up to 2,000	several solvent-refined mineral base oils	13 w 5 d/w	no significant skin irritation; no systemic effects	Cox/Cruzan 1986 (cited in CONCAWE 1997[20])

Table F-5 Long-term toxicity and carcinogenicity studies.

animal species	**doses**	**test substance**	**duration**	**results**	**reference**
inhalation	*mg/m³*				
dog (9) rabbit (23) rat (80 males) hamster (106 and 112) mouse (130 CAF_1/JAX)	5 or 100 MMD 1.3 µm	aerosol of light white naphthenic oil	6-26 m	dogs 100 mg/m³: pulmonary alveolar, hilar lymph node oil deposition, lipid granuloma formation after 12 m of exposure. all animals: no significant difference in tumour incidence.	Wagner *et al.* 1964[129]
dog rat mouse gerbil	5 or 100	complex oil mixture with acetone vapour (the base oil was paraffinic white oil)	2 y 6 h/d 5 d/w	oil particles in lung macrophages of all species at both concentrations; oil micro-granulomas in dogs and rats at 100 mg/m³	Stula/Kwon 1978[114]
mouse (132 strain A) rat rabbit monkey	63 or 132	car lubricating oil diesel engine lubricating oil	100-365 d	mice, rats, rabbits unaffected no increased; lung tumour incidence; monkeys: relatively large amounts of oil accumulated in the lungs (cf. mice); no evidence of lipid pneumonia; incidence of infectious pneumonia greatly increased	Lushbaugh *et al.* 1950[78]

dermal

mouse (100) (100)		paraffinic oil used in cotton spinning heavy fraction (distilled between 300-360°C under 12 mm pressure) lighter fraction (240-300°C)	2/w	tumours: 10 benign 11 malignant 1 benign no malignant	Twort/Ing 1928 (cited in IARC 1984[61])
mouse (30 C3H)	50 µL	paraffinic distillate (BaP content <0.1 mg/kg)	2-3/w	4 skin papillomas 2 skin carcinomas	Bingham/ Barkley 1979 (cited in IARC 1984[61])
mice (24) (24) (24) (24)		undiluted jute batching oil (BaP <1 mg/kg) 7,12-dimethylbenz-[a]anthracene PAHs plus mineral oil controls		skin tumours: 6 malignant 2 malignant 11 malignant 0 malignant	Roe *et al.* 1967 (cited in IARC 1984[61])
mouse (100)		heavy distilled fraction (300-360°C, 12 mm pressure) from a praffinic oil extracted with sulphuric acid		no skin tumours	Twort/Ing 1928 (cited in IARC 1984[61])
mouse (100/fraction)		borneo crude oil (viscosity 1351.o mm^2/sec) fraction 1-5 (3.7-34.7 mm^2/sec) faction 6 (62.7 mm^2/sec) fraction 7 (167.8 mm^2/sec) fraction 8 (303.8 mm^2/sec) fractions 9-12 (726.7-4033.0 mm^2/sec) derived by vacuum distillation from Borneo crude oil treated with sulph-uric acid + clay	45 w 5/w	malignant skin tumours: 35 0 23 50 67 lower (not further specified)	Twort/Ing 1939 (cited in IARC 1984[61])

mouse (15 or 30 C3H/HeJ males)	50 mg	undiluted oil (refined by small amount of 93% sulphuric acid and clay) (viscosity 20.5 mm^2/sec at 37.8°C);	2/w	refined paraffinic distillate: 70% skin tumour incidence no tumours	Bingham *et al.* 1966 (cited in IARC 1984[61])
mouse (30 C3H/HeJ males)	50 mg	undiluted paraffinic solvent-refined oil (viscosity 20.5, 41 and 540 mm^2/sec at 37.8°C)	80 w 2/w		
mouse		undiluted naphthenic solvent-refined oil (viscosity 31.9 mm^2/sec at 37.8°C)		no tumours	Bingham *et al.* 1965 (cited in IARC 1984[61])
rabbit (21)	0.5 g	high-boiling portion of a catalytically cracked oil	2 y 3/w	all animals developed papillomas 3 animals developed carcinomas within 4 y	Smith *et al.* 1951 (cited in ACGIH 2010[4]; IARC 1984[61])
rabbit (6 New Zealand white)	0.625 mg 1.875 mg 5.625 mg 0 mg	undiluted high-boiling catalytically cracked oil	2/w 2 x 9 cm^2 on ears and 2 x 9 cm^2 on sides	3 papillomas 0 carcinoma (4.6% tumour-bearing mice) 8 papillomas 9 carcinoma (26.6% tumour-bearing mice) 14 papillomas 29 carcinoma (69.4% tumour-bearing mice) 0 papillomas 1 carcinoma (1.5% tumour bearing mice)	Shubik/ Saffiotti 1955; Saffiotti/ Shubik 1963 (cited in IARC 1984[61])
monkey (rhesus: 3 male and 3 female)		high-boiling fraction of catalytically cracked oil		all developed skin papillomas; 2 developed carcinomas within 4 y	Smith *et al.* 1951 (cited in ACGIH 2010[4]; IARC 1984[61])
oral					
rat (30 BDI, BD111 and W)	136 mL/ animal	2% liquid paraffin	500 d	no significant tumour induction	Schmahl/ Reiter 1953 (cited in ACGIH 2010[4]; IARC 1984[61])

rat (RDRL: 50 male and 50 female)	5% in diet	petrolatum (snow-white US pharmacopeia XVI grade, white US pharmacopeia XVI grade and yellow national formulary XI grade)	2 y	no treatment-related tumour increase	Oser *et al.* 1965 (cited in ACGIH 2010[4]; IARC 1984[61])
rat (F344)	2.5 and 5% w/w in diet	liquid paraffin (viscosity 70 mm^2/sec at 40°C)	2 y	no carcinogenic effects	Takahasi 1996 (cited in CONCAWE 1997[20])
rat (F344)	2.5 and 5% in diet	medium-viscosity liquid paraffin	104 w	granulomatous inflammation in mesenteric lymph nodes in both dose group and sexes; no statistically significantly increase in tumour incidence	Shoda *et al.* 1997[104]
rats (F344), male, female	60; 120; 240; 1,200 mg/kg bw/d adjusted to account for bw changes	paraffinic, viscosity 70 mm^2/sec at 40°C, severely hydrotreated: P70(H); idem P100(H)	24 m	no treatment-related mortality, neoplastic lesions, changes in clinical health, haematology, serum, urine chemistry; higher food consumption in highest dose group with increased bw in the males receiving P100(H); increased mesenteric lymph node weights with increased number of infiltrating histiocytes; increased levels of mineral hydrocarbons in the liver	Trimmer *et al.* (2004)[124]
subcutaneous injection					
mouse (Swiss-Webster, 50male and 50 female)	100 mg	petrolatum (snow-white US Pharmacopeia XVI grade, white US pharmacopeia XVI grade and yellow national formulary XI grade)	single (18 m observation)	no treatment-related tumour increase	Oser *et al.* 1965 (cited in ACGIH 2010[4]; IARC 1984[61])
rat (30 BDI, 30 BDIII and 30 W)	2.5 mL	liquid paraffin	single	no local tumours	Schmahl/ Reiter 1953 (cited in ACGIH 2010[4]; IARC 1984[61])
(26 BDI, 26 BDIII and 26 W)	1 mL	yellow petrolatum	(observation until death)	one osteosarcoma near injection site	

Intraperitoneal

mouse (BALB/c: 40 females 32 females 32 females) (56 BALB/c)	 0.4 mL 0.5 mL 0.5 mL	highly refined mineral oil: technical grade white oil (Bayo F, viscosity 14-18 mm^2/sec at 37.8°C); US pharmacopeia grade (primol D, viscosity 37-71 mm^2/sec, 37.8°C)	 single single ?	5-14 m after injection: 8 2 22 intraperitoneal plasma-cell neoplasms 13 plasma-cell neoplasms	Potter/Boyce 1962 (cited in ACGIH 2010[4]; IARC 1984[61])
mouse (36 DBA/s females) (12 CBA females)	0.5 mL	primal D (high viscosity)	3, at 10, 15, 21 w of age	15 (42%) peritoneal reticulum cell sarcomas leukaemia: 3 plasma-cell 3 myeloid 2 lymphocytic 1 peritoneal reticulum-cell sarcomas 1 lymphocytic leukaemia	Rask-Nielsen/ Ebbesen, 1965 (cited in IARC 1984[61])
mouse (IC and C3H) (BALB/c)		low-viscosity oil (bayol F)	?	oil granulomas, no plasma-cell tumours oil granulomas plasma-cell tumours	Hermann, 1966 (cited IARC 1984[61])
mouse (BALB/c)	0.5 mL of Primol D; 0.1-5 ng and 5 µg endotoxin	high-viscosity oil (primol D) and bacterial endotoxins	3 weekly i.p. injections of endotoxins	increased incidence of plasma-cell tumours by endotoxin in ng doses	Bober *et al.* 1976 (cited in IARC 1984[61])
rat (30 BD I, 30 BDIII, and 30 W of both sexes) (8)	9 mL over 40 weeks	liquid paraffin yellow petrolatum	several injections within 40 w	4 sarcomas in abdominal cavity (2 appeared to be of testicular origin) no tumours	Schmahl/ Reiter 1953 (cited in ACGIH 2010[4]; IARC 1984[61])

Table F-6 Genotoxicity and mutagenicity.

test system	doses	test substance	results	remarks	reference
In vitro					
S. typhimurium strain TA98	?	vacuum distillates distillation range + PAH content: 380-500°C + 78 g/L 300-430°C + 54 g/lL solvent-refined vacuum distillates distillation range + PAH content: 380-500°C + 20g/L 300-430°C + 9.7g/L	 + with S9 + with S9 + with S9 + with S9	the mutagenic activity of the refined samples was less than that of the unrefined samples	Hermann *et al.* 1980a,b (cited in IARC 1984[61])
S. typhimurium strain TA98		hydrotreated petroleum residue (distillation range: 400-500°C; PAH content: 2.5 g/L)	+ with S9		Hermann *et al.* 1980a,b (cited in IARC 1984[61])
S. typhimurium strain TA98	20 µL/plate	white oil of medicinal quality (PAH content: 0.64 g/L)	- with S9		Hermann *et al.* 1980a,b (cited in IARC 1984[61])
S. typhimurium strain TA98	20 µL/plate	highly refined steel-hardening oil (PAH content: 2.6 g/L); used highly refined steel-hardening oil (PAH content: 8.3 g/L	- with S9 + with S9 + without S9		Hermann *et al.* 1980a,b (cited in IARC 1984[61])
S. typhimurium strain TA1537 TA1538 TA98 TA100		pooled sample of 15 commercially available 10W-40 gasoline-engine oil pooled sample of used oil (produced by operating gasoline engines with the same oils)	- with S9 - without S9 + with S9 + without S9		Hermann *et al.* 1980a,b (cited in IARC 1984[61])
S. typhimurium		unused oil used oil obtained from four different cars	- +	both without metabolic activation	Wang *et al.* 1978 (cited in IARC 1984[61])
S.typhimurium strain TA98		DMSO extracts of 5 unused crankcase oils; 1 used crankcase oil	- +	with metabolic activation by a presumably un-induced rat-liver system	Payne *et al.* 1978 (cited in IARC 1984[61])
S. typhimurium strain TA98	20 µg/plate	highly refined crankcase oil corresponding used crankcase oil	- with S9 + with and without S9		Hermann *et al.* 1980a,b (cited in IARC 1984[61])

S. typhimurium strain TA1535 TA1537 TA1538 TA98 TA100		7 unused oil (including re-refined used oils) used oil from sumps of 2 cars with 4-stroke gasoline engines after 5-6 m of use, and a pooled sample of used oil obtained from a service station	+ without S9; - most oils with S9; + with S9 (all strains) + without S9 (one or more strains)	the IARC working group reported incomplete reporting of the data	Peake/Parker 1980 (cited in IARC 1984[61])
S. typhimurium		one of the unused oils of the study described above (including re-refined used oils) retested	-		Schreiner/ Mackerer 1982 (cited in IARC 1984[61])
Ames *Salmonella* assay	?	4 different low-aromatic oil-based drilling fluids	- with and without metabolic activation	modified assay to improve sensitivity to water-insoluble complex mixtures	NPD 1984 (cited in Eide 1990[33])
modified Ames assay	?	unrefined oils	+		Blackburn *et al.* 1984 (cited in CONCAWE 1997[20])
		highly refined oils	-		McKee/ Przygoda 1987; Blackburn *et al.* 1984 (cited in CONCAWE 1997[20])
mouse lymphoma bone marrow cytogenetic assays		7 samples	- all but one of the 7 samples negative	the clastogenic result with a 72 mm^2/s viscosity oil (at 40°C) was inexplicable as similar oils of lower and higher viscosities were inactive.	Conaway *et al.* 1984 (cited in CONCAWE 1997[20])
mouse lymphoma		solvent extracted paraffinic oils	-		Mc Kee/ Przygodas 1987 (cited in CONCAWE 1997[20])
micronucleus assays		solvent extracted paraffinic oils	-		Mc Kee *et al.* 1990 (cited in CONCAWE 1997[20]
Syrian hamster embryo cells mouse C3H 10T1/2 cells		2 insulation oils from highly refined mineral-base oils	+ +	transformation enhanced transformation	IARC 1978[62]

Syrian hamster embryo cells	unused, new, re-refined and used crankcase oils	+	transformation	IARC 1978[62]
Ames test	oil mist in cold rolling steel plant	-	oil mists contained only trace amounts of PAHs	Monarca *et al.* 1984[83]

Table F7 Reproduction toxicity (fertility and development).

animal species	**doses**	**test substance**	**duration**	**results**	**reference**
duck (Malard: Anas platyrhynchos)	1-15 µL on egg shells	used crankcase oil (lead content: 4600 mg/kg);	applied to the egg shell	embryolethal and teratogenic effects	Hoffman *et al.* 1982 (cited in IARC 1984[61])
quails (Colinus virginianus)	>15 µL on egg shells	unused crankcase oil (lead content: 2 mg/kg)		less embryolethal, not teratogenic	
		mixed aliphatic hydrocarbons present in oils		not embryolethal or teratogenic	
rat	2000 mg/kg bw/d dermal	3 lubricating oil base stocks	19 days (days 0-19 of gestation	no abnormal development	Mobil unpublished data (cited in CONCAWE 1997[20])
rat (Sprague-Dawley)	5 mL/kg/d by gavage	highly refined white oil (CAS 8012-95-1)	14 days (days 6-19 of gestation)	no evidence of teratogenicity	McKee *et al.* 1987a,b (cited in CONCAWE 1997[20])
			13 weeks before breeding	number, weight, survival of offspring: normal	

Annex **G**

IARC and EU carcinogenic classifications of various mineral base oils

Table G Overview of the IARC and EU/GHS classifications of the carcinogenicity of various mineral base oils.[41,63]

substance	EINECS	CAS number	classification[a] IARC	EU/GHS
unrefined or mildly refined base oils (acid-treating, chemically neutralised)				
crude oil distillation streams				
->light paraffinic distillates (petroleum)	265-051-5	64741-50-0	sufficient evidence	1A
->heavy paraffinic distillates (petroleum)	265-052-0	64741-51-1	sufficient evidence	1A
->light naphthenic distillates (petroleum)	265-053-6	64741-52-2	sufficient evidence	1A
->heavy naphthenic distillates (petroleum)	265-054-1	64741-53-3	sufficient evidence	1A
->vacuum distillates		64741-49-7	sufficient evidence	-
acid-treating streams				
->acid-treated light paraffinic distillates (petroleum)	265-121-5	64742-21-8	sufficient evidence	1A
->acid-treated heavy paraffinic distillates (petroleum)	265-119-4	64742-20-7	sufficient evidence	1A
->acid-treated light naphthenic distillates (petroleum)	265-118-9	64742-19-4	sufficient evidence	1A
->acid-treated heavy naphthenic distillates (petroleum)	265-117-3	64742-18-3	sufficient evidence	1A
->acid-treated residual oil		64742-17-2	sufficient evidence	-

chemically neutralised streams				
->chemically neutralized light paraffinic distillates (petroleum)	265-128-3	64742-28-5	sufficient evidence	1A
->chemically neutralized heavy paraffinic distillates (petroleum)	265-127-8	64742-27-4	sufficient evidence	1A
->chemically neutralized light naphthenic distillates (petroleum)	265-136-7	64742-35-4	sufficient evidence	1A
->chemically neutralized heavy naphthenic distillates (petroleum)	265-135-1	64742-34-3	sufficient evidence	1A
highly refined base oils				
white mineral oil				
->white mineral oil (petroleum)	232-455-8	8042-47-5	inadequate evidence	-
->light white mineral oil (petroleum)	295-550-3	92062-35-6	inadequate evidence	-
severely hydrotreated oil				
->hydrotreated bright stock-based lubricating oil (petroleum), C>25	276-735-8	72623-83-7	inadequate evidence	-
->hydrotreated bright stock-based lubricating oil (petroleum)	295-425-3	92045-44-8	inadequate evidence	-
->hydrotreated solvent-refined bright stock-based lubricating oil (petroleum)	295-426-9	92045-45-9	inadequate evidence	-
other lubricant base oils (unspecified refining severity)[b]				
clay-treated streams				
->clay-treated light paraffinic distillates (petroleum)	265-138-8	64742-37-6	-	1B
->clay-treated heavy paraffinic distillates (petroleum)	265-137-2	64742-36-5	-	1B
->clay-treated light naphthenic distillates (petroleum)	265-147-7	64742-45-6	-	1B
->clay-treated heavy naphthenic distillates (petroleum)	265-146-1	64742-44-5	-	1B
->clay-treated residual oil (petroleum)	265-143-5	64742-41-2	-	1B
solvent-refining streams				
->solvent-refined light paraffinic distillates (petroleum)	265-091-3	64741-89-5	-	1B
->solvent-refined heavy paraffinic distillates (petroleum)	265-090-8	64741-88-4	-	1B
->solvent-refined light naphthenic distillates (petroleum)	265-098-1	64741-97-5	-	1B
->solvent-refined heavy naphthenic distillates (petroleum)	265-097-6	64741-96-4	-	1B
->solvent-refined residual oil (petroleum)	265-101-6	64742-01-4	-	1B
->solvent-deasphalted residual oil (petroleum)	265-096-0	64741-95-3	-	1B
hydrotreating streams				
->hydrotreated light paraffinic distillates (petroleum)	265-158-7	64742-55-8	-	1B
->hydrotreated heavy paraffinic distillates (petroleum)	265-157-1	64742-54-7	-	1B
->hydrotreated light naphthenic distillates (petroleum)	265-156-6	64742-53-6	-	1B

->hydrotreated heavy naphthenic distillates (petroleum)	265-155-0	64742-52-5	-	1B
->hydrotreated residual oil (petroleum)	265-160-8	64742-57-0	-	1B
petrolatum	232-373-3	8009-03-8	-	1B
complex-dewaxing streams				
->complex-dewaxing light naphthenic distillates (petroleum)	265-180-7	64742-76-3	-	1B
->complex-dewaxing heavy naphthenic distillates (petroleum)	265-179-1	64742-75-2	-	1B
extracts				
->light paraffinic distillates solvent extract (petroleum)	265-104-2	64742-05-8	-	1B
->heavy paraffinic distillates solvent extract (petroleum)	265-103-7	64742-04-7	-	1B
->light naphthenic distillates solvent extract (petroleum)	265-102-1	64742-03-6	-	1B
->heavy naphthenic distillates solvent extract (petroleum)	265-111-0	64742-11-6	-	1B
->residual oil solvent extract (petroleum)	265-110-5	64742-10-5	-	-
solvent-dewaxing streams				
->solvent-dewaxed light paraffinic distillates (petroleum)	265-159-2	64742-56-9	-	1B
->solvent-dewaxed heavy paraffinic distillates (petroleum)	265-169-7	64742-65-0	-	1B
->solvent-dewaxed light naphthenic distillates (petroleum)	265-168-1	64742-64-9	-	1B
->solvent-dewaxed heavy naphthenic distillates (petroleum)	265-167-6	64742-63-8	-	1B
->solvent-dewaxed residual oil (petroleum)	265-166-0	64742-62-7	-	1B
catalytic-dewaxing streams				
->catalytic-dewaxed light paraffinic distillates (petroleum)	265-176-5	64742-71-8	-	1B
->catalytic-dewaxed heavy paraffinic distillates (petroleum)	265-174-4	64742-70-7	-	1B
->catalytic-dewaxed light naphthenic distillates (petroleum)	265-173-9	64742-69-4	-	1B
->catalytic-dewaxed heavy naphthenic distillates (petroleum)	265-172-3	64742-68-3	-	1B
hydro-cracked stream				
->heavy hydrocracked distillates (petroleum)	265-077-7	64741-76-0	-	1B

[a] -, not classified.

[b] The list of the *other lubricant base oils* is not complete and includes about 50 additional base oils with CAS numbers in Annex I (see [41]).

Annex **H**

Advice of the Subcommittee on the Classification of Carcinogenic Substances

The Subcommittee on the Classification of Carcinogenic Substances has been asked by the Dutch Expert Committee on Occupational Safety to advise on the carcinogenic properties of working with MWF that contain mineral base oils.

MWF are usually divided into straight oil MWF, soluble MWF, semi-synthetic MWF, and synthetic MWF. Straight oil MWF, soluble MWF, and semi-synthetic MWF contain mineral base oils. Of these, soluble and semi-synthetic MWF also contain water. All MWF contain additives to enhance their performance and stability.

The mineral base oils used in MWF nowadays are sufficiently refined to contain negligible amounts of PAC. Based on method IP 346 according to Note L of the 21st adaptation in 1994 of the European Council Directive on the classification, packaging, and labelling of dangerous substances, these mineral base oils do not have a carcinogenic classification in any of the categories in the European Union.

During (re)use, MWF become contaminated. Occasionally, genotoxic substances have been detected in water-based MWF. It appeared that genotoxic substances might be formed due to the presence of specific (combinations of) additives in the MWF. The present-day fluids as supplied to the end-user are not allowed to contain such (combinations of) additives. However, no data are available that allow to conclude that *unused* MWF do indeed not have genotoxic or carcinogenic properties.

According to the Subcommittee, several epidemiological studies show associations between cumulative exposure to mineral-oil-containing MWF and cancer of the larynx, oesophagus, and rectum, but the associations are weak and not consistent. Taking into account the formation of genotoxic compounds in the past, and the wide variety of additives still in use, there is cause for concern that genotoxic compounds might still be formed during the (re)use of present-day MWF. However, the evidence is weak and further experiments are needed before a final conclusion can be reached. The latency period for the development of cancer adds to this concern. It means that the carcinogenicity of working with present-day MWF can only be assessed after a period of about twenty years.

The Subcommittee concludes that there is a lack of carcinogenic and genotoxic data on *unused* MWF. Therefore, the Subcommittee recommends not to classify *unused* MWF. This recommendation is comparable to not classifiable in any of the categories in the European Union.

In addition, the Subcommittee is of the opinion that *working with MWF* has been insufficiently investigated. While the available data do not warrant a classification as *carcinogenic to humans* or as *should be regarded as carcinogenic to humans*, they indicate that there is *cause for concern for man*. Therefore, the Subcommittee recommends classifying *working with MWF* as suspected human carcinogenic. This recommendation is comparable to classification in EU category 3. The situation is, furthermore, comparable to subcategory B of this category.

The Subcommittee consisted of:

- G.J. Mulder, *chairman*
  Emeritus Professor of Toxicology, Leiden University, Leiden
- P.J. Boogaard, *advisor*
  Toxicologist, Shell International BV, The Hague
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Benelux N.V., Terneuzen
- R.A. Woutersen
  toxicologic Pathologist, TNO Quality of Life, Zeist and Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen

- A.A. van Zeeland
  Professor of Molecular Radiation Dosimetry and Radiation Mutagenesis, Leiden University Medical Center, Leiden
- E.J.J. van Zoelen
  Professor of Cell Biology, University Medical Centre St Radboud, Nijmegen
- A.S.A.M. van der Burght, *scientific secretary*
  Health Council of the Netherlands, The Hague
- J.M.Rijnkels, *scientific secretary*
  Health Council of the Netherlands, The Hague

Meeting date: October 22, 2008

In the period of time elapsing between the above presented evaluation of the Subcommittee on the Classification of Carcinogenic Compounds and the publication of this report, a new EU classification regulation (Regulation EC No. 1272/2008; 'CLP' Regulation) based on the Globally Harmonised System (GHS) of the United Nations came into force (see Annex I). This led the Subcommittee to update its classification system ('GR_{GHS}'; see Annex J). As described above, the Subcommittee recommended *working with MWF* into category 3B. This corresponds to category 2 in the new system which is comparable to EU category 2 (see Annex J).

Regulation (EC) No 1272/2008

of the European Parliament and of the Council on classification, labelling, and packaging of substances and mixtures

3.6 Carcinogenicity

3.6.1 Definition

Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

3.6.2 Classification criteria for substances

See Table on the next page.

3.6.2.1 For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

3.6.2.2 Specific considerations for classification of substances as carcinogens.

3.6.2.2.1 Classification as a carcinogen is made on the basis of evidence from reliable and acceptable studies and is intended to be used for substances which have an intrinsic property to cause can-

Table 3.6.1 Hazard categories for carcinogens.

Categories	Criteria
Category 1:	Known or presumed human carcinogens. A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A:	Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B:	Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
Category 2:	Suspected human carcinogens. The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

(1) Note: See 3.6.2.2.4.

cer. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

3.6.2.2.2 Classification of a substance as a carcinogen is a process that involves two interrelated determinations: evaluations of strength of evidence and consideration of all other relevant information to place substances with human cancer potential into hazard categories.

3.6.2.2.3 Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms ‘sufficient’ and ‘limited’ have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows:

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence;
- limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

- sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites
- limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, *e.g.* (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

3.6.2.2.4 Additional considerations (as part of the weight of evidence approach (see 1.1.1)). Beyond the determination of the strength of evidence for carcinogenicity, a number of other factors need to be considered that influence the overall likelihood that a substance poses a carcinogenic hazard in humans. The full list of factors that influence this determination would be very lengthy, but some of the more important ones are considered here.

3.6.2.2.5 The factors can be viewed as either increasing or decreasing the level of concern for human carcinogenicity. The relative emphasis accorded to each factor depends upon the amount and coherence of evidence bearing on each. Generally there is a requirement for more complete information to decrease than to increase the level of concern. Additional considerations should be used in evaluating the tumour findings and the other factors in a case-by-case manner.

3.6.2.2.6 Some important factors which may be taken into consideration, when assessing the overall level of concern are:

a tumour type and background incidence;
b multi-site responses;
c progression of lesions to malignancy;
d reduced tumour latency;
e whether responses are in single or both sexes;
f whether responses are in a single species or several species;
g structural similarity to a substance(s) for which there is good evidence of carcinogenicity;
h routes of exposure;
i comparison of absorption, distribution, metabolism and excretion between test animals and humans;
j the possibility of a confounding effect of excessive toxicity at test doses;
k mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity.

Mutagenicity: it is recognised that genetic events are central in the overall process of cancer development. Therefore evidence of mutagenic activity in vivo may indicate that a substance has a potential for carcinogenic effects.

3.6.2.2.7 A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes.

3.6.2.2.8 The classification shall take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity.

3.6.2.2.9 It is important that whatever is known of the physico-chemical, toxicokinetic and toxicodynamic properties of the substances, as well as any available relevant information on chemical analogues, i.e. structure activity relationship, is taken into consideration when undertaking classification.

3.6.4 Hazard communication

3.6.4.1 Classification for carcinogenicity:

Category 1A or Category 1B:

Hazard statement H350: May cause cancer *<state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>*.

Category 2:

Hazard statement H351: Suspected of causing cancer *<state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard>*.

Annex **J**

Carcinogenic Classification of Substances by the Subcommittee

The Subcommittee on the Classification of Carcinogenic Substances expresses its conclusions in the form of standard phrases:

Category	Judgement of the Committee (GR_{GHS})	Comparable with EU Category	
		67/584/EEC before 12/16/2008[a]	EC No 1272/2008 as from 12/16/2008
1A	The compound is known to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	1	1A
1B	The compound is presumed to be carcinogenic to man. • It acts by a stochastic genotoxic mechanism. • It acts by a non-stochastic genotoxic mechanism. • It acts by a non-genotoxic mechanism. • Its potential genotoxicity has been insufficiently investigated. Therefore, the mechanism of action is not known.	2	1B
2	The compound is suspected to be carcinogenic to man.	3	2
3	The available data are insufficient to evaluate the carcinogenic properties of the compound.	Not applicable	Not applicable
4	The compound is probably not carcinogenic to man.	Not applicable	Not applicable

[a] The previous classification system of the Subcommittee was based on this 67/584/EEC guideline.