Health Council of the Netherlands

Molybdenum and molybdenum compounds

Health-based recommended occupational exposure limit

Gezondheidsraad
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Molybdenum and molybdenum compounds*
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Geachte minister,

Graag bied ik u hierbij aan het advies over de gevolgen van beroepsmatige blootstelling aan molybdeen en molybdeenverbindingen.

Dit advies maakt deel uit van een uitgebreide reeks, waarin gezondheidskundige advieswaarden worden afgeleid voor concentraties van stoffen op de werkplek. De conclusies van het genoemde advies zijn 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. W.A. van Gool,
voorzitter

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Molybdenum and molybdenum compounds

Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2013/30, The Hague, November 11, 2013

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).

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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 waaraan mensen tijdens hun beroepsuitoefening blootgesteld kunnen worden. Deze advieswaarden vormen vervolgens de basis voor de grenswaarden, die de minister vaststelt om de gezondheid van werknemers te beschermen.

In dit advies bespreekt de commissie de gevolgen van blootstelling aan molybdeen en molybdeenverbindingen* en stelt zij een gezondheidskundige advieswaarde vast. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór oktober 2013 zijn verschenen.

Fysische en chemische eigenschappen

Puur molybdeen is een natuurlijk voorkomend zilverachtig metaal dat in verschillende oxidatietoestanden kan voorkomen, waarvan molybdeen(IV) en molybdeen(VI) de stabielste vormen zijn. In de natuur wordt molybdeen vooral

* De in dit advies geëvalueerde molybdeenverbindingen zijn metallisch molybdeen, molybdeniet, molybdeenchloride, molybdeentrioxide, ammoniummolybdaat, ammoniumparamolybdaat, calciummolybdaat en natriummolybdaat.

aangetroffen als molybdaat, dat vervolgens een verscheidenheid aan molybdeenverbindingen kan vormen. Sommige molybdeenverbindingen lossen bij 20°C goed op in water, zoals ammoniummolybdaat, ammoniumparamolybdaat en natriummolybdaat; andere lossen minder goed op, zoals molybdeentrioxide, of lossen niet op in water, zoals metallisch molybdeen, molybdeniet en molybdeenchloride.

Molybdeen wordt gebruikt in de metaalproducerende en -verwerkende industrie.

Monitoring

In Nederland wordt de ISO-methode (ISO 15202) gebruikt voor het kwantificeren en identificeren van metalen in de lucht op de werkvloer. Molybdeen in stof (totaal, inhaleerbaar of respirabele fractie in stof) kan gemeten worden met atoom-absorptie-spectroscopie of atoom-emissie-spectroscopie.

Grenswaarden

In Nederland zijn voor molybdeen en molybdeenverbindingen geen wettelijke grenswaarden vastgesteld. Ook zijn er geen grenswaarden vastgesteld door de Europese Commissie. Sommige andere landen hanteren voor oplosbare molybdeenverbindingen grenswaarden (tijdgewogen gemiddelde concentratie over acht uur) van 0,5 tot 5 mg molybdeen/m^3.* Voor metallisch molybdeen en onoplosbare molybdeenverbindingen gelden grenswaarden van 3 tot 15 mg molybdeen/m^3. De grenswaarden zijn niet zonder meer vergelijkbaar met elkaar, omdat deze gebaseerd zijn op bemonstering van verschillende stoffracties (molybdeengehalte in totaal, inhaleerbaar of respirabel stof).

Kinetiek

Onderzoek heeft aangetoond dat dieren en mensen door inademing en inname via voedsel en drinkwater, molybdeen en molybdeenverbindingen opnemen in het lichaam. Daarbij hangt de snelheid waar het lichaam deze verbindingen via het voedsel opneemt af van de oplosbaarheid van de verbindingen en de voedselsamenstelling. In het algemeen is de opname via het maagdarmstelsel snel en vrijwel compleet. Het is niet bekend hoe snel en efficiënt de opname via inademing is.

* mg/m^3: milligram molybdeen per kubieke meter lucht

Molybdeen is een essentieel sporenelement dat mensen en dieren nodig hebben om normale biologische processen goed te laten verlopen. Molybdeen wordt in lage concentraties aangetroffen in alle lichaamsvloeistoffen en – weefsels. Er vindt in het lichaam geen noemenswaardige stapeling van molybdeen plaats. Molybdeen kan de placenta passeren en is aangetroffen in moedermelk.

Het metabolisme van molybdeen is gekoppeld aan het koper- en zwavelmetabolisme. Uitscheiding via de urine – de belangrijkste route van eliminatie – is snel en versneld bij voedsel dat rijk is aan koper en sulfaat.

Effecten

Waarnemingen bij mensen

Het beschikbare onderzoek onder mensen die beroepsmatig zijn blootgesteld aan molybdeen(verbindingen) heeft een beperkte waarde voor de afleiding van een gezondheidskundige advieswaarde, omdat betrouwbare blootstellinggegevens ontbreken. Daarnaast is sprake van gelijktijdige blootstelling aan andere potentieel toxische stoffen, en zijn de onderzoeken niet goed beschreven. Mensen die beroepshalve blootstonden aan in ieder geval molybdeentrioxide klaagden over gewrichtspijn, rugpijn, hoofdpijn, moeilijke ademhaling, borstpijn en vermoeidheid. De laatste klachten kunnen wijzen op milde obstructieve longziekten. Ook werden verhoogde gehaltes aan urinezuur in het bloed aangetroffen. De blootstellingsniveaus waarbij dergelijke klachten optraden, varieerden van 1,6 mg/m^3 (molybdeen in respirabel stof in een molybdeenverwerkende ‘roostfabriek’) tot 600 mg/m^3 in stof van mijnen.

Bij Armeense dorpsbewoners werden jichtachtige verschijnselen waargenomen en verhoogde gehaltes urinezuur in het bloed. Zij hadden een gemiddelde dagelijkse inname van 10 tot 15 milligram molybdeen via het voedsel (en 5 tot 10 milligram koper). De gemiddelde dagelijkse inname ligt normaal tussen de 0,1 en 0,3 milligram. In een Amerikaanse drinkwateronderzoek zijn geen effecten op de gezondheid geconstateerd; het drinkwater bevatte tenminste 200 microgram molybdeen per liter water (normaalwaarden: tussen de 10 en 60 microgram).

Gegevens over mogelijke kankerverwekkendheid van molybdeen(verbindingen) voor de mens zijn beperkt. In een bevolkingsonderzoek naar sterftegevallen door kanker is een zwakke correlatie van longkanker gevonden onder mensen die beroepshalve langdurig blootstonden aan molybdeen; in een ander onderzoek onder vrouwen in Japan werd een positieve correlatie gevonden met kanker in de alvleesklier. Door gebrek aan betrouwbare blootstellingniveaus, en doordat

mogelijke andere factoren aanwezig waren die kanker kunnen hebben veroorzaakt in de onderzochte populaties, vallen uit deze onderzoeken geen conclusies te trekken.

In een klinische studie werden afwijkingen in spermakwaliteit en spiegels van mannelijke geslachtshormonen waargenomen. Voor zover bekend zijn er geen andere onderzoeken uitgevoerd waarin is nagegaan of molybdeen en molybdeenverbindingen de vruchtbaarheid bij de mens kunnen verminderen en de ontwikkeling van het nageslacht kunnen aantasten.

Waarnemingen bij dieren

Bepaalde molybdeenverbindingen, met name de wateroplosbare, bleken irritatie te geven aan neus, ogen en luchtwegen.

Inademing
Blootstelling tot aan 100 mg molybdeentrioxide/m^3 (in aerosolen) gedurende dertien weken veroorzaakte geen nadelige gezondheidseffecten en geen pathologische afwijkingen in weefsels van ratten en muizen. Cavia's die vijf dagen achter elkaar werden blootgesteld aan meer dan 300 mg/m^3 (concentratie molybdeen in totaal stof in de lucht), vertoonden irritatie aan de luchtwegen, verloren eetlust en gewicht, en hadden last van diarree, ongecoördineerde spieractiviteiten en haaruitval.

Inademing van 10 tot 100 mg molybdeentrioxide/m^3 (in aerosolen) voor zes uur per dag, vijf dagen per week gedurende twee jaar, veroorzaakte in ratten en muizen, vergeleken met een niet-blootgestelde groep, een statistisch significante toename van hyalinedegeneratie in het neusweefsel, metaplasie en hyperplasie in het strotklepje, en chronische ontstekingsverschijnselen in de longen. In hetzelfde onderzoek is ook bekeken of molybdeentrioxide kanker veroorzaakte, maar dat leverde tweeslachtige resultaten op. Er werden in geen enkel orgaan in het lichaam van ratten en muizen tumoren gevonden, behalve longtumoren in muizen, maar het aantal muizen met tumoren vertoonde geen verband met de mate van de blootstelling.

Uitslagen van tests die kunnen aangeven of stoffen het DNA kunnen beschadigen en daardoor kanker kunnen veroorzaken, geven aan dat de geëvalueerde molybdeentrioxide, ammoniummolybdaat en natriummolybdaat waarschijnlijk niet het DNA beschadigen.

Er zijn verder geen duidelijke aanwijzingen gevonden dat inademing van molybdeentrioxide (tot 100 mg/m^3, de hoogst geteste concentratie, gedurende dertien weken) de fertiliteit van mannelijke muizen en ratten aantast.

Orale inname

In een dieronderzoek werd een statistisch significante afname van het absolute lichaamsgewicht waargenomen in mannelijke ratten bij de hoogste dosering aan natriummolybdaat (60 mg molybdeen/kg lichaamsgewicht). De dieren kregen de stof via de voeding toegediend gedurende 90 dagen. Ook bij vrouwlijke ratten werd een afname van het absolute lichaamsgewicht geconstateerd ten opzichte van niet blootgestelde dieren. Er werden in hetzelfde onderzoek geen andere duidelijk aan molybdeen gerelateerde effecten gevonden. Er zijn ook andere kortdurende dieronderzoeken uitgevoerd maar daaruit kunnen geen conclusies worden getrokken. De reden daarvan is dat de onderzoeken met te weinig dieren waren uitgevoerd. Er zijn geen drinkwater- of dieetstudies uitgevoerd naar mogelijke kankerverwekkende eigenschappen van molybdeenverbindingen.

Wel zijn er dierexperimenten uitgevoerd naar vruchtbaarheids- en ontwikkelingseffecten. Daaruit komen aanwijzingen dat bepaalde molybdeenverbindingen wellicht schade aan de vruchtbaarheid van mannelijke dieren (en mogelijk ook aan vrouwlijke dieren) kunnen veroorzaken. In een onderzoek werd bijvoorbeeld een statistisch significante afname van spermabeweeglijkheid en het aantal spermacellen waargenomen in ratten, die gedurende 60 dagen en vijfmaal per week natriummolybdaat via een maagsonde kregen toegediend (dosis 30 en 50 mg natriummolybdaat/kg lichaamsgewicht per dag). Bij deze doseringen zijn geen andere effecten gerapporteerd. Veel van deze experimenten zijn echter slecht gerapporteerd. Ook het hierboven beschreven onderzoek is slecht gerapporteerd. In andere dierexperimenten werden geen effecten op de vruchtbaarheid waargenomen.

Evaluatie

De commissie vindt de gegevens van epidemiologische onderzoeken onvoldoende om een gezondheidskundige advieswaarde te kunnen afleiden, vanwege factoren als gecombineerde blootstelling en gebrek aan details over blootstelling en karakteristieken van de onderzochte groepen. Er zijn wel gegevens van enkele dierexperimentele onderzoeken beschikbaar, die als basis voor een gezondheidskundige advieswaarde zouden kunnen dienen. Voor het afleiden van een gezondheidskundige advieswaarde gebruikt de commissie de benchmarkdosis (BMD) software van de Amerikaanse *Environmental Protection Agency*, waarmee het best passende model voor een blootstellingsresponsrelatie kan worden bepaald. Dit model is vervolgens gebruikt om een blootstellingsniveau af te leiden (de BMDL, de onderste concentratie van het 95 procent betrouwbaarheidsinterval

van de BMD), dat als vertrekpunt dient voor het afleiden van een gezondheidskundige advieswaarde.

Molybdeentrioxide

Wat molybdeentrioxide betreft vormt volgens de commissie het tweejarig dierexperimenteel onderzoek, waarin ratten en muizen van beide geslachten aerosolen van molybdeentrioxide inhaleerden met een concentratie oplopend tot 100 mg/m^3 het beste uitgangspunt. De meest relevante effecten die in dit onderzoek naar voren kwamen waren: metaplasie in het strottenklepje in beide diersoorten en in beide geslachten; hyalinedegeneratie in het neusweefsel, en chronische ontsteking en metaplasie in longweefsel. Deze laatste effecten waren minder consistent en beperkten zich tot slechts één diersoort en/of geslacht. Alle effecten in deze dieren beschouwt de commissie als relevant voor de mens. Uit de BMD-analyse werd een BMDL van 0,29 mg molybdeentrioxide/m^3 afgeleid (metaplasie in het strottenklepje), dat overeenkomt met een 10 procent extra risico op dit effect vergeleken met het achtergrondrisico*.

Voor het vaststellen van een gezondheidskundige advieswaarde wordt nog rekening gehouden met verschillende onzekerheden. Zo zijn er verschillen tussen diersoorten. De commissie acht het echter niet nodig om daarvoor te compenseren, omdat sprake is van oppervlakkige lokale effecten. Een andere onzekerheid is dat mensen onderling verschillend kunnen reageren op blootstelling. Daarvoor past de commissie een onzekerheidsfactor van drie toe. Toepassing van deze factor levert een gezondheidskundige advieswaarde voor molybdeentrioxide op van 0,1 mg molybdeentrioxide/m^3. Deze waarde is gebaseerd op inhaleerbare stofblootstelling en is gemiddeld over een achturige werkdag.

Aangaande de kankerverwekkendheid beveelt de commissie verder aan molybdeentrioxide te classificeren in categorie 2 (verdacht kankerverwekkend voor de mens)**. Door een gebrek aan gegevens is het niet mogelijk de stof te classificeren voor effecten op de vruchtbaarheid en de ontwikkeling, en effecten tijdens lactatie.

Natriummolybdaat

Voor natriummolybdaat zijn twee dierexperimenten beschikbaar waarin blootstellingsresponsrelaties zijn bestudeerd. De eerste is die waarin duidelijke effec-

* De commissie kiest standaard voor dichotome (kwantale) diergegevens een extra risico van 10%. Zij kan hiervan afwijken als daar gegronde wetenschappelijke redenen voor zijn.

** Zie bijlage F voor het classificatiesysteem.

ten zijn gevonden in de testis van ratten die via een maagsonde de stof kregen toegediend (bij 30 en 50 mg natriummolybdaat/kg lichaamsgewicht per dag, vijf dagen per week, gedurende 60 dagen). De andere is het dierexperiment waarin een duidelijke gewichtsafname was te zien in vooral mannelijke ratten, die de stof via de voeding kregen toegediend bij een dosis van 60 mg molybdeen/kg lichaamsgewicht gedurende 90 dagen.

Wat de eerste studie betreft is de commissie bezorgd over het optreden van vruchtbaarheidseffecten. Dat die kunnen optreden lijkt te worden bevestigd door andere dierexperimentele studies en door een humane studie, wat het relevant maakt voor de mens. Daar staat tegenover dat de commissie constateert dat de betreffende studie slecht gerapporteerd is en daardoor de vraag oproept hoe betrouwbaar de gegevens zijn voor een kwantitatieve risicoanalyse.

De studie waarin gewichtsafname is beschreven is goed uitgevoerd en gerapporteerd. Dit was ook de studie waarin geen andere noemenswaardige effecten optraden. Op basis van deze studie heeft de commissie een BMDL berekend van 10,9 mg molybdeen/kg lichaamsgewicht, die correspondeert met een 10 procents afname van lichaamsgewicht door blootstelling ten opzichte van het lichaamsgewicht in niet-blootgestelde dieren*. Omdat het een orale dosis betreft en de gezondheidskundige advieswaarde gebaseerd is op een concentratie in de lucht is deze omgerekend. Dit levert een inhalatoire BMDL op van 41,20 mg molybdeen/m^3.

Voor het vaststellen van een gezondheidskundige advieswaarde wordt nog rekening gehouden met verschillende onzekerheden, zoals verschillen tussen diersoorten. Omdat het gaat om systemische effecten hanteert de commissie een factor drie om te compenseren voor verschillen tussen diersoorten. De commissie hanteert verder ook nog een factor drie om te compenseren voor verschillen tussen mensen onderling. Toepassing van deze twee factoren levert een gezondheidskundige advieswaarde voor natriummolybdaat op van 4,6 mg molybdeen/m^3 (afgerond). Deze waarde is gebaseerd op inhaleerbare stofblootstelling en is gemiddeld over een achturige werkdag.

Door een gebrek aan gegevens is het niet mogelijk de stof te classificeren voor kankerverwekkendheid. De commissie beveelt wel aan molybdaten te classificeren voor effecten op de vruchtbaarheid, namelijk in categorie 2 (‘wordt ervan verdacht de vruchtbaarheid te schaden’). Door een gebrek aan gegevens is het niet mogelijk de stof te classificeren voor effecten op de ontwikkeling en effecten tijdens lactatie.

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* De commissie kiest standaard een 10 procents toe- of afname in gewicht als respons voor de berekening van een BMDL.

Metallisch molybdeen en alle andere molybdeenverbindingen

Door een gebrek aan gegevens kan de commissie voor deze stoffen geen gezondheidskundige advieswaarde afleiden. Door een gebrek aan gegevens is het voor de commissie verder niet mogelijk voorstellen te doen voor classificatie wat betreft mogelijke kankerverwekkendheid, vruchtbaarheidseffecten, ontwikkelingseffecten en effecten tijdens lactatie.

Aanbevelingen

Gezondheidskundige advieswaarden

De Commissie GBBS van de Gezondheidsraad stelt de volgende gezondheidskundige advieswaarden voor bij beroepsmatige blootstelling van:

- Molybdeentrioxide, te weten 0,1 mg molybdeentrioxide/m^3 (= 0,07 mg molybdeen/m^3).
- Natriummolybdaat, te weten 9,9 mg natriummolybdaat/m^3 (= 4,6 mg molybdeen/m^3).

gebaseerd op inhaleerbare aerosol of stofblootstelling, gemiddeld over een achturige werkdag. De beschikbare gegevens voor metallisch molybdeen en andere molybdeen-verbindingen zijn onvoldoende om een voorstel voor een gezondheidskundige advieswaarde te kunnen doen.

Classificaties

Wat de kankerverwekkendheid betreft beveelt de commissie aan om molybdeentrioxide te classificeren in categorie 2 (‘verdacht kankerverwekkend voor de mens’)*. De gegevens van andere molybdeenverbindingen zijn onvoldoende om een voorstel tot classificatie te kunnen doen.

Wat de effecten op de vruchtbaarheid betreft, stelt de commissie voor molybdaten te classificeren in categorie 2 (‘wordt ervan verdacht de vruchtbaarheid te schaden’). Voor de andere molybdeenverbindingen kan geen voorstel worden gedaan in verband met een gebrek aan gegevens. Door dat gebrek aan gegevens is voor geen enkele molybdeenverbinding een evaluatie mogelijk op ontwikkelingseffecten en effecten tijdens lactatie.

* Zie bijlage F voor het classificatiesysteem.

Executive summary

Scope

At request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council, proposes health-based recommended occupational exposure limits (HBR-OELs) for chemical substances in the air in the workplace. These recommendations serve as a basis in setting legally binding occupational exposure limits by the minister.

In this report, the Committee discusses the consequences of occupational exposure to molybdenum and molybdenum compounds*, and recommends a health-based occupational exposure limit. The Committee's conclusions are based on scientific papers published before October 2013.

Physical and chemical properties

Pure molybdenum is a naturally occurring silvery white metal that has several oxidation states, the most stable being molybdenum(IV) and molybdenum(VI). In nature, molybdenum occurs predominantly as molybdate, which may form a

* The evaluated molybdenum compounds in this report are: metallic molybdenum, molybdenite; molybdenum chloride; molybdenum trioxide; ammonium molybdate; ammonium paramolybdate; calcium molybdate; and, sodium molybdate.

wide variety of molybdenum compounds. At 20°C, some molybdenum compounds dissolve in water, such as ammonium molybdate, ammonium paramolybdate, and sodium molybdate; others are less soluble, such as molybdenum trioxide; or, insoluble, such as, metallic molybdenum, molybdenite, and molybdenum chloride.

Molybdenum is used in the metal producing and processing industry.

Monitoring

In the Netherlands, the ISO method (ISO 15202) for identifying metals in workplace air is used. Molybdenum in dust (total, inhalable or respirable dust fraction) can be measured using atomic absorption spectroscopy or atomic emission spectroscopy.

Current limit values

Neither in the Netherlands nor in the European Commission, legally binding occupational exposure limits have been set for molybdenum and molybdenum compounds. In some other countries, occupational exposure limits (8h-TWA) have been set for soluble molybdenum compounds, namely 0.5 up to 5 mg molybdenum per m^3; and, for metallic molybdenum and insoluble molybdenum compounds, 3 to 15 mg molybdenum per m^3. The limits cannot be compared just like that, because they are based on samples taken from different particulate dust fractions (content of molybdenum in total, inhalable or respirable dust).

Kinetics

As shown by various animal studies and a few human studies, molybdenum and molybdenum compounds are taken up by the body through inhalation, and consumption of food and drinking water. The absorption rate after oral intake depends on the solubility of the compounds and composition of the diet. Overall, absorption via the gastro-intestinal tract is rapid and almost complete. It is not known how fast and efficient absorption via inhalation is.

For humans and animals, molybdenum is an essential trace element that is needed for normal biological processes. It is present in low concentrations in all body fluids and tissue. There is no apparent bioaccumulation of molybdenum in the body. Molybdenum compounds can cross the placental barriers and molybdenum is found in human milk.

The metabolism of molybdenum compounds is related to copper and sulphur metabolism. Excretion via the urine – the main route of elimination – is rapid, and enhanced by the presence of high dietary levels of copper and sulphate.

Effects

Observations in humans

Studies on people, who were occupationally exposed to molybdenum (compounds), are of limited value in deriving health-based occupational exposure limits, because of a lack of reliable exposure data, concomitant exposure to other potentially toxic compounds, and poor descriptions of the studies. Overall, workers who were at least exposed to molybdenum trioxide reported complaints, such as joint pain (gout-like symptoms), back pain, headache, and mild obstructive lung disease (including breathing difficulties, chest pain and fatigue). Also increased levels of uric acid and ceruloplasmin have been reported compared to non-exposed workers. Exposure levels to molybdenum at which symptoms occurred were found to be as low as 1.6 mg/m^3 (molybdenum in respirable dust in a molybdenum roasting plant) to 600 mg/m^3 (dust in mines).

Among Armenian villagers, gout-like symptoms and increased blood levels of uric acid have been observed. They had an average dietary intake of molybdenum of 10 to 15 mg per day (and of copper of 5 to 10 mg per day). The average normal daily intake varies between 0.1 and 0.3 mg molybdenum per day. In an American drinking-water study, no adverse health effects were found by consumption of drinking water that contained at least 200 µg molybdenum per litre water (normal mean values: between 10 and 60 µg).

Data on carcinogenic activity in humans are limited. Positive but weak correlations were found for lung cancer among molybdenum-exposed workers with a long exposure history, and for pancreas cancer in females in a Japanese population. However, due to a lack of reliable exposure and intake levels, and the presence of other potentially carcinogenic factors in the investigated populations, no conclusions can be drawn from these studies.

In a clinical study, lowered semen quality and changes in male reproductive hormone level were observed. No other investigations have been performed in which adverse effects of molybdenum and molybdenum compounds on fertility, and development of progeny, in humans was examined.

Animal experiments

Depending on the molybdenum compound, in particular soluble compounds showed to be irritating the nose, eyes, and respiratory tract.

Inhalation
In rats and mice exposed to up to 100 mg molybdenum trioxide/m^3 (in aerosol) for thirteen weeks, no adverse health effects or pathological lesions were found. Guinea pigs exposed to very high levels of molybdenum trioxide (> 300 mg/m^3; concentration molybdenum in total dust in air) for five weeks, showed signs of respiratory irritation, loss of appetite and weight, diarrhea, muscular incoordination, and loss of hair.

Groups of rats and mice were exposed to molybdenum trioxide for two years. Animals were exposed to the compound at concentrations of 0 (control), 10, 30 or 100 mg molybdenum trioxide/m^3 (in aerosol) for 6 hours per day, five days per week, for 106 weeks. In the respiratory tract of exposed animals the following effects were observed: hyaline degeneration in the respiratory and olfactory epithelium of the nose; laryngeal squamous metaplasia in the epiglottis, and laryngeal hyperplasia; and, chronic inflammation of the lungs. Some of these effects were statistically significantly increased compared to non-exposed groups at 10 mg/m^3 onwards. In the same study, also carcinogenicity of the compound was investigated with equivocal results, in that no exposure-related increases in tumour development was found in any organ in rats and mice, except for lung tumours in mice, and that the findings in mice were not dose-related.

Based on the limited evidence available, the Committee is of the opinion that molybdenum trioxide, ammonium molybdate and sodium molybdate are probably not genotoxic.

No significant signs of adverse effects on fertility have been found in male rats and mice exposed to molybdenum trioxide at a concentration of up to 100 mg/m^3 (higher concentrations not tested) for thirteen weeks.

Oral intake
In male rats which were given sodium molybdate in the diet, a statistically significantly decrease in absolute body weight (and body weight gain) was observed at the highest dose (60 molybdenum mg/kg bw). Also in female rats a reduction of the absolute body weight was observed when compared to non-exposed animals. In the same study, no other effects were found which could be related to molybdate exposure. Other short- and mid-term animal studies have been performed, but from none of these a clear conclusion on the adverse effects

could be made. The reason for this is that the studies used a low number of animals. Furthermore, there are no animal carcinogenicity studies performed in which molybdenum compounds have been given via the diet or drinking water.

A number of animal studies have been published on fertility and developmental effects. These studies indicate that certain molybdenum compounds may reduce the fertility in male rats (and possibly also in females). For instance, in one study, a statistically significant reduction of sperm motility and total sperm count in rats has been reported. The rats received sodium molybdate by gavage at a concentration of 30 and 50 mg sodium molybdate/kg bw/day, for five days a week during 60 days. At these exposure levels no other adverse effects have been described. However, many of the reproduction toxicity studies have been poorly reported. This also applies for the study described in more detail. Furthermore, in some animal studies no reproduction toxicity have been observed at all.

Evaluation

Overall, the Committee considers the current epidemiological data insufficient for quantitative hazard assessment, because of the presence of confounding factors, such as concomitant exposure, and missing details on exposure and population characteristics. However, the results of a few animal studies could serve as starting point in deriving health-based recommended occupational exposure limits (HBR-OELs). For this purpose. DECOS used the benchmark dose (BMD) software from the US Environmental Protection Agency to assess the best fitting model of the exposure- response relationships. This model was then used to derive an exposure level, the BMDL (the lowest concentration of the 95% confidence interval of the benchmark dose), that could serve as point of departure in estimating an HBR-OEL.

Molybdenum trioxide

Regarding molybdenum trioxide, according to the Committee, the two-year inhalation study, in which rats and mice of both sexes inhaled molybdenum trioxide aerosols at concentrations of up to 100 mg molybdenum trioxide/m^3, is the best point of departure. The most relevant effects in this study included: squamous metaplasia in the epiglottis (larynx) in both species and in both sexes; and, hyaline degeneration in the nose, and chronic inflammation and metaplasia in the lungs. The latter effects were less consistent among the animal species and sexes. All these respiratory effects are considered relevant for humans. BMD-analysis revealed a BMDL of 0.29 mg molybdenum trioxide/m^3 (squamous

metaplasia in the laryngeal epiglottis), which corresponds to an extra 10% risk compared to background risk levels*.

For the assessment of the HBR-OEL, several aspects and uncertainties were considered. For instance, interspecies differences should be taken into account. However, the Committee noticed that the effects were local effects and, therefore, no additional extrapolation for interspecies differences is needed. However, differences among people should be taken into account. The Committee used a factor of three to compensate for this. Consequently, the Committee recommends an HBR-OEL for molybdenum trioxide of 0.1 mg molybdenum trioxide/m^3, based on personal inhalable dust exposure, as an eight-hour time weighted average concentration.

Based on the available carcinogenicity data, the Committee recommends, furthermore, classifying molybdenum trioxide in category 2 (suspected carcinogen to man)**. Due to a lack of data, no classifications on fertility, developmental toxicity or lactation can be proposed.

Sodium molybdate

For sodium molybdate two animal studies are available, in which concentration-response relationships have been studied. The first, is a study in which clear fertility effects are observed in male rats, which received the compound by gavage (30 and 50 mg sodium molybdate/kg bw/day, five days during 60 days). The other one is a study in which a clear reduction in body weight and body weight gain is observed, in particular in male rats, which received the compound via the diet at a concentration of 60 mg molybdenum/kg bw for 90 days.

Regarding the first study, the Committee is concerned about the occurrence of fertility effects. That these effects may occur appears to be confirmed by other animal studies, and by a human study, which makes it relevant for humans. On the other hand, the Committee noted that the study is poorly reported, raising the question how reliable the data are for quantitative risk-analysis.

The study in which reduced body weight and body weight gain have been described is well-performed. This was also the study in which no other notable adverse health effects were observed. Based on this study, the Committee calculated a BMDL of 10.9 mg molybdenum/kg bw, which corresponds to a decrease in body weight of 10% due to exposure, compared to the body weight in

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* The Committee uses 10% extra risk as a default for dichotomous (quantal) animal data. The default may be modified based on scientific considerations.

** See Annex F for the classification system.

non-exposed animals*. Since this concerns an oral dose and the health-based recommended occupational exposure level should be based on a concentration in the air, the BMDL is converted. This results in a inhalation BMDL of 41.20 mg molybdenum/m^3.

For the assessment of the HBR-OEL, several aspects and uncertainties were considered. For instance, interspecies differences should be taken into account. Since the effects were systemic, the Committee proposes to adjust for interspecies differences with a factor of three. Furthermore, for differences between people, the Committee uses another uncertainty factor of three. Consequently, the Committee recommends an HBR-OEL for sodium molybdate of 4.6 mg molybdenum/m^3 (rounded off), based on personal inhalable dust exposure, as an eight-hour time weighted average concentration.

Due to a lack of data, no classification on carcinogenicity can be proposed for sodium molybdate. However, the Committee recommends a classification in category 2 for effects on fertility ('suspected human reproductive toxicant') of all molybdates. Due to a lack of data, no classifications on developmental toxicity or lactation can be proposed.

Metallic molybdenum and any other molybdenum compounds

Due to insufficient data, the Committee is not able to propose an HBR-OEL for metallic molybdenum and any other molybdenum compounds. It is also not able to propose an HBR-OEL for soluble molybdenum compounds as a group, or for insoluble molybdenum compounds as a group.

Due to a lack of data, no classification on carcinogenicity, fertility, developmental toxicity or lactation can be proposed for metallic molybdenum or any other molybdenum compounds.

Recommendations

Health-based recommended occupational exposure limits

The Committee recommends a health-based occupational exposure limit for:

- molybdenum trioxide, namely of 0.1 mg molybdenum trioxide/m^3 (= 0.07 mg molybdenum/m^3)
- sodium molybdate, namely of 9,9 mg sodium molybdate/m^3 (= 4,6 mg molybdenum/m^3).

* The Committee uses a de- or increase in body weight of 10% as a default response for calculating a BMDL.

based on personal inhalable aerosol or dust exposure, measured as an eight-hour time weighted average concentration. The available data are insufficient to recommend an HBR-OEL for metallic molybdenum and any other molybdenum compounds.

Classifications

Regarding carcinogenicity, the Committee recommends classifying molybdenum trioxide in category 2 ('suspected carcinogen to man')*. The available data are insufficient to evaluate the carcinogenic properties of metallic molybdenum and other molybdenum compounds.

Regarding reproduction toxicity, the Committee recommends classifying sodium molybdate and other molybdates in fertility category 2 ('suspected human reproductive toxicant'). The available data on metallic molybdenum or any other molybdenum compounds are insufficient to evaluate fertility effects. For the same reason, data on molybdenum or any molybdenum compounds are insufficient to evaluate developmental toxicity and effects on lactation.

* See Annex F for the classification system.

Chapter 1

Scope

1.1 Background

At 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 chemical substances that are used in the workplace. The purpose of these evaluations is to recommend a health-based occupational exposure limit for concentrations in the air, provided the database allows derivation of such a value. In the Netherlands, these recommendations serve as a basis in setting public occupational exposure limits by the minister.

In this advisory report, such an evaluation is made for molybdenum and molybdenum compounds:

- (Metallic) molybdenum
- Ammonium paramolybdate
- Molybdenite
- Molybdenum trioxide
- Ammonium molybdate
- Calcium molybdate
- Molybdenum chloride
- Sodium molybdate

1.2 Committee and procedure

This document contains the assessment of DECOS, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter (in English) to the state secretary can be found in Annex C.

In 2010 and in 2013 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 D. The Committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

The Committee's recommendations on the health-based occupational exposure limit of molybdenum and molybdenum compounds have been based on publicly available scientific data. Data were obtained from the online databases Toxline and Medline (PubMed), using "molybd? OR CAS 7439-98-7" in combination with "toxic? OR epidemio? OR occupational?" as key words. The final search, in Medline (PubMed), was performed in October 2013.

Chapter 2

Identification, properties and monitoring

2.1 Chemical identification

Pure molybdenum (Mo) is a naturally occurring silvery white metal that has several oxidation states, the most stable being +4 (Mo(IV)), and +6 (Mo(VI)).[1] In soil and natural water, molybdenum occurs predominantly as the molybdate anion (MoO_4^{2-}), which may form a wide variety of complex polymolybdate compounds, such as ammonium paramolybdate. Table 1 shows the chemical identification of the evaluated molybdenum compounds.[2,3,4]

2.2 Physical and chemical properties

The physical and chemical properties of the evaluated molybdenum compounds are shown in Table 2.[2,3,4,1] Molybdenum and molybdenum compounds show differences in water solubility:

- *soluble* molybdenum compounds (at around 20°C): sodium molybdate, ammonium molybdate, and ammonium paramolybdate
- *low* solubility in water (at around 20°C): molybdenum trioxide
- *insoluble* molybdenum compounds (at around 20°C): metallic molybdenum, molybdenite, calcium molybdate, and molybdenum chloride.

At room temperature, the molybdate anion (MoO_4^{2-}) is soluble and will form upon contact of molybdenum-containing minerals with oxygen and water.

Table 1 Identification of the evaluated molybdenum compounds.

	Molecular formula	Synonyms	CAS#	EINECS#	RTECS#
Molybdenum	Mo	Metallic molybdenum	7439-98-7	231-107-2	QA4680000
Molybdenite	MoS_2	Molybdenum (IV) sulfide, molybdenum disulfide	1317-33-5	215-263-9	QA4697000
Molybdenum chloride	$MoCl_5$	Molybdenum (V) chloride	10241-05-1	233-575-3	Not specified
Molybdenum trioxide	MoO_3	Molybdenum (VI) oxide, Molybdenum peroxide	1313-27-5	215-204-7	QA4725000
Ammonium molybdate	$(NH_4)_2MoO_4$	Ammonium molybdate (VI), Diammonium molybdate	13106-76-8	236-031-3	QA4900000
Ammonium paramolybdate	$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$	Ammonium molybdate (IV) tetrahydrate	12054-85-2	Not specified	Not specified
Calcium molybdate	$CaMoO_4$	Calcium molybdate (VI), Powellite	7789-82-4	232-192-9	EW2975000
Sodium molybdate	Na_2MoO_4	Sodium molybdate (VI), Disodium molybdate	7631-95-0	231-551-7	QA5075000

Table 2 Chemical and physical properties of the evaluated molybdenum compounds.

	Molybdenum	Molybdenite	Molybdenum chloride	Molybdenum trioxide
Molecular weight	95.94	160.07	273.20	143.94
Physical form	Gray-black or silver-white metal	Black powder or crystals	Grey-black crystals; hygroscopic	White-yellow crystals
Melting point (˚C)	2,623	2,375	194	801
Boiling point (˚C)	4,639	Not specified	268	1,155 sublimates
Density (g/cm^3)	10.2	5.06	2.93	4.70
Vapour pressure	3.47 Pa (2,617 ˚C)	Not specified	Not specified	Not specified
Solubility	Insoluble in water; dilute in acid and alkaline solutions	Insoluble in water; soluble in concentrated acid solutions	Insoluble in water; soluble in ethanol and ethyl ether	Solubility in water: 0.1- 0.5 g/100 mL at 20 °C; soluble in concentrated acid and alkali solutions
	Ammonium molybdate	Ammonium paramolybdate	Calcium molybdate	Sodium molybdate
Molecular weight	196.04	1,235.86	200.02	205.92
Physical form	White to off-white powder	Colourless or green-yellow crystals	White crystals	Colourless crystals
Melting point (˚C)	Decomposes	Decomposes	965; decomposes	687
Boiling point (˚C)	Not specified	Not specified	Not specified	Not specified
Density (g/cm^3)	2.28	2.50	4.35	≈3.5
Vapour pressure	Not applicable	Not applicable	Not applicable	Not applicable
Solubility	Soluble in water, acids and alkaline solutions	Solubility in water, 43 g/100 mL at 20°C; insoluble in ethanol	Solubility in water, 9.5 mg/100 mL at 20°C; soluble in conc. acid solutions	Solubility in water, 44 g/100 mL at 20°C; Solubility of sodium molybdate dihydrate, 65 g/100 mL at 20°C

2.3 EU classification and labelling

Based on Regulation (EC) No 790/2009, which is an adaption of Regulation (EC) No 1272/2008 of the European Parliament, and of the Council on Classification, labelling and packaging of substances and mixtures (16 December 2008), molybdenum trioxide was given the hazard statement codes:

- H319: causes serious eye irritation
- H335: may cause respiratory irritation
- H351: suspected of causing cancer.

According to the same regulation molybdenum trioxide is classified in carcinogenic category 2 ("suspected human carcinogen").

No hazard statement codes or classifications have been assessed by the European Commission, regarding other molybdenum compounds evaluated in this report.

2.4 Analytical methods

In the Netherlands, a method for monitoring and identifying metals in workplace air is used according to ISO 15202 (International Organization for Standardization).[5] In the United States of America, both the National Institute for Occupational Safety and Health (NIOSH), and the Occupational Safety and Health Administration have described methods for sampling soluble or insoluble molybdenum compounds. This includes the use of a 0.8 μm mixed cellulose ester filter, or a low tare weight ash polyvinyl chloride filter, respectively, to be used in a 37-mm cassette filter holder estimating the 'total dust' fraction. Within Europe, size fractions for measurement of airborne particles in workplace atmospheres have been standardized (reference: EN 481: Workplace atmospheres – size fraction definitions for measurement of airborne particles, 1993, Brussels, CEN). In this standard, three fractions have been defined (inhalable, thoracic, and respirable fraction).

In general, molybdenum is identified using atomic absorption spectroscopy, or inductively coupled argon plasma – atomic emission spectroscopy (ICP-AES). The latter method is also proposed by NIOSH for identifying metals in biological samples, such as in the urine, blood and tissue. Identification of molybdenum in air or biological samples can also be done by using instrumental neutron activation analysis.[6]

Chapter 3

Sources

3.1 Natural occurrence

Molybdenum is found in the earth's crust as a natural element. The compound is contained in various minerals, the most important being molybdenite. Molybdenite can occur as the sole mineral in an ore body, but is often found as a by-product of other ores, such as copper and tungsten ores. Molybdenite is principally obtained from its natural resources by mining, the largest producers being found in the United States.

Since molybdenum minerals are present everywhere in soil and natural water resources – although in low levels –, secondary natural sources of exposure may be the consumption of certain vegetables and drinking water. Also combustion of coal and municipal sewage sludge may pose a source of exposure.[1,3]

3.2 Man-made sources

*3.2.1 Extraction and processing**

Molybdenite ores and other ores containing molybdenite are recovered by mining in open pits or underground mining. The extracted rocks containing the ores of interest are then crushed and ground into powder. Using flotation, the

* Source: International Molybdenum Association (IMOA), www.imoa.info.

molybdenite minerals are separated from gangue, reaching a molybdenite concentration of between 85% and 92%. If necessary, also acid leaching is used to remove copper and lead impurities.

In the next process molybdenite is roasted into technical grade molybdenum trioxide. Part of the technical grade molybdenum trioxide is then further processed into pure molybdenite (using sublimation), or into a wide range of pure molybdenum chemicals, such as molybdates (using wet chemical processes). Metallic molybdenum is produced by hydrogen reduction of pure molybdenum trioxide or ammonium molybdate.[3]

3.2.2 *Use**

The vast majority of molybdenum is used in metallurgical applications, such as stainless steel and cast iron alloys. The addition of molybdenum to steel alloys improves the strength and thermal resistance of the alloy, and reduces the corrosive potential. Furthermore, metallic molybdenum enhances the adherence of siliceous material to metals and is, therefore, useful in metal-ceramic composites. Molybdenum trioxide is used as a corrosion inhibitor, and as a blue dye for ceramic glazes and enamels. Molybdenite is applied in dry lubricants and chemical catalysts. Molybdenum salts are used in fertilizers (2-6 ppm molybdenum) for leguminous plants. Ammonium tetrathiomolybdate is a chelating agent used in patients having elevated concentrations of copper (Wilson's disease).[1]

* Source: International Molybdenum Association (IMOA), www.imoa.info.

Chapter 4

Exposure

4.1 General population

The major source of exposure to the general population is consumption of plant-based foods and drinking water. The molybdenum content in the plant-based foods depends on the content of the soil in which the plants are grown, and the type of plants. Certain legumes, grain products, and nuts are the major contributors of dietary molybdenum, whereas animal products, fruits, and many other vegetables are generally low in molybdenum.[7,8]

- *Urban air.* Minimal concentrations of molybdenum of 0.01 to 0.03 μg/m^3 have been reported in urban air.[9]
- *Surface and drinking water.* In US surface waters, concentrations of molybdenum have been reported ranging from 0.002 to 1.50 mg/L (mean 0.06 mg/L).[7] Molybdenum concentrations in drinking water are worldwide typically less than 0.01 mg/L, although in areas near mining sites, the molybdenum concentrations may reach up to 0.20 mg/L.[8,9]
- *Food products*. Highest levels of molybdenum have been reported to be: 0.96 mg/kg fresh weight in nuts; 0.31 mg/kg fresh weight for canned vegetables; and, 0.23 mg/kg fresh weight for cereals.[8,10]
- *Average daily intake*. From household food surveys, it is estimated that the average daily intake ranges between 0.09 and 0.28 mg per day.[11-13]

Note: Molybdenum is an essential trace element, which acts in human and animal metabolism as a cofactor for several enzymes, such as sulfite oxidase, xanthine oxidase, and aldehyde oxidase, and as an electron transport agent.[8,9,14,15] These enzymes catalyze basic metabolic reactions in the carbon, sulphur and nitrogen cycles. The American Institute of Medicine set an estimated average requirement at 0.034 mg per day for adults.[8]

4.2 Working population

Table 3 summarizes exposure levels in the workplace of various industries. Overall, data are limited and sometimes incomplete. As shown in the table exposure levels differ considerably, depending on industry and sampling characteristics.

Table 3 Occupational exposure levels.

Source of exposure	Job activities	Sampling characteristics	Exposure levels (in µg/m^3)
Russian steel foundry (Goljakova 1971 [in Russian]; cited in 16)	Production of steel containing • 4% molybdenum • 17% molybdenum • Not specified	Molybdenum content in • air samples • air samples • air samples within breathing zone of workers *Note*: Exposure and sampling characteristics not further specified.	 • 1,390 (average) • 5,400 (average) • 220 (average; with peaks up to 500)
Russia (Moglevskaya 1963 [in Russian]; cited in 14,16-18)	Workers (N=19) exposed to molybdenum and molybdenum trioxide. No further specifications given.	Concentration molybdenum in workplace air. No further specifications given.	1,000-19,000
Russian mining and metallurgy industry (Eolajan 1965 [in Russian]; cited in 16,18)	Miners and metallurgy workers. No further specifications given.	Molybdenum and molybdenum trioxide. Exposure and sampling characteristics not specified.	60,000-600,000
US molybde-num roasting plant where molybdenum sulphide is converted to molybdenum oxides; Colorado[19]	N = 25 workers: • Base of the roaster • 7.3 m away from roaster • 13.4 m away from roaster • Base of the roaster • 7.3 m away from roaster • 13.4 m away from roaster	Molybdenum content in: • respirable dust, area sample • respirable dust, area sample • respirable dust, area sample • total dust, area sample • total dust, area sample • total dust, area sample • Soluble molybdenum in total dust (8-hr TWA), area sample	 • 1,020 • 1,580 • 4,490 • 3,040 • 9,110 • 33,280 • 9,470

Swedish industrial vacuum furnace production factory[15]	Processing of sintered and laminated molybdenum sheet metal:	Molybdenum content in total dust:	
	• grinding	• Personal (N=1), 200 minutes sampling time	• 1,500 – 2,000
	• grinding, cutting, heating	• Personal (N=1), 70 minutes sampling time	• 7,900
	• area sampling	• Stationary air sampling, 300 minutes sampling time	• 700
Production of stainless steel vessels, Czech Republic[6]	• Welding	• Personal; total suspended particulate matter (N=15)	• 0.27-9.7 (median 1.45)
	• Polishers	• Personal; total suspended particulate matter (N=9)	• 0.03-4.2 median 0.82)
	• Others	• Personal; total suspended particulate matter (N=15)	• 0.14-0.60 (median 0.32)
	• All	• Area; particle equivalent aerodynamic diameter 2-10µm	• 0.02-0.09 (median 0.03)
	• All	• Area; particle equivalent aerodynamic diameter <2µm	• 0.09-0.50 (median 0.15)
	Exposure to welding fumes and airborne particulate matter originating from various activities in the production of stainless steel vessels, mainly polishing and shaving.	*Note*: workers involved in polishing were equipped with respirators, while welders did not use them. Welding and polishing workplaces were equipped with local exhausts.	
Finnish stainless steel melting shop[20]	In a melting shop ferrochrome was combined with alloying materials, such as nickel and molybdenum.	• Personal sampling • Stationary area sampling Sampling characteristics of molybdenum not further specified.	• 0.3 median; 2.3 maximum • 0.6 median; 4.0 maximum

Chapter 5

Kinetics

5.1 Absorption

Overall, reports suggest that soluble molybdenum compounds are readily absorbed, whereas insoluble compounds are not. A brief summary is given below.

5.1.1 Inhalation

No human data are available on inhalation exposure.

In one animal study published in 1945, guinea pigs were used for a short-term inhalation study to test for tissue distribution and gross pathology.[21] The animals (24-25 animals per group) inhaled high amounts of dust containing molybdenum trioxide (average concentration of 205 mg molybdenum/m^3, corresponding to 310 mg molybdenum trioxide/m^3), molybdenite (286 mg molybdenum/m^3, corresponding to 607 mg molybdenite/m^3), or calcium molybdate (159 mg molybdenum/m^3, corresponding to 388 mg calcium molybdate/m^3). Exposure was performed for one hour per day, five days per week for a total of five weeks. At the end of the exposure period half of the animals were killed for analysis of molybdenum content in various tissues organs (i.e., the liver, kidneys, lungs, spleen and bones). The other half of the animals were allowed to live for two weeks longer, with no molybdenum exposure,

before they were also sacrificed. Data were compared with non-exposed controls.

After exposure, molybdenum trioxide dust was found in all tissues examined (the highest amounts in the kidneys and bones). Calcium molybdate was mainly found in the lungs, the kidneys and bones. Molybdenite dust gave merely negative results (according to the authors, no data presented). The authors also reported on exposure to molybdenum sulphide. High levels of molybdenum sulphide were found in the lungs, but levels of molybdenum in the liver, kidneys, spleen and bones did not exceed the levels found in non-exposed animals. The authors considered molybdenum sulphide as a very insoluble compound, and molybdenum trioxide dust (and fume) as soluble compounds. No quantitative data or further details were presented on how much of the molybdenum compounds were actually absorbed by the lungs.

5.1.2 Oral intake

Giussani et al. (2006) investigated the intestinal absorption of molybdenum in seven healthy volunteers by simultaneous oral administration (water, tea or composite meals), and intravenous injection, of stable isotopes of molybdenum.[22] For this, isotopic solutions were prepared using metal molybdenum powders enriched in ^{95}Mo and ^{96}Mo, respectively. Their results indicated that molybdenum ingested in orally (in liquid form) was rapidly and totally absorbed into the circulation. The rate and extent of absorption depended on the composition of the meals. A comparable result was reported by Werner et al. (1998).[23]

Turnlund et al. (1995) investigated molybdenum absorption, excretion and retention with stable isotopes, in four healthy volunteers.[24] They were given a low-molybdenum diet (22 µg/day) for 102 days, followed by the same diet supplemented with molybdenum (ammonium paramolybdate dissolved in deionized water) to contain 467 µg/day for another eighteen days. The stable isotopes ^{100}Mo (prepared for diet), ^{97}Mo (prepared for intravenous injections) and ^{94}Mo (used as an isotopic diluents) were used as tracers. The isotopes were purchased as metal powders. The oral absorption of ^{100}Mo averaged 88% in the low-molybdenum diet, and 93% in the high-molybdenum diet. Turnlund also studied molybdenum kinetics after consumption. Using a comparable design as the previous study, and using compartmental kinetic models, it was estimated that the residence time for molybdenum in the gastro-intestinal tract was at 1.7 ± 0.4 days; in plasma molybdenum retention time averaged 22 ± 4 minutes,

whereas slow-turn-over tissue (possibly hepatic) retention averaged 58 ± 16 days.[25]

In various animal species (e.g., guinea pigs, rabbits) absorption of ingested soluble and insoluble molybdenum compounds was reported, the absorption being dependent on solubility and diet composition, and varying between 40 and 85%.[10,14,21,26]

5.1.3 Dermal uptake

Sodium molybdate dihydrate was tested in vitro for dermal absorption using skin membranes according to OECD guideline 428*. Doses applied to the skin were 105 and 542 µg/cm^2. The percentage of the doses absorbed by the skin, including stratum corneum were 0.21 and 0.16% (after eight hours of exposure and 16 hours post-exposure monitoring). No other human or animal data available.

5.2 Distribution

In humans and various animal species, molybdenum is present in low concentrations in all the fluids and tissues in the body; in plasma, molybdenum is bound to α_2-macroglobulin in the form of molybdate.[1] The greatest amounts are found in the kidneys, liver, and the bones; with smaller levels in the adrenal glands.[10,14,21,26]

Overall, substantial individual variation in the molybdenum blood level occurs, because plasma molybdenum reflects molybdenum intake by food and water products.[13] Average plasma concentrations range between 0.3 to 1.1 µg/L (3 to 11 nmol/L).[1,3,9,13] This level may increase up to 400 µg/L in persons near areas rich in molybdenum or near molybdenum mining centers.[9]

There is no apparent bioaccumulation of molybdenum in human or animal tissue, and when exposure is withdrawn, the tissue concentrations quickly return to normal.[9]

Molybdenum can cross the placental barriers, and is furthermore found in human milk, with a concentration in the milk ranging from 1 to 35 µg/L.[1,7,10,27-29]

5.3 Biotransformation and metabolism

No data are available on the biotransformation of molybdenum compounds.

* Data obtained from the European Chemicals Agency: //echa.europa.eu/.

The metabolism of molybdenum is related to copper and sulphur metabolism; molybdenum salts are capable of inhibiting absorption of copper in the intestines through yet partly unknown mechanisms.[9]

5.4 Elimination

Under normal exposure conditions, molybdenum intake and excretion are balanced in humans and animals. The excretion is rapid, and is enhanced by the presence of high dietary levels of copper and sulphate, and, furthermore, by increased exposure to the compound itself.[9,3] Taking these factors into account, in humans, percentages of urinary excretion ranged between 17 and 80% of the dose.[9,21] Referring to the study by Turnland et al. (1995; see Section 5.1.2), of the dose molybdenum fed during intake of the low-molybdenum diet (in the form of ^{100}Mo), in a twelve day period, 20% was excreted in the urine, 12% in the feces, and 68% remained in the body.[24] The excretion percentages of ^{100}Mo in the group fed high-molybdenum diet, were 71% (in the urine) and 7.3% (in the feces); the percentage retention in the body was 21%. In animals percentages of urinary excretion of between 36 and 90% have been reported.[9,21] The kidneys are the main route of excretion. Furthermore, kinetic modelling suggested that low intake resulted in adaptation to conserve body molybdenum, whereas high intake results in increased elimination of molybdenum.[30,31]

The blood half-life for molybdenum may vary from several hours in laboratory animals up to several weeks in humans.[1,9]

5.5 Biological monitoring

NIOSH has described methods for the identification of metals in urine, blood and tissue, using inductively coupled argon plasma – atomic emission spectroscopy (ICP-AES). The identification of molybdenum in biological material can also been done using instrumental neutron activation analysis (INAA).[6]

Chapter 6

Mechanism of action

Several reviews have been published in which the mechanisms of toxic actions of molybdenum are discussed.[1,3,9,16,32,33] Overall, the available data are limited, and it is not always clear whether humans or animals have been studied. It is known that ruminants (e.g., cattle, goats, sheep) are more sensitive in developing symptoms of toxicity than non-ruminant monogastric animals (e.g., humans, rodents, poultry). This is probably due to a higher dietary copper requirement in ruminants. A summary of the main findings in the reviews is given below.

6.1 Copper deficiency

In ruminants, excess molybdenum intake can induce secondary copper deficiency, which may be enhanced by high dietary sulphate intake. In the gastro-intestinal tract micro-organisms convert sulphate in sulphide, which on its turn forms insoluble complexes with molybdenum (thiomolybdates). Next, these thiomolybdates form insoluble complexes with copper, thus leading to reduced absorption of copper. The absorption of copper may be further reduced by the fact that high levels of sulphide may form insoluble complexes with copper itself.

When copper is absorbed, it is transported through the blood to all body parts by binding to ceruloplasmin, a plasma α-globulin. Smaller amounts are bound to albumin, but the copper bound to this plasma protein is not bioavailable. Thiomolybdates bind also to albumin, and this new formed complex has a high

affinity for copper. The consequence is that less copper is bound to ceruloplasmin, resulting in reduced bioavailability, and a higher risk of copper deficiency.

Copper deficiency in humans is rare. However, in one Russian study, investigators reported liver dysfunction with hyperbilirubinemia among workers, who were chronically exposed to molybdenum, which was explained by the rise of free α-globulins (e.g., ceruloplasmin).[3] Furthermore, Walravens et al. (1979) showed that free plasma ceruloplasmin levels (and uric acid levels) were higher in workers exposed to soluble molybdenum compounds (including molybdenum trioxide), compared to unexposed controls.[19] The workers were exposed to airborne concentration of molybdenum of 9.5 mg/m^3 (8h-TWA). However, urinary copper levels were normal. That molybdenum can increase free plasma ceruloplasmin was also demonstrated in patients having Wilson's disease. The disease is characterized by decreased free ceruloplasmin. Treatment with tetrathiomolybdate successfully increased free plasma levels of ceruloplasmin.

Molybdenum is an essential cofactor for several enzymes, such as sulphite oxidase.[1,34,35] The enzyme oxidizes sulphite into sulphate. Therefore, it is conceivable that excess intake of molybdenum may increase the formation of sulphate. Sulphate has a double role in molybdenum induced copper deficiency, in that it inhibits gastrointestinal absorption of molybdenum by blocking its carrier proteins, and – after absorption – accelerates excretion of molybdenum by inhibiting tubular resorption of molybdenum from the kidneys (at least in animals, such as rats, rabbits and poultry).[1,34,35]

Molybdenum can inhibit sulphide oxidase (present in the liver), resulting in higher levels of sulphide in tissue. These sulphides can form insoluble copper-sulphide complexes, and, therefore, may induce copper deficiency.[1,34,35]

6.2 Gout

Molybdenum is also an essential cofactor in the enzyme xanthine oxidase. Excess intake of molybdenum may stimulate the activity of this enzyme. Xanthine oxidase converts xanthine into uric acid (by oxidation), which is excreted as urate in urine. High amounts of uric acid may crystallize in the joint, which can result in gout-like diseases and other bone/joint disorders. Higher levels of uric acids have been reported after airborne exposure to soluble molybdenum compounds in workers, who were exposed to 9.5 mg molybdenum/m^3 (8h-TWA).[19] In another study, no change in uric acid excretion was found when people took up to 1.54 mg molybdenum per day by diet.[36]

Chapter 7

Effects

7.1 Observations in humans

Few data are available on human toxicity due to excess exposure to molybdenum and molybdenum compounds.

7.1.1 Irritation and sensitization

Dueva and Stepanian (1989) reported that approximately twenty percent of 352 Russian workers, who were engaged in molybdenum productions, showed signs of work-related dermatoses.[37] The study was published in Russian, and no further details in English were available.

7.1.2 Acute and short-term toxicity

No relevant data available.

7.1.3 Non-carcinogenic long-term toxicity

Several studies have been presented on the working and general population without information on exposure data, and lacking non-exposed groups as controls. Furthermore, not always simultaneous exposure to other potentially toxic compounds could be excluded. A number of these studies were published

in Russian, of which a brief English description was found only in reviews. For completeness, a brief summary of these limited studies is given in Table 4.

In two studies, non-exposed control groups were included, and clear descriptions were given on exposure and/or effect measurements. The first is Walravens et al. (1979), who examined twenty-five male workers from a molybdenum roasting plant, and twenty-four controls, who were not exposed.[19] Respirable particles mainly consisted of molybdenum trioxide and other undefined soluble oxides of molybdenum. The 8-hour TWA, measured as molybdenum in respirable dust, was 1.6 mg/m^3, and measured as molybdenum in total dust, 9.5 mg/m^3 (stationary sampling). Medical complaints were reviewed by medical questionnaires. Seven workers had no complaints. The others reported joint pain, back pain, headache, diarrhea, and/or nonspecific hair or skin changes. Pulmonary lung function tests revealed a mild decrease in FEV_1 in three workers (72-76% of control), and a marked decrease in two workers (67-68% of control), indicative of mild obstructive lung disease. No evidence for molybdenum-induced gout was found.

Table 4 Summary of the epidemiological studies on molybdenum-related adverse health effects, with limitations in design or descriptions of the results.

Study population	Findings	Reference
General population		
Adult Armenian villagers *a)* 10-15 mg molybdenum/day, 5-10 mg copper/day; n=184 *b)* 1-2 mg molybdenum /day, 10-15 mg Cu/day; n=78.	Gout-like symptoms (pain, swelling, inflammation and joint deformities), and increased blood uric acid levels were observed in 57/184 subjects (31%) and in 14/78 control subjects (18%). Both plasma molybdenum and plasma xanthine oxidase activity were positively correlated with plasma uric acid levels. Increasing urinary copper excretion was positively related to increasing plasma molybdenum levels.	Kovalskii et al. (1961); cited in [1,3,7,9,14,16-18], summarized in [38]
Working population		
Russian workers from a copper-molybdenum processing plant.	Increased levels of uric acid in the blood, and symptoms of arthralgia. No quantitative data on the workers and the exposure available.	Akopian et al. (1964); cited in [3,14,17]
Russian miners (n=500) exposed to dust with 60-600 mg molybdenum/m^3, and unknown levels of copper.	In many miners, non-specific symptoms such as weakness, fatigue, anorexia, headaches, pains in the joints and muscles, tremor of hands and general central nervous system effects were noted. Symptoms may be caused by co-exposure to other potentially toxic substances.	Eolian (1965); cited in [14,16,18]
Russian workers (n=19): man: 6-19 mg molybdenum/m^3 and molybdenum trioxide for 4-7 yrs; women: 1-3 mg molybdenum/m^3 and molybdenum trioxide for 5 yrs.	All workers were symptomatic and 3 out of 19 had X-ray findings indicative of pneumoconiosis. The symptoms included breathing difficulties, chest pain and general fatigue. The information and findings of this study are however insufficient to conclude that the condition of the three workers was due to their work environment or that molybdenum was the causative agent.	Mogilevskaya (1967); cited in [9,14,16-18,39]

Finnish steel melting shop workers. Personal: median 0.3 µg molybdenum/m^3 (maximum 2.3 µg/m^3); Area: median 0.6 µg molybdenum/m^3 (maximum 4.0 µg/m^3).	The molybdenum levels were considered to be low. The authors concluded that an average exposure time of 23 years in modern ferrochromium and stainless steel production, with low exposure to dusts and fumes containing hexavalent and trivalent chromium, nickel and molybdenum, did not lead to respiratory changes detectable by lung function tests or radiography. Note: co-exposure to other potentially toxic substances is likely.	Huvinen et al. (2002)[20]
One Swedish industrial furnace maker (age 36). Personal: 1.5-7.9 mg molybdenum/m^3. Area: 0.7 mg molybdenum/m^3	Subject had symptoms of acute arthritis with high plasma uric acid (564 µmol/L) levels. Gout was treated but nausea and hyperhydrosis stayed. Subject did not improve after cessation of the occupational molybdenum exposure. The authors stated that the association between molybdenum exposure and gout may be circumstantial.	Seldén et al. (2005)[15]

Plasma levels of molybdenum ranged between 9 and 365 ng/mL in workers, and between <5 to 34 ng/mL in controls; also plasma uric acid and ceruloplasmin levels were on average higher in workers than in controls (workers *versus* controls: uric acid, 59 *versus* 50 mg/mL, $p<0.025$; ceruloplasmin, 505 *versus* 305 mg/mL, $p<0.005$). In urine, molybdenum levels were elevated in workers (workers *versus* controls: 120-11,000 *versus* 4-347 µg/L), but copper levels were normal (<40 µg/L). The authors remarked that variations in plasma and urine levels could be explained by differences in collection time among the workers. Also they noted the high turnover rate of the workers, which rendered epidemiological study difficult.

The second is Ott et al. (2004), who investigated respiratory symptoms and bronchoalveolar lavage abnormalities (BAL) among 43 Austrian workers from a metal plant, of which 33 suffered from respiratory symptoms.[40] The study also included 23 non-exposed controls. No exposure measurements were performed, but the authors stated that all the workers were exposed to a similar level of molybdenum trioxide particles in air. The most common symptoms reported, included chest pain, dyspnoea, and cough. None of the exposed workers showed firm radiological signs of interstitial lung disease. In lung function testing, symptomatic and asymptomatic workers did not significantly differ; both groups showed a higher FEV_1 and FVC than the control group ($p<0.05$). In BAL cytology of exposed symptomatic workers, higher counts of lymphocytes ($p<0.001$) and neutrophils ($p<0.01$); lower counts of alveolar macrophages ($p<0.01$); and a higher CD4/CD8 positive T-lymphocytes ratio ($p<0.05$) were found, compared with asymptomatic and control workers. This finding may represent a molybdenum trioxide-induced subclinical alveolitis.

In a two-year drinking-water study among residents from two Colorado cities (Denver and Golden), Chappell et al. (1979) evaluated the effects of ingestion of (unspecified) molybdenum.[34] The Denver residents (n=42) consumed 2 to 50 µg molybdenum per litre drinking water, whereas the Golden residents (n=13) consumed at least 200 µg per litre drinking water. No adverse health effects were observed that could be related to molybdenum exposure in any of the residents. Plasma molybdenum levels were within the normal range; however, mean free plasma ceruloplasmin levels and urinary molybdenum levels were higher among the Golden residents than the Denver residents (ceruloplasmin, 403 *versus* 304 mg/L; urinary molybdenum, 187 *versus* 87 µg/day).

7.1.4 *Carcinogenicity*

Droste et al. (1999) investigated the relationship between lung cancer and exposure to occupational carcinogens in a general case-control study in an industrial region of Belgium.[41] A total of 478 lung cancer patients and 536 controls were interviewed. Based on job task exposure, the investigators reported 52 cases with an association between occupational exposure to molybdenum and lung cancer, with an adjusted odds ratio of 2.1 (95% confidence interval, 1.2-3.7). Dividing the 52 cases in four groups by duration of exposure, only the persons who had been exposed for more than 21 years to molybdenum (n=19) showed significantly elevated odds ratios (3.3; 95% confidence interval, 1.3-8.3). It is, however, difficult to relate lung cancer cases to molybdenum exposure, because of concomitant exposure to other potentially carcinogenic substances and metals.

In a population-based study, Nakadaira et al. (1995) tried to correlate selenium and molybdenum exposure to cancer mortality in the general population.[42] Although they found a positive correlation with female cancer mortality of the pancreas, and inverse correlations with female cancer mortality of the oesophagus and rectum, no clear conclusion can be drawn from this study. This is due to a lack of reliable information on daily intake, and unknown other sources of cancer risk.

Suggestions have been made that oesophageal cancer in South Africa, China, and Russia, could be attributed to a low intake of molybdenum.[43] However, in at least one study, no such an association could be made.[43]

7.1.5 *Genotoxicity*

Cytogenetic damage, measured as chromosome aberrations and sister-chromatid exchanges, was increased in lymphocytes of workers in a metallurgical plant, with more than 10 years of occupational exposure to molybdenum, molybdenite, and molybdenum trioxide (Babaian et al. 1980; Bobyleva et al. 1993; cited in[39]).[44,45] The Committee noted that most likely the workers were exposed to several other potentially harmful metals.

7.1.6 *Reproduction toxicity*

In 2008, Meeker et al. reported on semen quality (sperm count, sperm concentration, percent motile sperm, and sperm morphology), and metals in blood among men recruited through fertility clinics (N=219).[46] They found molybdenum-dependent decreases in sperm concentration and normal morphology, when adjusted for age, current smoking, and the impact of multiple metals on semen quality simultaneously (odds ratios (OR) for sperm concentration: metal percentile 70-85th, 2.2 (95% confidence interval (CI), 0.7-7.6); metal percentile >85th, 6.26 (95% CI, 1.6-25.0). OR for sperm morphology: metal percentile 70-85th, 0.9 (95% CI, 0.4-2.2); metal percentile >85th, 3.4 (95% CI, 1.2-9.7)).

Two years later, Meeker et al. reported on reproductive hormone levels (serum FSH, LH, inhibin B, testosterone, and SHBG) among the same group of men.[47] The authors found a significant inverse trend between molybdenum concentrations in blood and testosterone levels, also when correcting for exposure to other metals. They also found an interaction between high molybdenum levels and low zinc levels. In addition, 37% of men with a low zinc level had a reduction in testosterone levels.

No other investigations have been presented in which adverse effects of molybdenum and molybdenum compounds on fertility, and development of progeny, in humans was examined.

7.2 Effects in laboratory animals

7.2.1 *Mortality after single exposure*

In Table 5, data on mortality are shown of animals exposed once-only to metallic molybdenum compounds.

Table 5 Data on mortality in animals after a single exposure to molybdenum or molybdenum compounds.

Compound	Route of exposure	Animal species	Mortality	Concentration (mg molybdenum per m^3 or kg bw)	Exposure design	Source
Molybdenum trioxide dust	Inhalation	Rat	0% (at 4 weeks)	12,000 - 15,000 mg/m^3	Single exposure for one hour	ACGIH 2003[48]
Ammonium paramolybdate dust	Inhalation	Rat	0% (at 4 weeks)	3,000 - 5,000 mg/m^3	Single exposure for one hour	ACGIH 2003[48]
Molybdenum trioxide[a]	ip	Guinea pig	75% (at day 4) 75% (at 4 weeks) 75% (at 4 months)	Approx. 400 mg/kg bw	N=8; single injection	Fairhall 1945[21]
Ammonium molybdate[a]	ip	Guinea pig	100% (at 4 days) 100% (at 4 weeks) 100% (at 4 months)	Approx. 800 mg/kg bw	N=12; single injection	Fairhall 1945[21]
Sodium molybdate	ip	Rat	100%	114-117 mg/kg bw	Single injection	Maresh et al. 1940 (source ACGIH 2003)[48]
Metallic molybdenum dust	Inhalation	Rat	0% (at 4 weeks)	25,000 to 30,000 mg/m^3	Single exposure of one hour	ACGIH 2003[48]
Molybdenite[a]	ip	Guinea pig	17% (at 4 days) 17% (at 4 weeks) 25% (at 4 months)	Approx. 800 mg/kg bw	N=12; single injection	Fairhall 1945[21]
Calcium molybdate[a]	ip	Guinea pig	0% (at 4 days)0% (at 4 weeks) 17% (at 4 months)	Approx. 400 mg/kg bw	N=6; single injection	Fairhall 1945[21]

[a] Data from one and the same experiment, intraperitoneal (ip) injection, guinea pigs (Fairhall 1945).

7.2.2 *Irritation and sensitization*

Exposure to sodium molybdate causes skin and eye irritation. Molybdenum trioxide also irritates the respiratory tract. No skin or eye irritation was observed upon exposure to calcium and zinc molybdate.[14,49,50] No data are available on irritation of the respiratory tract after inhalation of molybdenum or molybdenum compounds.

Molybdenum chloride was identified as sensitizer in the Guinea Pig Maximization Test.[49] At the highest challenge concentration that did not cause erythema in non-sensitized animals, 13 out of 20 sensitized animals showed reactions at 24 hours after challenge, and 10 out of 20 sensitized animals at 48 hours after challenge.

The results of a study by Abdouh et al. (1995) were in line with this finding.[51] Using the auricular lymph node assay in C57B1/6 mice, in which the compound was applied topically on the dorsum of both ears at different concentrations (0.1-5.0%), for three consecutive days, statistically significant

and dose-related increases in the weight, and cellularity of the draining auricular lymph node weight were noted. The authors argued that the increase in the cell numbers and weight of the auricular lymph nodes may have been nonspecific, because they did not observe T-cell activation. However, it should be noted that the lymph node test performed by Abdouh et al. was not according the current guidelines for performing the Local Lymph Node Assay, and in addition, that a shift in T-cell activation in the lymph node is not a criterion for the identification of sensitizers.

No data are available on (specific/nonspecific) sensitization of molybdenum or molybdenum compounds after inhalation.

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Table 6 Summary of data on mortality in animals after short-term repeated exposure to molybdenum or molybdenum compounds.

Compound	Route of exposure	Animal species	Mortality	mg molybdenum per m^3 or kg bw	Exposure design	Source
Molybdenum trioxide aerosol[a]	Inhalation	Rat	0%	Up to 300 mg/m^3	N=5/sex; 6 hrs/day, 5x/week,14 days	NTP 1997[43]
Molybdenum trioxide aerosol[a]	Inhalation	Rat	0%	Up to 100 mg/m^3	N=10/sex; 6.5 hrs/day, 5x/ week,13 weeks	NTP 1997[43]
Molybdenum trioxide aerosol[a]	Inhalation	Mouse	0%	Up to 300 mg/m^3	N=5/sex; 6 hrs/day, 5x/week,14 days	NTP 1997[43]
Molybdenum trioxide aerosol[a]	Inhalation	Mouse	0%	Up to 100 mg/m^3	N=10/sex; 6.5 hrs/day, 5x/ week,13 weeks	NTP 1997[43]
Molybdenum trioxide dust[b]	Inhalation	Guinea pig	51%	Approx. 205 mg/m^3	N=24; 1 hr/day, 5x/week, five weeks.	Fairhall 1945[21]
Molybdenum trioxide fume[b]	Inhalation	Guinea pig	8.3%	Approx. 191 mg/m^3	N=25; 1 hr/day, 5x/week, five weeks.	Fairhall 1945[21]
Ammonium paramolybdate aerosol[c]	Inhalation	Rat	100% (at 30 days)	500 - 2,500 mg/m^3	One hour daily for 30 days	Mogilevskaya 1967 (Source ACGIH 2003)[48]
Molybdenum trioxide[d]	Oral	Rat	50% (at 120 days)	Approx. 125 mg/kg bw	N=8; daily ingestion	Fairhall 1945[21]
Molybdenum trioxide[e]	Oral	Guinea pig	100% (at 27 days)	Approx. 330 mg/kg bw	N=8; daily ingestion	Fairhall 1945[21]
Ammonium molybdate[b]	Oral	Rat	100% (at 13 days)	Approx. 660-1,250 mg/kg bw/day	N=8; daily ingestion	Fairhall 1945[21]
Ammonium molybdate[b]	Oral	Rat	25% (at 232 days)	Approx. 66-125 mg/kg bw/day	N=8; daily ingestion	Fairhall 1945[21]

Metallic molybdenum aerosol[c]	Inhalation	Rat	0% (at 30 days)	12,000 tot 15,000 mg/m^3	One hour daily for 30 days	Mogilevskaya 1967 (Source ACGIH 2003)[48]
Molybdenite dust[b]	Inhalation	Guinea pig	4.2%	Approx. 286 mg/m^3	N=25; 1 hr/day, 5x/week, five weeks	Fairhall 1945[21]
Calcium molybdate dust[b]	Inhalation	Guinea pig	0.8%	Approx. 159 mg/m^3	N=24; 1 hr/day, 5x/ week, five weeks	Fairhall 1945[21]
Molybdenite[d]	Oral	Rat	0% (at 44 days)	Approx. 3,300 - 6,250 mg/kg bw	N=8; daily ingestion	Fairhall 1945[21]
Calcium molybdate[d]	Oral	Rat	50% (at 137 days)	Approx. 101 mg/kg bw/day	N=10; daily ingestion	Fairhall 1945[21]
Calcium molybdate[d]	Oral	Rat	100% (at 128 days)	Approx. 232 mg/kg bw/day	N=10; daily ingestion	Fairhall 1945[21]
Calcium molybdate[e]	Oral	Guinea pig	25% (at 95 days)	Approx. 280-420 mg/kg bw	N=8; daily ingestion	Fairhall 1945[21]

[a] Data from one and the same experiment, inhalation, rats and mice (NTP 1997).
[b] Data from one and the same experiment, inhalation, guinea pigs (Fairhall 1945).
[c] Data from one and the same experiment, inhalation, rats (Mogilevskaya 1967).
[d] Data from one and the same experiment, oral, rats (Fairhall 1945).
[e] Data from one and the same experiment, oral, guinea pigs (Fairhall 1945).

7.2.3 *Short-term toxicity*

Mortality

In Table 6, a summary of data on mortality is given, which were obtained from short-term animal studies. Symptoms included diarrhea, coma, and death from cardiac failure.[43]

In a short-term study, rats were fed daily molybdenum compounds at various doses for up to 232 days.[21] A computation of the relative toxicities of the compounds revealed oral LD_{50} values of approximately 125, 101, and 333 mg molybdenum/kg bw, for molybdenum trioxide (after approx. 120 days in test), calcium molybdate (after approx. 135 days in test), and ammonium molybdate (no data given), respectively.

Inhalation exposure

The US National Toxicology Program performed a series of inhalation studies on molybdenum trioxide, using F344/N rats and B6C3F$_1$ mice of both sexes.[43]

In a first study, the animals (N=5/group/sex) were exposed to the compound at a concentration of 0, 3, 10, 30, 100, and 300 mg molybdenum trioxide/m^3 (in aerosol) for six hours a day, five days a week for a total of two weeks. Statistically significant weight loss was observed in all animals, which were exposed to 300 mg/m^3, and in male rats exposed to 100 mg/m^3. No local or systemic toxicity was observed. Haematology and clinical chemistry were not investigated.

In a second study, the animals (N=10/group/sex) were exposed to the compound at a concentration of 0, 1, 3, 10, 30, and 100 mg molybdenum trioxide/m^3 (in aerosol) for six and a half hours a day, five days a week for a total of thirteen weeks. No effects on body weight (gain) were observed. No mortality and no clinical findings or pathological lesions related to molybdenum exposure were observed. No significant differences in absolute or relative organ weights, haematology or clinical chemistry parameters were observed either.

Fairhall et al. (1945) exposed guinea pigs (N=24-26/group) to dusts of molybdenum trioxide (205 mg molybdenum/m^3, corresponding to 311 mg molybdenum trioxide/m^3), molybdenite (286 mg molybdenum/m^3, corresponding to 608 mg molybdenite/m^3), and calcium molybdate (159 mg molybdenum/m^3, corresponding to 389 mg calcium molybdate/m^3) for one hour a day, five days a week for a total of five weeks.[21] Molybdenum trioxide exposure caused respiratory irritation, loss of appetite and weight, diarrhea, muscular incoordination, and loss of hair. Daily exposure to molybdenite dust induced increased respiration during exposure, whereas calcium molybdate did not cause any clinical signs of toxicity.

See also Table 8 for a brief summary of animal inhalation studies on non-carcinogenic effects.

Oral exposure

The International Molybdenum Association (IMOA) commissioned two separate animal experiments, in which Sprague-Dawley CD rats were given sodium molybdate dihydrate by gavage or via the diet.[52] In one experiment, the animals (5 animals/sex/ group) were given the compound by gavage (once daily) or in their diet (*ad libitum*), for 28 consecutive days. Doses administered were 0, 4 or 20 mg molybdenum/kg bw/day. Also one group of animals received the compound by gavage twice daily (10 mg/kg bw/administration for a total of 20 mg/kg bw/day). At the end of the treatment, all animals were killed and postmortem examinations, including microscopic pathology, were performed. Analysis of blood samples revealed that molybdenum was present in the system.

The investigators did not find exposure-related adverse effects on any in-life parameters (survival, body and organ weights, food consumption).

In the other experiment, the animals (10 or 20 animals/sex/group) were fed sodium molybdenum dihydrate at doses of 0, 5, 17, and 60 mg molybdenum/kg bw/day, for 91 or 92 days.[53] At the end of the treatment ten animals of each group were killed for postmortem examinations. The remaining ten animals (in groups administered 0 or 60 mg molybdenum/kg bw/day) were allowed to recover for a further 60 days, before they were also killed for postmortem examinations. In males and females, the mean body weight changes from baseline were statistically significantly decreased at the highest dose level (see Table 7). Furthermore, a statistically significant decrease in absolute body weight was observed among male animals from the highest dosed group. These reductions were partially explained by lower food intake. Furthermore, microscopic examinations revealed slight diffuse hyperplasia of the proximal tubules in the kidneys of two female rats fed 60 mg molybdenum/kg bw/day.

Table 7 Summary of body weight and body weight gain in rats given sodium molybdate in the diet for 90 days.[53]

	0 mg/kg bw	5 mg/kg bw	17 mg/kg bw	60 mg/kg bw
Mean body weight (grams ± SD)				
Males[a]	587.1 ± 50.3	583.9 ± 41.4	576.3 ± 47.9	498.5 ± 32.9[b]*
Females[a]	296.1 ± 20.5	313.2 ± 32.8	313.2 ± 32.8	279.5 ± 25.2
Mean body weight changes from baseline (grams ± SD)				
Males[a]	246.3 ± 38.9	242.6 ± 37.6	240.1 ±33.9	164.4 ± 30.1[b]*
Females[a]	69.4 ± 15.1[b]	81.2 ± 21.6	82.9 ± 19.4	49.2 ±20.3*

* $p<0.001$. Dose concerns mg molybdenum/kg bw. With permission of IMOA.

[a] n=20 in groups 0 and 60 mg/kg bw; n=10 in groups 5 and 17 mg/kg bw.

[b] n=19 in animals in group.

Bompart et al. (1990) investigated the effect of ammonium paramolybdate on renal function.[54] Male Sprague-Dawley rats (N=7/group) received the compound by gavage at doses of 0, 40, or 80 mg molybdenum/kg bw/day for a total of eight weeks (60 days). Once every two weeks the animals were housed in metabolism cages to collect urine over 24 hours. Statistically significant changes in renal function were only observed in the highest-dose group. The changes included: a lower body weight and absolute kidney weight; a higher relative kidney weight; a reduced urinary creatinine clearance; and, an increased urinary kallikrein excretion (at day 60 only). However, no changes in activity or effects were observed in any of the groups regarding blood pressure, and proximal brush-border enzymes (alanine aminopeptidase, γ-glutamyltransferase). Based on the

results, the authors concluded that the glomerulus and the distal tubule were more sensitive to chronic molybdenum exposure than the proximal tubule.

Groups of eight to ten male white rats received molybdenite, molybdenum trioxide, calcium molybdate or ammonium molybdate added in the diet at levels of 10 to 500 mg per animal (corresponds to approximately 100 to 5,000 mg molybdenum/kg bw, based on an animal weight of 100 gram), for up to 232 days.[21] No signs of toxicity were apparent in rats ingesting molybdenite. However, in rats receiving molybdenum trioxide, calcium molybdate or ammonium molybdate, loss of appetite, weight loss, a rough fur, and a tendency to become quiet and listless, were observed. The Committee noted the high mortality rate of 25% (ammonium molybdate) to 50% (molybdenum trioxide, calcium molybdate) in the lowest-dose groups, up to 100% (all three compounds) in the highest-dose groups. No mortality was observed in the groups receiving molybdenite.

In a limited study, adult and weanling rabbits received sodium molybdate in their diet for up to 4 gram per kg diet (highest dose corresponds to approximately to 120-160 mg molybdenum/kg bw, assuming that a rabbit on average ingests 30 to 40 gram of food per kg bw). They developed anaemia, anorexia, loss of weight, alopecia, slight dermatosis, and defects in the skeletal system.[55] Early mortality in the highest two dose groups (2 and 4 gram molybdenum/kg diet) reached 100%. The Committee noted the very low number of animals per dose group (N=2). It was not possible to recalculate the dose in mg molybdenum/kg bw *per day.*

See also Table 8 for a brief summary of oral animal studies on non-carcinogenic effects.

Table 8 Summary of studies on non-carcinogenic effects in animals, which were exposed to molybdenum and molybdenum compounds.

Compound	Level (mg/m^3 as molybdenum)	Animal species	Exposure design	Health effects
Inhalation				
Molybdenum trioxide aerosol	0, 3, 10, 30, 100, or 300 (in mg molybdenum trioxide/m^3)	Rats and mice (n= 5/group /sex)	6 hrs/day, 5 days/week, two weeks	No local or systemic toxicity found (NTP1997)[43]
Molybdenum trioxide aerosol	0, 3, 10, 30, or 100 (in mg molybdenum trioxide/m^3)	Rats and mice (n= 10/group/ sex)	6.5 hrs/day, 5 days/ week, thirteen weeks	No local or systemic toxicity found (NTP 1997)[43]
Molybdenum trioxide aerosol	0, 10, 30, or 100	Rats and mice (n= 50/group/ sex)	6 hrs/day, 5 days/week, 106 weeks	Signs of pathological respiratory tract effects observed from 10 mg/m^3 onwards (NTP 1997)[43]

Molybdenum trioxide dust	205	Guinea pigs (n=24-26/group)	1 hr/day, 5 days/week, five weeks	Respiratory irritation, loss of appetite and weight, diarrhea, muscular oncoordination, and loss of hair (Fairhall 1945)[21]
Calcium molybdate dust	159	Guinea pigs (n=24-26/group)	1 hr/day, 5 days/week, five weeks	No clinical signs of toxicity found (Fairhall 1945)[21]
Molybdenite dust	286	Guinea pigs (n=24-26/group)	1 hr/day, 5 days/week, five weeks	Increased respiration (Fairhall 1945)[21]
Oral intake				
Molybdenum trioxide	100 to 5,000	Rats (n=8-10/group)	In diet for up to 232 days	Loss of appetite, weight loss, a rough fur, tendency to become quiet and listless; 50% mortality in lowest dose group, 100% in highest dose group (Fairhall 1945)[21]
Ammonium molybdate	100 to 5,000	Rats (n=8-10/group)	In diet for up to 232 days	Loss of appetite, weight loss, a rough fur, tendency to become quiet and listless; 25% mortality in lowest dose group, 100% in highest dose group (Fairhall 1945)[21]
Sodium molybdate dihydrate	0, 4, or 20 mg molybdenum/kg bw	Rats (n=5/group/ sex)	By gavage (once daily), or in diet, for 28 days	No exposure-related adverse health effects found (IMOA, 2011)[52]
Sodium molybdate dihydrate	0, 5, 17, or 60 mg molybdenum /kg bw	Rats (n=10 or 20/ group/sex)	In diet for 90 days; part of animals had recovery period of 60 days	At 60 mg/kg bw: statistically lowered body weight (males), and body weight gain (males and females). No other clear exposure-related effects observed[53]
Ammonium paramolybdate	0, 40 or 80	Rats (n=7/group)	By gavage/daily for eight weeks	Lowered body weight and absolute kidney weight; higher relative kidney weight; reduced urinary creatinine clearance; increased urinary kallikrein excretion in the highest-dose group only (Bompart *et al.* 1990)[54]
Calcium molybdate	100 to 5,000	Rats (n=8-10/group)	In diet for up to 232 days	Loss of appetite, weight loss, a rough fur, tendency to become quiet and listless; 50% mortality in lowest dose group, 100% in highest dose group (Fairhall 1945)[21]
Molybdenite	100 to 5,000	Rats (n=8-10/group)	In diet for up to 232 days	No signs of toxicity found; no mortality (Fairhall 1945)[21]

7.2.4 *Long-term toxicity and carcinogenicity*

Regarding carcinogenicity, the data were evaluated by the Subcommittee on the classification of carcinogenic substances of the DECOS. A summary of the findings and the conclusion of the Subcommittee are given in Annex E in this report.

In an inhalation study performed by the US National Toxicology Program, F344/N rats and $B6C3F_1$ mice of both sexes (N=50/group/sex) were exposed to molybdenum trioxide at concentrations of 0, 10, 30 and 100 mg molybdenum trioxide/m^3 (in aerosol), six hours per day, five days per week for a total of 106 weeks.[43,56] On all animals a complete necropsy was performed, followed by microscopic evaluations.

Survival rates of exposed rats were similar to those of the control groups. Also mean body weights were similar throughout the study. Furthermore, no clinical findings related to exposure were observed, and no significant differences in bone density or curvature between exposed and control animals. There was a significant dose-dependent increase in blood molybdenum levels in exposed animals. Comparable results were found for mice, except for a slightly lower survival rate of males exposed to 30 mg/m^3, and a higher mean body weight of exposed females (from week 11 onwards), compared to controls.

Respiratory tract effects: The most relevant findings on respiratory nonneoplastic and neoplastic lesions are summarized in Table 9. In summary, in exposed animals, nonneoplastic effects included: hyaline degeneration in the respiratory epithelium of the nose; hyaline degeneration in the olfactory epithelium of the nose (female rats, male and female mice); laryngeal squamous metaplasia in the epiglottis; laryngeal hyperplasia (mice only); chronic inflammation in the alveoli of the lungs (male and female rats); alveolar epithelium metaplasia (mice only); and, cellular histiocyte infiltration in the lungs (male mice only). Most of these effects were statistically significantly increased at an exposure concentration of 10 mg/m^3 onwards compared to non-exposed controls, despite the fact that some effects also occurred in non-exposed controls at relatively high incidence (olfactory epithelium hyaline degeneration in the nose, and chronic inflammation in the lungs of female rats; olfactory and respiratory epithelium hyaline degeneration in the nose of female mice; and, respiratory epithelium hyaline degeneration in the nose and lung adenomas in male mice).

Table 9 Occurrence of respiratory tract effects by molybdenum trioxide in a two-year carcinogenicity study using rats and mice.[43,56]

	0 mg/m³	10 mg/m³	30 mg/m³	100 mg/m³
Male F344/N rats				
Lung: alveolus chronic inflammation	2/50	3/50	25/50**	47/50**
Lung: alveolar/bronchiolar adenoma	0/50	0/50	0/50	3/50
Lung: carcinoma	0/50	1/50	1/50	1/50
Lung: adenoma/carcinoma	0/50	1/50	1/50	4/50
Nose: respiratory epithel. hyaline degeneration	2/50	7/49	48/49**	49/50**
Larynx: epiglottis, squamous metaplasia	0/49	11/48**	16/49**	39/49**
Female F344/N rats				
Lung: alveolus chronic inflammation	14/50	13/50	43/50**	49/50**
Lung: alveolar/bronchiolar adenoma	0/50	1/50	0/50	2/50
Lung: carcinoma	0/50	1/50	0/50	0/50
Lung: adenoma/carcinoma	0/50	2/50	0/50	2/50
Lung: squamous cell carcinoma	1/50	0/50	0/50	0/50
Nose: olfactory epithelium hyaline degeneration	39/48	47/49*	50/50**	50/50**
Nose: respiratory epithel. hyaline degeneration	1/48	13/49**	50/50**	50/50**
Larynx: epiglottis, squamous metaplasia	0/49	18/49**	29/49**	49/50**
Male B6C3F$_1$ mice				
Lung: alveolar epithelium hyperplasia	2/50	1/50	6/49	2/50
Lung: alveolar/bronchiolar epithelium metaplasia	0/50	32/50**	36/49**	49/50**
Lung: adenoma	9/50	14/50	10/49	9/50
Lung: carcinoma	2/50	16/50**	14/49**	10/50*
Lung: adenoma/carcinoma	11/50	27/50**	21/49**	18/50
Nose: inflammation suppurative	2/50	6/50	10/49	8/50*
Nose: olfactory epithelium atrophy	3/50	5/50	3/49	10/50*
Nose: resp. epithelium degeneration hyaline	11/50	13/50	11/49	41/50**
Larynx: hyperplasia	1/50	3/49	6/48	41/50**
Larynx: epiglottis, squamous metaplasia	0/50	26/49**	37/48**	49/50**
Female B6C3F$_1$ mice				
Lung: alveolar epithelium hyperplasia	1/50	3/50	3/49	6/49
Lung: alveolar/bronchiolar epithelium metaplasia	2/50	26/50**	39/49**	46/49**
Lung: adenoma	1/50	4/50	8/49*	9/49*
Lung: carcinoma	2/50	2/50	0/49	6/49
Lung: adenoma/carcinoma	3/50	6/50	8/49	15/49**
Nose: olfactory epithelium degeneration hyaline	22/49	14/50	14/49	36/49**
Nose: resp. epithelium degeneration hyaline	26/49	23/50	28/49	48/49**
Larynx: hyperplasia	1/49	1/50	7/49	35/50**
Larynx: epiglottis, squamous metaplasia	1/49	36/50**	43/49**	49/50**

* $p<0.05$; ** $p<0.01$.

No significant neoplastic respiratory effects were found in exposed rats. However, some evidence of carcinogenic activity was found in exposed mice: a statistically significantly increased incidence of alveolar/bronchiolar adenoma or carcinoma was observed compared to controls, with the notion that in the control group of male mice also cases of lung tumours were observed.

Overall, the investigators of the NTP-study considered the evidence for respiratory carcinogenicity of molybdenum trioxide in this study equivocal.

Non-respiratory tract effects: Neoplastic lesions were observed in some exposure groups, including: clitoral gland adenomas/carcinomas (female rats); mammary gland fibroadenomas, adenomas and carcinomas (female rats); hepatocellular carcinomas (male mice); and, hepatocellular adenomas and skin sarcomas (non-significant increase in female mice). Also a decrease in lesions were observed in exposed animals, such as a decrease of thyroid gland (C-cell) carcinomas (male rats), and of adrenal medulla pheochromocytoma (female rats). However, due to a lack of dose- related responses, a non-significant increase/decrease, or questions on relevance of certain lesions for humans, the investigators could not relate any of these effects to exposure to molybdenum trioxide.

Stoner et al. (1976) and Shimkin et al. (1977) reported on a study, in which inbred strain A/Strong mice (N=20/group) were exposed to molybdenum trioxide by repeated intraperitoneal injections (a total of 19 injections, thrice weekly).[57,58] The total doses applied were 0, 950, 2,375 and 4,750 mg molybdenum/kg bw (maximum tolerated dose). The animals were killed 30 weeks after the first injection. A statistically significant increase in the average number of lung tumours per mouse was observed in the highest-dose group compared to controls (1.13±0.2 *versus* 0.42±0.1 in exposed *versus* control, respectively). All the responses were however weak, and no distinction was made between the type of tumours. No differences were found concerning number of animals with tumours (10 *versus* 9 of twenty animals in each group, exposed *versus* control). The Committee noted the short duration of the study, that the route of exposure is not relevant to human exposure, and that the mice were highly susceptible to lung tumour development. This makes it difficult to make a final conclusion on the relevance for humans.

In three separate initiation-promotion carcinogenicity studies using rats, sodium molybdate was applied in drinking water or diet, in combination with treatment with the tumour initiators *N*-nitroso-*N*-methylurea, *N*-nitrososarcosine ethyl ester, or *N*-methyl-*N*-benzylnitrosamine.[59-61] The presence of sodium molybdate reduced the incidences of oesophageal, fore stomach and mammary gland

tumours, compared to tumour initiator-treated controls. No groups were included receiving sodium molybdate only.

7.2.5 *Mutagenicity and genotoxicity*

In vitro assays

Molybdenum trioxide: The compound scored negative in an Ames test with *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537, and in *Escherichia coli* strain WP2P *uvrA*, both with and without metabolic activation.[62,63]

Furthermore, no increased incidence of sister chromatid exchanges, and chromosome aberrations, were observed in assays with Chinese Hamster Ovarian cells, both with and without metabolic activation.[43] In addition, in a micronucleus assay using primary human lymphocytes, with and without a metabolic activation system, the compound did not show any clastogenic or aneugenic properties (concentrations added up to 1439 µg/mL, which is the maximum that should be tested according to the OECD guidelines).[64]

Ammonium molybdate: Ammonium molybdate (10 µM; exposure duration, 24 hours) induced chromosome aberrations, and sister-chromatid exchanges, in human lymphocytes (Bobyleva et al. 1991; in Russian, summarized in English in[39]).[45] The Committee noted that the data presented are insufficient to conclude whether or not ammonium molybdate showed clastogenic potential.

In a micronucleus assay using human lymphocytes, a concentration-related increase of the number of micronucleated cells was observed for ammonium molybdate (dose applied, 0.1-2 mM; viability of the cells ranged between 61% and 68%, which is above the minimum of 40 to 50% cell viability according to the OECD guidelines).[39] The Committee noted that the increase was minimal.

Armitage (1997) reported on ammonium *octa*molybdate and did not find mutagenic activity when using the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, with and without metabolic activation.[65]

Sodium molybdate: The compound was tested in the Ames test with *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537, with or without metabolic activation (final concentration up to 5,000 µg/plate).[66,67] Using the Microtitre® fluctuation test, sodium molybdate did not induce

mutation in the *tk* locus in mouse lymphoma cells (L5178Y) in the absence and presence of a metabolic activation system.[68] Concentrations tested were up to 2,060 µg/mL (= 10 mM).

In a micronucleus assay using human lymphocytes, a minimal (little more than twofold over the control level) concentration-related increase of the number of micronucleated cells for the compound (0.1-5 mM) was observed (viability of the cells ranged between 63% and 73%).[39] However, in another micronucleus assay using a shorter treatment procedure, sodium molybdate (concentration tested up to 10 mM) did not induce concentration-related increase in micronuclei using primary human lymphocyte cultures, in the absence or presence of a metabolic activation system.[69]

In vivo assays

Sodium molybdate: In a micronucleus test, male C57BL/6J mice (N_{total}, 15; N_{group}, not given) were intraperitoneally injected with 0, 200 or 400 mg sodium molybdate per kg bw for two consecutive days.[39] The femoral bone marrow cells were harvested 48 hours after the final injection. A statistically significant (p<0.05) increase in micronuclei frequency in polychromatic erythrocytes was observed at both doses tested, compared with the negative control. The Committee noted that the increase, although it was statistically significant, was small, and that it was not dose-related. The first observation might be explained by the fact that cells were harvested 48 hours after the final injection and not after 6 hours, which is recommended according to the OECD guidelines.

7.2.6 Transformation assays

Molybdenum (in the form of particulates): The C3H10T½ mouse fibroblast cell line was used to assess cytotoxicity and neoplastic transformation incidence.[70] Molybdenum showed marked toxicity only at the highest tested concentration of 500 µg/mL. Molybdenum did not induce transformation.

Molybdenum trioxide. The compound was tested in the Syrian hamster embryo (SHE) cell transformation assay (at reduced pH 6.7); it gave a significant increase in morphological transformations after 24 hours of exposure, with concentrations of ≥75 µg/mL (cytotoxic concentration, 200 µg/mL).[71]

Sodium molybdate. The C3H10T½ mouse fibroblast cell line was used to assess cytotoxicity and neoplastic transformation incidence. Significant transformation into neoplastic foci was observed at 10 µg/mL sodium molybdate (p<0.01). However, the relevance of the positive finding is unclear, because at

higher concentrations up to 500 µg/mL, no cellular transformation was detected.[70]

7.2.7 *Reproductive toxicity*

Data on reproduction toxicity were evaluated by the Subcommittee on the classification of reproductive toxic substances of the DECOS. A summary of the findings and the conclusion of the Subcommittee are given in Annex G in this report.

Fertility

Molybdenum trioxide: In a NTP-study, Fischer 344 rats (N=10/sex/dose) and $B6C3F_1$ mice (10/sex/dose) were exposed to 0, 10, 30, and 100 mg molybdenum trioxide/m^3 (in aerosol) by inhalation, for 6.5 hour per day, 5 days per week for thirteen weeks.[43] Body and organ weights, clinico-chemical and hematological parameters, and histopathological findings were not different from the control values.

In exposed male rats, sperm counts were unaffected. In addition, no statistically significant effect was observed on the concentration of epididymal spermatozoa. At 10, 30 and 100 mg/m^3, rats showed slightly decreased absolute epididymis weights (0.48 g, 0.49 g and 0.47 g, respectively) compared to unexposed rats (0.50 g). However, these effects were not statistically significant.

In exposed mice, absolute cauda epididymis weight was slightly increased (0.025 g *versus* 0.018 g in controls) at 10 mg/m^3, and absolute testis weight was slightly decreased (0.10 g *versus* 0.12 g in controls) at 100 mg/m^3. However, these effects were not statistically significant. No statistically significant effects were observed on sperm count, and on the concentration and motility of epididymal spermatozoa in any of the treatment groups.

The NTP also performed a long-term carcinogenicity study, in which rats and mice were exposed to the same molybdenum trioxide levels as in the thirteen-week study (for details on study design see Section 7.2.4). Examination included the occurrence of non-neoplastic lesions. No lesions were found in the genital system of males and females that could be related to exposure to molybdenum. The NTP did not specifically examine sperm pathology.

Sodium molybdate: In a dose-range finding study, sodium molybdate dihydrate was administered in the diet *ad libitum* to pregnant Sprague-Dawley rats (N=10/group) at doses of 0, 1, 5, 10 and 20 mg molybdenum/kg bw/day from 6 to 20

days of gestation.[72] At gestation day 20, the animals were sacrificed and gross necropsy was performed. No molybdenum-related general effects (maternal body weight, weight gains, organ weights, clinical observations, feed consumption), and fertility effects (ovarian corpora lutea counts, placental weight and disposition) were observed.

Pandey and Singh (2002) administered to groups of 10 adult male Druckery rats (body weight at start of experiment averaged 120 grams) 0, 10, 30, or 50 mg sodium molybdate per kg bw by gavage, 5 days/week for 60 days.[73] No effects on body weight or clinical signs that could be related to treatment were observed. At 50 mg/kg bw, testis, epididymis, seminal vesicles, and prostate gland weights (absolute and/or relative weights) were statistically significantly decreased, and an accumulation of molybdenum was seen in these organs. At 30 mg/kg bw, epididymis weight, absolute weight of seminal vesicles, and relative weight of the prostate gland were statistically significantly decreased. At both concentrations, degeneration of the seminiferous tubules in the testis was observed. The authors derived an NOAEL of 10 mg sodium molybdate/kg bw from this study. Details of the results for the most relevant effects are given in Table 10.

In a separate experiment by the same investigators (Pandey and Singh, 2002), male Druckery rats (N=20/group) were treated with 0 or 30 mg sodium molybdate/kg bw, 5 days/week for 12 weeks, and mated with untreated females during 2 weeks thereafter.[73] The fertility index was 60% for treated males and 80% for untreated controls. The pregnant unexposed females were sacrificed on

Table 10 Relevant fertility effects of male Druckery rats, which were orally exposed to sodium molybdate for 60 days.[73]

Effect (mean ± SE)	0 mg/kg bw	10 mg/kg bw	30 mg/kg bw	50 mg/kg bw
Absolute organ weight (gram):				
Testis	2.5±0.08	2.50±0.03	2.40±0.05	2.40±0.03
Epididymis	0.81±0.01	0.78±0.02	0.50±0.02*	0.49±0.02
Seminal vesicle	0.18±0.01	0.17±0.02	0.09±0.012*	0.08±0.01*
Prostate gland	0.11±0.01	0.11±0.006	0.09±0.004	0.05±0.01*
Relative organ weight (organ to whole animal; gram):				
Testis	1.20±0.03	1.20±0.03	1.15±0.03	1.15±0.03*
Epididymis	0.38±0.01	0.37±0.01	0.30±0.02*	0.32±0.02*
Seminal vesicle	0.08±0.001	0.08±0.01	0.05±0.01	0.05±0.008*
Prostate gland	0.05±0.006	0.05±0.004	0.04±0.002*	0.03±0.005*
Sperm motility (%)	86.0±2.3	85.0±0.08	65.0±1.2*	49.1±1.3*
Total epididymal sperm count/epididymis ($x10^7$)	8.0±0.17	8.2±0.08	6.0±0.07*	5.0±0.05

* $p \leq 0.05$

day 20 of gestation. The number of implantations, live foetuses and foetal body weight were significantly decreased in litters of dams mated with exposed males. Implantation loss was statistically significantly increased compared to controls. The effects on developmental parameters seemed to be related to an effect of sodium molybdate on male fertility.

The Committee considers the effects observed in male rats in the study by Pandey and Singh (2002) relevant for humans. On the other hand, however, the study is poorly reported, raising uncertainties about for instance, the duration of the study. In addition, it is not clear to the Committee why the reduction of total sperm count in the highest exposed group is not statistically significant, whereas the data presented in the paper indicate otherwise. Also the authors did not indicate from which exposure group data are presented in Table 6 of the publication.

The International Molybdenum Association (IMOA) commissioned two separate animal experiments, in which Sprague-Dawley CD rats were given sodium molybdate dihydrate by gavage or via the diet.[52] See Section 7.2.3, oral exposure, for a detailed description of the studies. Regarding the 28-day study, histopathology did not reveal abnormalities in the kidneys, testes or epididymis. The Committee emphasizes that adverse effects on male fertility could have occurred after 28 days, because the spermatogenesis cycle in rats takes approximately ten weeks. Furthermore, it is known that, for instance, effects on the seminiferous tubuli can develop in the long term. However, in the other experiment by IMOA (the 90-day study) also no molybdenum-related adverse effects were observed on the gonads, estrous cycles or sperm parameters in any of the exposed groups.[53]

In a poorly reported study, Jeter et al. (1954) administered doses of <1, 20, 80, or 140 ppm molybdenum (approximately <0.04, 0.9, 3.5, 6.2 mg molybdenum/kg bw/day*) as disodium molybdate dihydrate in diets containing 5 ppm copper (normal copper content 1.8 ppm) to Long-Evans rats** (N=4-8/sex/group) for about 20 weeks.[74] The growth rates of male rats at 20, 80 or 140 ppm molybdenum, and of females at 80 and 140 ppm molybdenum, were statistically significantly decreased over the first eleven weeks.

Depigmentation of the hair and alopecia were observed in some rats fed 20, 80 or 140 ppm molybdenum. Animals were allowed to mate from eleven weeks onwards. At 80 and 140 ppm molybdenum, males were successful in mating in

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* Assuming a mean body weight of 425 grams and a food intake of 18.75 grams per day.

** Age and body weights of rats at the start of the study were not given; only average weight gains at wk 11.

one of four cases. Mating of the treated males with untreated females did not result in pregnancy. In contrary, mating of females given 80 or 140 ppm molybdenum with untreated males resulted in pregnancy rates of 100%. Histopathologic examination of the testes of males treated with 80 and 140 ppm molybdenum revealed degeneration of the seminiferous tubules.

Weanling female Sprague-Dawley rats (N=21/group) were given drinking water with 0, 5, 10, 50 and 100 mg/L molybdenum* as sodium molybdate dihydrate for 6 weeks (Fungwe et al. 1990).[75] Thereafter, rats were exposed during three oestrus cycles before being mated with untreated males (N=15/group) or sacrificed (N=6/group). The mated females remained exposed during gestation until necropsy on day 21. During the first six weeks of the study, no effects on body weight became apparent. At 10 mg/L and higher, oestrus cycle lengths were statistically significantly prolonged compared to control females. Pregnancy rate was not affected by treatment.

In the dominant lethal assay, C57BL/6J male mice were treated with 0, 200 and 400 mg sodium molybdate per kg bw, and mated with untreated C3H/J female mice.[39] Pregnancy rate was 10% decreased in the highest exposure group (not significant), and an overall dose-dependent increase in total post-implantation loss was observed (6.7%, 10.6%, 16.3%, respectively). This increase was mostly represented by early resorptions (p=0.003) in the first week after treatment. The authors suggest that sodium molybdate induces dominant lethality at the post-meiotic stage of spermatogenesis. The Committee noted that the number of corpera lutea in females, which were mated with males treated at 400 mg/kg bw, was lower than that in controls. This might have affected pregnancy rate, and thus the post-implantation loss.

Ammonium molybdate: The effect of ammonium molybdate (AM) and thiomolybdate (TM, presumably ammonium tetrathiomolybdate) in drinking water on the trace element status, reproductive capacity of guinea pigs was studied by Howell et al. (1993).[76]

Mature female (n=8/dose) and male (12 in total) Hartley albino guinea pigs, weighing around 500-600 grams were fed *ad libitum* on a diet containing 212 µmol Cu/kg. When each female entered the third oestrus cycle, males were introduced twice a day. Females of dose groups A (control), B (261 µmol AM/L), C (261 µmol TM/L), and D (130 µmol TM/L) received molybdenum

* Assuming a mean water intake of 50 to 125 mL/kg bw/day for SD rats, the units in mg/L correspond to a daily intake of approximately 0.25-0.625 mg/kg bw (5 mg/L), 0.5-1.25 mg/kg bw (10 mg/L), 2.5-6.25 mg/kg bw (50 mg/L), and 5.0-12.5 mg/kg bw (100 mg/L).

compounds from the first day of the oestrus cycle onwards, whereas treatment of group E (261 µmol TM/L) and F (130 µmol TM/L) females was started immediately after mating.*

Subcutaneous oedema was found only in 1/8 and 4/8 female adult guinea pigs of the high TM dose groups, C and E. Upon X-ray examination, an ossified ridge in the mid shaft region of the femur was observed in the TM-dose groups (frequencies: 3/5, 0/7, 4/5, and 1/7 for groups C, D, E, and F, respectively), but not in the AM-treated animals nor in any of the pups. The reason for reporting the results for less than eight animals was not given, but it might be that animals that died (pregnant or non-pregnant) were excluded from examination**. All adult females had oestrus cycles and conception rates were reported to be unaffected. Details on developmental effects in dams are described in the following section.

Developmental toxicity

Sodium molybdate: In a dose-range finding study, sodium molybdate dihydrate was administered in the diet *ad libitum* to pregnant Sprague-Dawley rats (N=10/group) at doses of 0, 1, 5, 10 and 20 mg molybdenum/kg bw/day from 6 to 20 days of gestation.[72] At gestation day 20, the animals were sacrificed and gross necropsy was performed. No molybdenum-related developmental toxicity (pre- and postimplantation loss, fetal numbers, sex ratio, body weights and or fetal external malformations) was observed.

Based on the previous outcome, the study was repeated with higher doses. Sodium molybdate dihydrate was given to maternal Sprague Dawley rats (N=25/group) via the diet at doses of 0, 3, 10, 20 and 40 mg molybdenum/kg bw/day from 6 to 20 days of gestation.[77] At gestation day 20, the animals were sacrificed and gross necropsy was performed. No treatment-related effects were observed on maternal body weight, weight changes, feed consumption, clinical observations, pregnancy indices or maternal organ weights. Also no treatment-related effects were observed regarding numbers of ovarian corpora lutea, uterine implantation sites and losses, number of fetuses, fetal sex ratios, fetal body weights, fetal external, visceral or skeletal malformations or variations in the fetuses per females. The Committee cannot make a final conclusion on the

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* Assuming a mean water intake of 100 to 170 mL/kg bw/day for guinea pigs, the units in µmol/L correspond to a daily intake of approximately 8.70 mg AM/kg bw (261 µmol/L), 11.55 mg TM/kg bw (261 µmol/L), and 5.75 mg/kg bw (130 µmol/L).

** In the discussion section of the study it is stated that "Of 32 animals receiving TM, eight had changes in the shaft of the femur".

present and the previous study, since a lack of maternal toxicity in combination with a lack of developmental effects may indicate that the chosen exposure levels were too low to induce adverse health effects. In that case, and according to OECD-guideline 414 (prenatal developmental toxicity study), further investigations are needed.

Weanling female Sprague-Dawley rats (N=21/group) were given drinking water with 0, 5, 10, 50 and 100 mg/L molybdenum* as sodium molybdate dihydrate for 6 weeks (Fungwe et al. 1990).[75] Thereafter rats were exposed during three oestrus cycles before being mated with untreated males (N=15/group) or sacrificed (N=6/group). The mated females remained exposed during gestation until necropsy on day 21.

During the first 6 weeks of the study, no effects on body weight became apparent. During gestation, weight gain of the dams was statistically significantly decreased at 10, 50 and 100 mg/L, but these changes were attributed to reduced foetal weights. The number of resorptions was increased in females treated at 10 mg/L and above. Litter size did not differ between treatment groups and controls, but foetal weight and length were decreased at 10, 50 and 100 mg/L. Growth retardation was observed (less mature hepatic structure, delayed transfer of foetal haemopoiesis to bone marrow, delayed foetal oesophageal development, and myelination in the spinal cord) in the foetuses at 10 mg/L and above. Blood and hepatic enzymes of the dams were affected at 5 mg/L and above. Plasma ceruloplasmine was statistically significantly increased in all gestating dams, but not in dams sacrificed after three oestrus cycles. Hepatic xanthine oxidase/dehydrogenase, and sulphite oxidase, were statistically significantly increased in all treated females in the study.

In a poorly reported study by Jeter et al. (1954), Long-Evans rats (N=4-8/sex/group) received <1, 20, 80 or 140 ppm molybdenum as sodium molybdate (approximately <0.04, 0.9, 3.5, 6.2 mg molybdenum/kg bw/day**) in diet containing 5 ppm copper (normal copper content 1.8 ppm) for about 20 weeks.[74] The growth rates of male rats at 20, 80 or 140 ppm molybdenum, and of females at 80 and 140 ppm molybdenum, were statistically significantly decreased over the first eleven weeks. Depigmentation of the hair and alopecia were observed in some rats fed 20, 80 or 140 ppm molybdenum. Animals were allowed to mate from eleven weeks onwards.

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* Assuming a mean water intake of 50 to 125 mL/kg bw/day for SD rats, the units in mg/L correspond to a daily intake of approximately 0.25-0.625 mg/kg bw (5 mg/L), 0.5-1.25 mg/kg bw (10 mg/L), 2.5-6.25 mg/kg bw (50 mg/L), and 5.0-12.5 mg/kg bw (100 mg/L).

** Assuming a mean body weight of 425 grams and a food intake of 18.75 grams per day.

No effects on pup weight at day zero of lactation were identified. During lactation, increased weight loss of the mothers compared to controls was observed at 80 and 140 ppm molybdenum, and pup weight gain was decreased at the same dose levels. This was attributed to reductions in milk production and possible excretion of molybdenum into milk.

Ammonium molybdate and ammonium tetramolybdate: Howell et al. (1993) studied the effect on the trace element status, and reproductive capacity of guinea pigs of ammonium molybdate (AM) and thiomolybdate (TM, presumably ammonium tetrathiomolybdate) in drinking water.[76] Mature female (N=8/dose) and male (12 in total) Hartley albino guinea pigs, weighing around 500-600 grams, were fed *ad libitum* a diet containing 212 µmol copper/kg diet. When each female entered the third oestrus cycle, males were introduced twice a day. Females of dose groups A (control), B (261 µmol AM/L), C (261 µmol TM/L), and D (130 µmol TM/L) received molybdenum compounds from the first day of the oestrus cycle onwards, whereas treatment of group E (261 µmol TM/L) and F (130 µmol TM/L) females was started immediately after mating.* Details on fertility effects are described in the previous section.

At birth, two animals of each litter were retained with the mother for a further six weeks. All dams and pups were X-rayed after they had been killed. Clinical signs observed in several dams of the high TM-dose groups included hair loss, transient diarrhoea, subcutaneous oedema, and mortality before or during pregnancy. No changes in ossified femur was observed in any of the pups. There appeared to be a reduced pregnancy rate in AM-treated females, and an increased 'aborted resorbing' in high TM-dose females. The mean number of pups born alive was reduced in groups B, C, D and E, but not in group F. Pup body weight was slightly decreased at birth in the TM-treated groups.

Six weeks after birth, body weights of group C pups (high TM dose) were still reduced. Administration of AM or TM usually resulted in an increase in the concentration of molybdenum in the organs examined (the liver, kidneys, femur, and brain). This increase was statistically significant in the liver, kidneys, and femur at all ages in the group given AM; and, in the liver and kidneys at birth in all groups given TM with the exception of the liver in group E. However, the concentration of molybdenum was statistically significantly depressed in the femur of the pups from group F killed at six weeks.

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* Assuming a mean water intake of 100 to 170 mL/kg bw/day for guinea pigs, the units in µmol/L correspond to a daily intake of approximately 8.70 mg AM/kg bw (261 µmol/L), 11.55 mg TM/kg bw (261 µmol/L), and 5.75 mg/kg bw (130 µmol/L).

Molybdate: Schroeder et al. (1971) exposed five pairs of Charles River CD mice to 10 mg/L molybdenum (as molybdate; cation unknown) in deionized drinking water for up to six months, while the diet contained 0.45 ppm molybdenum.* The study was poorly reported.[78] Animals were allowed to breed freely during this period. Animals were at random selected from the first three litters to form the F_1, and allowed to breed to form the F_2 (period not indicated). Animals of the first two F_2 litters were selected to form the F_3-generation.

No mortality was observed in the F_0-generation. Molybdenum did not affect the growth rate in the F_0-generation. Age at first litter and interval between litters were similar to control values. No other data on this generation are available. In the F_1-generation, no differences between treatment group and controls were reported for number of litters, litter size and number of runts. Fifteen of the 238 F_1 mice died early (not further specified). In the selected animals of the F_1-generation, one female died. The interval between the litters was increased (43 *versus* 28 days in controls), but the age at first litter was not affected. The number of F_2 litters, litter size, and dead young were similar to controls. Five of the 26 litters were found dead compared to 0 out of 23 in controls. In the selected F_2, four maternal deaths were reported, and the age at first litter was increased from 62 to 79 days. No effect on interval between litters was found. The number of litters and litter size were decreased in treated animals. Four litters in the F_3 were found dead. The numbers of runts (11 *versus* 0 in controls) and dead young (34 *versus* 1 in controls) were increased.

Lactation

Sodium molybdate: In a poorly reported study by Jeter et al. (1954), Long-Evans rats (N=4-8/sex/group) received <1, 20, 80 or 140 ppm molybdenum as sodium molybdate (approximately <0.04, 0.9, 3.5, 6.2 mg Molybdenum/kg bw/day**) in diet containing 5 ppm copper (normal copper content 1.8 ppm) for about 20 weeks.[74] During lactation, increased weight loss of the mothers compared to controls was observed at 80 and 140 ppm molybdenum, and pup weight gain was decreased at the same dose levels. The authors assumed these decreases to be explained by reductions in milk production and possible excretion of molybdenum into milk.

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* Assuming a mean water intake of 167 to 200 mL/kg bw/day and a food intake of 120 to 150 g/kg bw/day, the total intake of molybdenum per day approximates 1.7 to 2 mg/kg bw.

** Assuming a mean body weight of 425 grams and a food intake of 18.75 grams per day.

7.3 Summary

7.3.1 *Observations in humans*

Studies involving the working population with occupational molybdenum exposure are of limited value, because of a lack of reliable exposure data, concomitant exposure to other potentially toxic compounds, and poor descriptions of the studies. Overall, workers who were at least exposed to molybdenum trioxide reported complaints, such as joint pain (gout-like symptoms), back pain, headache, and mild obstructive lung disease (including breathing difficulties, chest pain and fatigue). Also increased levels of uric acid and ceruloplasmin have been reported in workers compared to non-exposed controls. Exposure levels to molybdenum at which symptoms occurred were found to be as low as 1.6-9.5 mg/m^3 (molybdenum in respirable-total dust; molybdenum roasting plant) to up to 600 mg/m^3 (mine dust).

Among Armenian villagers, gout-like symptoms and increased levels of uric acid have been observed. They had an average dietary intake of molybdenum of 10 to 15 mg per day, and of copper of 5 to 10 mg per day. However, no adverse health effects were found in an American study, in which people consumed drinking water that contained at least 200 µg molybdenum per litre water.

Data on carcinogenic activity in humans are limited. Positive but weak correlations were found for lung cancer among molybdenum-exposed workers with a long exposure history, and for pancreas cancer in females in a Japanese population. However, due to a lack of reliable data on exposure and intake levels, and the presence of other potentially carcinogenic factors, no conclusions can be drawn.

One study reported on dose-dependent negative trends between serum molybdenum levels and sperm concentration, normal sperm morphology, and serum testosterone levels. No other studies were found on possible effects of molybdenum or molybdenum compounds on fertility, developmental toxicity, and lactation in humans.

7.3.2 *Animal experiments*

Depending on the molybdenum compound, some of them showed to be irritating the nose, eyes, and respiratory tract.

Inhalation exposure

In rats and mice exposed to molybdenum trioxide of up to 100 mg molybdenum trioxide/m^3 (in aerosol) for thirteen weeks, no adverse health effects or pathological lesions were found. Guinea pigs exposed to very high levels of molybdenum trioxide (> 300 mg/m^3) for five weeks, showed signs of respiratory irritation, loss of appetite and weight, diarrhea, muscular incoordination, and loss of hair.

Groups of rats and mice were exposed to molybdenum trioxide for two years. Animals were exposed to the compound at concentrations of 0 (control), 10, 30 or 100 mg molybdenum trioxide/m^3 (in aerosol) for six hours per day, five days per week, for 106 weeks. Statistically increased incidence of nonneoplastic respiratory tract effects in exposed animals included: hyaline degeneration in the respiratory and olfactory epithelium of the nose; laryngeal squamous metaplasia in the epiglottis, and laryngeal hyperplasia; and, chronic inflammation of the lungs. The effects were observed at 10 mg/m^3 onwards.

In the same study, described above, evidence for respiratory carcinogenicity of molybdenum trioxide was found to be equivocal, because in most animal groups, no significant neoplastic respiratory tract effects were found, except in mice. In those animals, a statistically significantly increased incidence in alveolar/bronchiolar adenomas and carcinomas have been observed, but the findings were not dose-related. Furthermore, no dose-related carcinogenic effects in other organs were observed.

Based on the limited evidence available, the Subcommittee is of the opinion that molybdenum trioxide, ammonium molybdate and sodium molybdate are probably not genotoxic.

No significant signs of adverse effects on fertility have been found in male rats and mice exposed to molybdenum trioxide at a concentration of up to 100 mg/m^3 (highest concentration tested) for thirteen weeks.

Oral exposure

Overall, data on adverse health effects in animal experiments after acute or subchronic oral exposure are limited, due to low number of animals in study. An exception is a 90-day study by IMOA, in which a statistically significant decrease in average body weight and change in body weight gain was observed in male rats exposed to 60 mg molybdenum/kg bw. At this dose, also the average body weights of female rats was statistically significantly decreased compared to

controls. No data were available on non-carcinogenic and carcinogenic long-term effects of oral exposure to molybdenum or molybdenum compounds only.

Reproduction toxicity: In a poorly reported 60-day study by Pandey and Singh (2002), oral exposure (by gavage) to sodium molybdate decreased sperm motility and total sperm count in male rats, in the absence of general toxicity (doses applied up to 50 mg sodium molybdate/kg bw). A number of other poorly reported studies support this finding. However, in one well performed 90-day study by IMOA, no fertility effects of sodium molybdate have been found in rats (another breed of rats than in the study by Pandey and Singh), when given in the diet at a dose of up to 60 mg molybdenum/kg bw. Pandey and Singh (2002) also found indications that female fertility was affected, but this is not confirmed in other studies. In addition, there are indications for developmental toxicity; however, the studies reporting on this issue were poorly reported. There are no indications to label for effects on lactation.

Chapter 8

Existing guidelines, standards and evaluations

8.1 General population

Since molybdenum is considered an essential trace element, shortage of molybdenum in the body may induce molybdenum deficiency. Although up to now no cases of deficiency have been reported in healthy people under normal dietary conditions, several institutions and authorities have suggested Reference Daily Intakes (RDI) and Estimated Average Requirements (EAR). Also, Tolerable Upper Intake Levels (UL; total uptake from food, water, and supplements) have been recommended, based on impaired reproduction and growth in animals.[8]

For adults, in 2006, the US Institute of Medicine adopted an RDI value of 45 µg molybdenum per day, an EAR value of 34 µg molybdenum per day, and an UL of 2,000 µg molybdenum per day.[8] A year earlier, the same values were set in Australia and New Zealand. A lower UL was adopted by the European Food Safety Authority, namely 600 µg molybdenum per day for adults, which is equivalent to approximately 10 µg molybdenum/kg bw/day.[35] The US Environmental Protection Agency adopted an oral Reference Dose of 5 µg molybdenum/kg bw/day.[38]

In the guidelines for drinking-water quality, the World Health Organization assessed a guideline value for molybdenum in drinking water of 70 µg/litre, which represents a concentration of molybdenum that does not result in any significant health risk to the consumer over a lifetime of consumption.[79]

No guidelines or standards exist for the general population regarding exposure to airborne molybdenum or molybdenum compounds.

8.2 Working population

In the Netherlands, no legally-binding occupational exposure limits exists for molybdenum and molybdenum compounds. Also, no exposure limits have been set by the European Commission. However, some individual European countries and in the United States have assessed exposure limits, dividing the soluble from the metal and insoluble molybdenum compounds. A summary is shown in Table 11.

Table 11 Occupational exposure limits of molybdenum and molybdenum compounds.

Country (Organization)	Monitoring	OEL (mg/m^3)	TWA	Type of exposure limit [a]	Valid since
Soluble compounds, measured as molybdenum					
Germany (DFG)[80]	-	-[b]	-	-	-
UK (HSE)[81]	Not specified	5	8h	OES	<1999
	Not specified	10	15min	OES	<1999
Denmark[82]	Not specified	5	8h	OEL	<2001
Finland	Not specified	0.5	8h	OEL	2007
Sweden[83]	In total dust	5	8h	OEL	1984
USA (ACGIH)[48]	In respirable particulate	0.5	8h	TLV	2001
USA (NIOSH)[48]	-	-	-	-	-
USA (OSHA)[48]	Not specified	5[c]	8h	PEL	1989
Metal and insoluble compounds, measured as molybdenum					
Germany (DFG)[80]	-	-[b]	-	-	-
UK (HSE)[81]	Not specified	10	8h	OES	<1999
	Not specified	20	15min	OES	<1999
Denmark[82]	Not specified	10	8h	OEL	<2001
Sweden[83]	In respirable dust	5	8h	OEL	1984
	In total dust	10	8h	OEL	1984
USA (ACGIH)[48]	In respirable particulate	3	8h	TLV	2001
	In inhalable particulate	10	8h	TLV	2001
USA (NIOSH)[48]	-	-	-	-	-
USA (OSHA)[48]	In total dust	15[c]	8h	PEL	1989

[a] OEL, occupational exposure limit; OES, occupational exposure standard; PEL, permissible exposure limit; TLV, threshold limit value.

[b] No OEL has been derived due to a lack of information.

[c] NIOSH considered the proposed PELs by OSHA to be inadequate.

8.3 Carcinogenic classification

Germany has classified molybdenum trioxide as a category 3B carcinogen.[80] Substances are classified in the category "for which *in vitro* or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories. Further studies are required before a final decision can be made".

The American ACGIH has classified soluble molybdenum compounds as an A3 carcinogen, indicating that it is a "confirmed animal carcinogen with unknown relevance to humans.[48] The agent is carcinogenic in laboratory animals at a relatively high dose […] that may not be relevant to worker exposure. Available epidemiological studies do not confirm an increased risk of cancer in exposed humans. Available evidence does not suggest that the agent is likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure".

Chapter 9

Hazard assessment

9.1 Hazard identification

A few epidemiological studies and laboratory animal studies have been performed to identify adverse health effects of certain molybdenum compounds. The following paragraphs contain short evaluations on the relevant toxic effects of molybdenum and molybdenum compounds after single and repeated exposure via food, drinking water, or inhalation.

Note: Molybdenum and molybdenum compounds are present in low amounts as natural elements in the environment. For humans and animals, the compound is an essential trace element that can be found in low amounts in all parts of the body. It serves as a cofactor of various enzymes involved in natural biochemical processes in the body.

Non-carcinogenic effects (excluding reproduction toxicity)

Various epidemiologic studies involving the working population, associate inhalation of molybdenum to for instance gout-like symptoms in the joints, weakness, fatigue, headaches, breathing difficulties, and chest pain.

Also, increased blood levels of uric acid have been reported. However, due to combined exposure to other potentially toxic compounds in most workplaces, and missing details on exposure and population characteristics, it is difficult to

conclude whether the observed symptoms are actually caused by molybdenum exposure. Exposure levels to molybdenum at which symptoms occurred, were found to be as low as 1.6-1.9 mg/m^3 (as respirable-total dust; molybdenum roasting plant) to up to 600 mg/m^3 (as mine dust).

Signs of short- and long-term clinical and pathological animal toxicity, and mortality, have been reported for several molybdenum compounds under various exposure and experimental conditions. The symptoms included respiratory tract effects after inhalation, and loss of appetite and body weight after oral intake. However, other animal studies did not find any clinical or pathological signs of toxicity. The studies are difficult to compare, because the choice of animal species, the choice of molybdenum compounds in study, and exposure and study designs, were mutually very divergent. In addition, the Committee considers part of the data insufficient in deriving health-based occupational exposure limits, because the number of animals in test was limited, or one dose or concentration have been tested only, so that for most animal studies no dose-response relationships can be assessed, with a few exceptions.

The first concerns the subchronic and chronic studies performed by the US National Toxicology Program, in which two different animal species are used, and a range of inhalation exposure levels of molybdenum trioxide aerosols. In particular, the two-year inhalation study with exposure concentrations ranging from 10 to 100 mg molybdenum trioxide/m^3 revealed pathological, upper respiratory tract effects in both rats and mice, of both sexes, such as hyaline degeneration in the nose epithelium, squamous metaplasia in the larynx, and chronic inflammation of the lungs (the latter in rats only). All these effects were statistically significantly increased in exposed animals compared to non-exposed controls.

In the study by Pandey and Singh (2002), statistically significantly reduced sperm motility and quality in rats exposed to 30 and 50 mg sodium molybdate/kg bw (the two highest dose-groups) were observed. The sodium molybdate was given orally by gavage. Another study on sodium molybdate is the subchronic study by IMOA, in which male and female rats were given sodium molybdate in the diet at doses of up to 60 mg molybdenum/kg bw for 90 days. In the highest dosed group a statistically significant decrease in mean body weight was observed in both sexes, compared to controls. Also the mean body weight gain was statistically significantly reduced, but in males only. Other adverse effects (slight diffuse hyperplasia of the proximal tubules in the kidneys of two female rats fed 60 mg molybdenum/kg bw/day) were non-significant.

For metallic molybdenum and other molybdenum compounds, no reliable data on dose-response relationships are available.

Carcinogenic effects

Data on carcinogenic activity of molybdenum and molybdenum compounds in humans are limited and give no conclusive information.

In the two-year inhalation study by the US National Toxicology Program, rats did not develop molybdenum trioxide-related tumours, whereas in some mice exposed at a concentration of 10 mg/m^3 to up to 100 mg molybdenum trioxide/m^3 (in aerosol), statistically increased incidence of alveolar/bronchiolar adenomas and carcinomas were found compared to controls (see Table 9). The investigators of the study did not consider these results dose-related, and stated that the evidence for respiratory tract carcinogenicity in rats and mice is equivocal, a reason being that in the male control group, high incidences of lung tumours have been observed.

From the available data on carcinogenicity, DECOS' Subcommittee on the classification of carcinogenic substances is of the opinion that molybdenum trioxide is a suspected carcinogen to man, and recommends classifying the compound in category 2* (see Annex E for further details on the Subcommittee's opinion). The available data on other molybdenum compounds and metallic molybdenum, are insufficient to evaluate the carcinogenic properties.

Reproduction toxicity

One epidemiology study reported on dose-dependent negative trends between serum molybdenum levels and sperm concentration, normal sperm morphology, and serum testosterone levels. Animal studies on reproduction toxicity of molybdenum compounds are limited to oral exposure to mainly (sodium) molybdates. Effects on male fertility were observed in two poorly reported studies (Pandey and Singh, 2002; Jeter et al. (1954).[84,85] In addition, there are indications that exposure to molybdates might affect female fertility (prolonged oestrus cycle) in the study of Fungwe et al. (1990). However, these effects were not confirmed by others (Howell et al. (1993) and IMOA (2011). Summarizing, there is weak evidence of fertility effects of molybdates.

Considering the available human and animal data on reproduction toxicity, DECOS' Subcommittee on the classification of reproductive toxic substances concluded that molybdates causes concern for human fertility (corresponding to a classification in category 2 for fertility effects), and that a lack of data precludes the assessment for effects on fertility of molybdenum trioxide (and

* See Annex F for the classification system.

other molybdenum compounds). Furthermore, due to a lack of data, the Subcommittee recommends not to classify molybdates and molybdenum trioxide for effects on development, and not to label for effects on lactation (see Annex G for further details on the Subcommittee's opinion).

Conclusion

Currently, the Committee considers the epidemiological data insufficient for quantitative hazard assessment, because of the presence of confounding factors, such as concomitant exposure, and missing details on exposure and population characteristics. Taking the whole set of animal data into account, a few studies have been performed showing data on exposure-response relationships, which are of interest for quantitative risk analyses. It concerns data on exposure to molybdenum trioxide and sodium molybdate.

9.2 Quantitative hazard assessment

In deriving a health-based recommended occupational exposure limit (HBR-OEL), the Committee performed benchmark dose-analysis (BMD-analysis).

9.2.1 Recommendation of an HBR-OEL (8-hour TWA) for molybdenum trioxide

The most clear and evident effects of molybdenum trioxide are found in a two-year inhalation study by US National Toxicology Program (1997), in which the substance induced non-neoplastic effects in the respiratory tract of rats and mice of both sexes.[43,56] Rats and mice of both sexes inhaled molybdenum trioxide aerosols at concentrations of 0, 10, 30 and 100 mg molybdenum trioxide/m^3 (in aerosol), six hours per day, five days per week, for a total of 106 weeks. On all animals, gross necropsy and microscopic pathology were performed.

Endpoints of interest. Results on respiratory tract effects are shown in Table 9. The most striking outcome is the induction of squamous metaplasia in the epiglottis (larynx), in that a statistically significant increase was observed in all animal species tested, and in both sexes; the lowest significant increase was found in groups that were exposed to 10 mg/m^3, whereas in non-exposed controls only one case was found (female mouse). The Committee also noted that at that concentration molybdenum trioxide induced other effects, such as hyaline degeneration in the nose, and chronic inflammation and metaplasia in the lungs, but these effects were less consistent, in that they were not observed in both

animal species and in both sexes. Overall, the Committee did not find indications that the observations in animals would not occur in humans.

Uncertainties. The Committee notes that some effects occurred at a high incidence in control animals (e.g., olfactory hyaline degeneration in the nose of female rats and mice). In addition, some other effects showed hardly any case in controls, but instead high incidences at the lowest exposure level (e.g., alveolar/ bronchial metaplasia in the lungs of male mice). Although, from a statistical viewpoint these effects still differed significantly (between controls and exposed groups), the high background in controls or high incidences in the lowest exposure groups weakens the strength or power of the data, making them less useful for quantitative hazard assessment. This has repercussions on BMD-analysis, in that the models used in the analysis do not fit adequately the data, and thus for these specific effects no reliable analysis can be performed.

The Committee prefers to include the degree of a specific pathological lesion, since it expects that in a low-dose group the effects might be less severe compared to the same lesion in a high-dose group. Such data on degree of severity could lower the uncertainty in the set of data for BMD-analysis, but these are not presented in the NTP-report nor in the scientific publication.[43,56]

BMD-analysis. In Annex H, data on effects are shown, from which a BMDL could be calculated. The BMDL is the 95% lower confidence limit of the BMD that corresponds with a 10% extra risk*. Because of the limited power of these carcinogenicity studies, BMD values based on lower percentage of extra risk are not reliable. The lowest BMDL is used as starting point in deriving an HBR-OEL; in this case a BMDL of 0.29 mg/m^3 (squamous metaplasia in the epiglottis of female mice).

HBR-OEL. For the establishment of an HBR-OEL several aspects have to be considered. One of these aspects is the difference between animals and humans. The Committee notes that in this case the squamous metaplasia and other respiratory effects are superficial and local, for which no compensation is needed. However, due to possible inter-individual differences among people, the Committee is of the opinion that an uncertainty factor of three is required. Adjusting the BMDL value of 0.29 mg/m^3 by the factor of three, an HBR-OEL for molybdenum trioxide is proposed of 0.1 mg molybdenum trioxide/m^3 (corresponding to 0.07 mg molybdenum/m^3). The HBR-OEL is based on personal inhalable dust exposure, measured as an eight-hour time weighted average concentration.

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* The Committee uses 10% extra risk as a default for dichotomous (quantal) animal data. The default may be modified based on scientific considerations.

9.2.2 Recommendation of an HBR-OEL (8-hour TWA) for sodium molybdate

As written in the previous section, regarding sodium molybdate, two animal studies are of interest, one showing reproduction toxicity in male rats (Pandey and Singh, 2002), and one showing reduction of body weight and body weight gain in male and female rats (IMOA, 2011).

The Committee considers the effects on the reproduction more sensitive and specific than reduction of the body weight. Effects on reproduction toxicity in male animals, and in humans, have been described in several studies, and therefore the effects found in the Pandey and Singh-study cannot be ignored (although none of the other studies can be used for quantitative risk analysis). The data of the Pandey-study appear to be consistent, showing comparable changes among the different effect parameters on sperm quality and motility. Also, the values of the parameters are in line with the values that would be expected when such effects occur. On the other hand, the Committee is aware of the poor reporting by Pandey and Singh, raising the question as to how the experiment was actually performed, and thus how reliable the data are for quantitative risk-analysis. It is not clear for instance, what the actual duration of the study was; whether the exposure concentration is expressed as molybdenum, sodium molybdate or sodium molybdate dihydrate; and, from which exposure group the data are presented in Table 6 of the publication. Furthermore, Pandey and Singh did not mark 'total sperm count' of the highest exposure group as statistically significant, whereas data indicate otherwise. It is unknown what the sensitivity is of the animal species they used, and, furthermore, the dietary composition may have influenced the outcome, but data on composition (in particular copper content) are not given.

Regarding the IMOA-study, it is well-performed but did not show reproduction toxicity. It is possible that effects on reproduction might have occurred at higher exposure levels, but then it would be difficult to assess whether such an effect was caused by the substance or by the occurrence of general toxicity, since at the highest exposure levels signs of general toxicity (changes in body weight and body weight gain) did occur. Also the study design was different from that by Pandey and Singh, since a different rat strain was used, and in the IMOA-study sodium molybdate was given in the diet, which reflects a more steady exposure, whereas in the Pandey-study the compound was given by gavage, which reflects a peak exposure pattern.

Taking all these considerations and uncertainties into account, the Committee decided not to use the data by Pandey and Singh in deriving a health-based

recommended occupational exposure limit. Instead, data of the IMOA-study on body weight and body weight gain reductions are used.

BMD-analysis. Data of the IMOA-study on the reduction of body weight and body weight gain are given in Table 7. In addition, in Annex I, data are shown, which showed statistically significant differences compared to controls, and from which a BMDL could be calculated. The BMDL is expressed as the 95% lower confidence limit of the BMD that corresponds with a decrease in body weight of 10% due to exposure, compared to the body weight in non-exposed animals*. The lowest BMDL is used as starting point in deriving an HBR-OEL, namely the BMDL of 10.9 mg molybdenum/kg bw (reduced body weight gain in male rats).

Adjustment from oral to inhalation exposure. The BMDL-value should be adjusted for obtaining a value for inhalation exposure. No quantitative data are available on inhalation bioavailability of sodium molybdate (and other molybdenum compounds) in humans and animals (see Section 5.1). Regarding oral bioavailability, absorption of molybdenum might reach 100% in humans. Therefore, the Committee uses the worst case assumption that 100% will be taken up, and will be available, after oral intake and inhalation. In addition, the Committee uses the formula below to adjust from oral to inhalation exposure concentration:

$$X = (x/y) \times (L/A) \times \text{oral dose}$$

in which X represents the exposure concentration in mg/m^3; x the percentage oral absorption (100%); y the percentage absorption (100%) after inhalation; L the body weight (the average weight of control animals during the experiment, 0.48 kg); A the breathing volume of the animals in rest (calculated to be 0.127 m^3 in 8 hours); and, oral dose represents the BMDL of 10.9 mg molybdenum/kg bw. Using this formula, the Committee calculated that the oral BMDL corresponds to an exposure concentration at 41.20 mg molybdenum/m^3 after inhalation.

HBR-OEL. For the establishment of an HBR-OEL several aspects have to be considered. One of these aspects is the difference between animals and humans. The Committee noted that in this case the effects were systemic, and, therefore, an uncertainty factor of three should be applied. In addition, due to possible inter-individual differences among people, the Committee is of the opinion that another uncertainty factor of three is required. Adjusting the BMDL value of 41.20 mg molybdenum/m^3 by these two factors, an HBR-OEL for sodium

* The Committee uses a de- or increase in body weight of 10% as a default response for calculating a BMDL.

molybdate is derived of 4.6 mg molybdenum/m^3 (rounded off; corresponds to 9.9 mg sodium molybdate/m^3). The HBR-OEL is based on personal inhalable dust exposure, measured as an eight-hour time weighted average concentration.

9.2.3 Metallic molybdenum and other molybdenum compounds

No individual HBR-OELs can be established for metallic molybdenum and other molybdenum compounds, due to a lack of data on exposure-response relationships for short-term and long-term non-lethal effects, or confounding, such as a limited number of animals in study.

Alternatively, the Committee has considered whether it would be possible to recommend an HBR-OEL for soluble and insoluble molybdenum compounds, as two separate groups, based on the recommendations made for molybdenum trioxide and sodium molybdate. In the literature, it was namely suggested that soluble molybdenum compounds would be more toxic than insoluble compounds. However, data are not only limited in reporting, but also vary considerable regarding study design (e.g., exposure duration, duration of study, route of exposure, number of exposure groups, animal species, effect end points). This makes comparison between soluble and insoluble compounds very difficult. Also part of the data concern mortality, which suggests that relative high exposure levels have been used. In conclusion, based on the data presented in this report, the Committee is of the opinion that there is insufficient reliable information available to propose HBR-OELs for soluble and/or insoluble molybdenum compounds as two separate groups.

In addition, the Committee noted that molybdenum trioxide when absorbed by the body, is present in the circulation as molybdate. This might suggest that molybdenum trioxide is expected to have the same systemic effects as sodium molybdate, and that the health-based recommended occupational exposure limits are interchangeable. The Committee, however, is of the opinion that the limits cannot be interchanged, because the solubility in water of both compounds differ more than a factor of 100 (see Table 2).

9.3 Groups at extra risk

Since no relevant occupational exposure data are available, no specific groups at risk can be identified.

9.4 Health-based recommended occupational exposure limits and classifications

Health-based recommended occupational exposure limits

The Committee recommends a health-based occupational exposure limit for:

- Molybdenum trioxide, namely of 0.1 mg molybdenum trioxide/m^3 (= 0.07 mg molybdenum/m^3)
- Sodium molybdate, namely of 9,9 mg sodium molybdate/m^3 (= 4,6 mg molybdenum/m^3).

Based on personal inhalable dust or aerosol exposure, measured as an eight-hour time weighted average concentration. The available data are insufficient to recommend an HBR-OEL for metallic molybdenum and any other molybdenum compounds.

Classifications

Regarding carcinogenicity, the Committee recommends classifying molybdenum trioxide, in category 2 ('suspected carcinogen to man')*. The available data are insufficient to evaluate the carcinogenic properties of metallic molybdenum and other molybdenum compounds.

Regarding reproduction toxicity, the Committee recommends classifying sodium molybdate and other molybdates in fertility category 2 ('suspected human reproductive toxicant'). The available data on metallic molybdenum or any other molybdenum compounds are insufficient to evaluate fertility effects. For the same reason, data on molybdenum or any molybdenum compounds are insufficient to evaluate developmental toxicity and effects on lactation.

* See Annex F for the classification system.

Chapter 10

Recommendations for research

Clear dose-response relationships concerning exposure of workers to molybdenum and molybdenum compounds should be examined. Unexposed control groups should always be included in the study design. Measurements of occupational exposure to molybdenum in air are needed in order to identify workers that are at risk and operations that lead to high exposure. Reproduction toxic properties of other molybdenum compounds should be further studied.

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A	Request for advice
B	The Committee
C	The submission letter
D	Comments on the public review draft
E	Evaluation by the Subcommittee on the classification of carcinogenic substances
F	Classification of substances with respect to carcinogenicity
G	Evaluation by the Subcommittee on the classification of reproductive toxic substances
H	BMD analysis: inhalation study on pathological respiratory tract effects by molybdenum trioxide
I	BMD analysis: diet study on body weight effects by sodium molybdate

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

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

- H.P.J. te Riele
  Professor of Molecular Biology, VU University Amsterdam, and the Netherlands Cancer Institute, Amsterdam
- I.M.C.M. Rietjens
  Professor of Toxicology, Wageningen University and Research Centre
- G.M.H. Swaen
  Epidemiologist, Exponent, the USA
- R.C.H. Vermeulen
  Epidemiologist/Environmental Hygienist, Institute for Risk Assessment Sciences, Utrecht University
- P.B. Wulp
  Occupational Physician, Labour Inspectorate, Groningen
- B.P.F.D. Hendrikx, *advisor*
  Social and Economic Council, The Hague
- J.M. Rijnkels, *scientific secretary*
  The health Council, The Hague

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 chairperson 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**

The submission letter (in English)

Subject	: Submission of the advisory report *molybdenum and molybdenum compounds*
Your Reference	: DGV/MBO/U-932342
Our reference	: U-7988/JR/fs/459-B69
Enclosed	: 1
Date	: December 11, 2013

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to *molybdenum and molybdenum compounds.*

This advisory report is part of an extensive series in which health-based recommended exposure limits are derived for the concentrations of various substances in the workplace. The advisory report in question was prepared by the Health Council's Dutch Expert Committee on Occupational Safety (DECOS) and assessed by the Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,
(signed)
Professor W.A. van Gool,
President

Annex **D**

Comments on the public review draft

A draft of this advisory report was released in 2010 for public review. The following organisations and persons have commented on the draft:

- Mr. J. Lentz, National Institute for Occupational Safety and Health, USA
- Ms. S. Carey, International Molybdenum Association, UK.

Based on new data, in 2013 an adjusted draft was released for public review. The following organisations and persons have commented on this draft:

- Ms. S. Carey, International Molybdenum Association, UK.

The comments and the replies by the Committee can be inspected at the website of the Health Council: www.healthcouncil.nl.

Annex **E**

Evaluation by the Subcommittee on the classification of carcinogenic substances

Evaluation of data on carcinogenicity and genotoxicity

There are no human data on the possible carcinogenic activity of molybdenum and molybdenum compounds.

The US National Toxicology program performed an extensive inhalation study in rats and mice concerning the carcinogenic effects of molybdenum trioxide.[43,56] In male mice, the number of animals with lung tumours was statistically significantly increased at the lowest exposure concentration of 10 mg/m^3 compared to controls. This increase, however, was not dose-dependent. The incidence of lung tumours (adenomas) in female mice was statistically significantly increased as well after exposure to 30 and 100 mg/m^3. In exposed male and female rats, no statistically significantly increased incidence in tumours was observed. Furthermore, the subcommittee noted that rats exposed to 30 mg/m^3 showed inflammatory changes in the lungs, comparable with the effects observed for particles. On the other hand, these inflammatory effects were not observed in mice. Overall, the subcommittee concludes that there is limited evidence of carcinogenicity of molybdenum trioxide in animals.

No mutagenic activity was observed for molybdenum trioxide, ammonium molybdate and sodium molybdate using in vitro assays. Molybdenum trioxide did not show clastogenic effects. In contrast to molybdenum trioxide, ammonium molybdate and sodium molybdate showed clastogenic effects, but these were minimal, and in one study negative (sodium molybdate). Overall, there is

insufficient evidence that the three molybdenum compounds have genotoxic potential. Therefore, the subcommittee is of the opinion that molybdenum trioxide, ammonium molybdate and sodium molybdate are probably not genotoxic.

Recommendation for classification

Based on the available information, the subcommittee is of the opinion that molybdenum trioxide is a suspected carcinogen to man, and recommends classifying the compound in category 2*.

The available data on other molybdenum compounds, including metallic molybdenum, are insufficient to evaluate the carcinogenic properties of these compounds.

The subcommittee

- R.A Woutersen, *chairman*
  Toxicologic Pathologist, TNO Quality of Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre
- J. Van Benthem
  Genetic Toxicologist, National Health Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center
- G.M.H. Swaen
  Epidemiologist, Dow Benelux NV, Terneuzen
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen
- J.M. Rijnkels, *scientific secretary*
  Health Council, The Hague

Date last meeting: June 2011.

* See Annex F for classification system.

Annex **F**

Classification of substances with respect to carcinogenicity

The Committee expresses its conclusions in the form of standard phrases:

Category	Judgement of the committee (GR_{GHS})	Comparable with EU Category	
		67/548/EEC (before 12/16/2008	EC No 1272/2008 (as from 12/16/2008
1A	The compound is known to be carcinogenic to humans. • 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, it is unclear whether the compound is genotoxic.	1	1A
1B	The compound is presumed to be as carcinogenic to humans. • 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, it is unclear whether the compound is genotoxic.	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

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[86]

Annex G

Evaluation by the Subcommittee on the Classification of reproductive toxic substances

Effects on fertility

In a cross-sectional study, Meeker et al. (2008, 2010) reported reduced sperm concentrations, sperm morphology, and serum testosterone levels in men exposed to molybdenum. According to the committee, more human studies are needed to reach a final conclusion on whether molybdenum is able to affect fertility in men. No other human studies are available concerning the effects of molybdenum and its compounds on fertility.

Molybdenum trioxide. In a study by the US National Toxicology Program, in rats and mice no statistically significant effects were observed on male fertility (sperm counts, concentration of epididymal spermatozoa, decreased epidydimus weight) after inhalation of molybdenum trioxide.

Molybdates. A number of studies were available concerning the effects on fertility after oral exposure to molybdates. In a poorly reported study, Pandey et al. (2002) demonstrated that oral exposure to sodium molybdate decreased the sperm motility and total sperm count in the absence of general toxicity (doses applied up to 50 mg/kg bw).[73] In addition, untreated pregnant rats showed increased implantation loss after mating with treated male rats. In another poorly reported study, Jeter et al. (1954) showed that the fertility of male rats (decreased number of litters) was decreased after exposure to disodium molybdate dihydrate in diets.[74] Furthermore, histopathologic examinations revealed degeneration of the seminiferous tubules. However, the body weight

gain of both male and female rats was statistically significantly decreased over the first eleven weeks. IMOA commissioned two animal experiments, in which rats were given sodium molybdate dihydrate at doses of up to 20 mg/kg/bw/day (28 days) or 60 mg/kg bw/day (90 days). No exposure-related fertility effects were observed.[52,53]

When female weanlings exposed to sodium molybdate dehydrate were mated with untreated male rats, Fungwe et al. (1990) found no effect on pregnancy rate, but the oestrus cycle length was statistically significantly prolonged.[75] On the other hand, no effect on oestrus cycle length of guinea pigs was observed by Howell et al. (1993) after oral molybdate treatment.[76] Also no changes in the oestrus cycles were observed in a study, in which female rats received sodium molybdate dihydrate in their diet for 90 days.[53]

A possible explanation for the observed adverse effects on sperm quality and male fertility could be the lower availability of copper. Molybdenum is known to be a copper chelator, which may lead to copper deficiency, as is described in cattle (see Chapter 6). Trace elements, such as copper (and zinc) play an essential role in spermatogenesis and male fertility.[87-89] Lower levels of copper may affect spermatogenesis, and thus sperm quality and male fertility, such as is observed in some animal studies.

In conclusion, effects on male fertility were observed in two poorly reported studies (Pandey and Singh, 2002; Jeter et al. (1954).[84,85] In addition, there are indications that exposure to molybdates might affect female fertility (prolonged oestrus cycle) in the study of Fungwe et al. (1990). However, these effects were not confirmed by Howell et al. (1993) and IMOA (2011). Summarizing, there are deficiencies in reporting of the studies but the effects cannot be ignored. Overall, there is evidence of fertility effects of molybdates in animals. In addition, a human study (Meeker et al., 2008, 2010) gave inconclusive indications for a possible effect of molybdate on male fertility. The subcommittee, therefore, recommends classifying molybdate compounds in category 2 ('*suspected human reproductive toxicant*') for effects on fertility.

About the effects of exposure to molybdenum trioxide, the subcommittee is of the opinion that a lack of appropriate data precludes the assessment of the compound for effects on fertility.

Effects on development

No human studies concerning the effects of molybdenum compounds on development are available.

Six studies in laboratory animals were available concerning the effects on development after oral exposure to molybdate compounds. Increased number of resorptions, and decreased foetal weight and foetal length were found in female Sprague Dawley rats (Fungwe et al. 1990).[75] Although these effects were observed in the presence of maternal toxicity (decreased weight gain of the dams), the committee agrees with the authors that the decreased maternal weight is probably due to weight loss of the progeny. In a poorly reported three-generation-study with only one exposure group, CD-mice showed an increase in early deaths among the progeny of the F_1-generation and F_3-generation (Schroeder 1971).[78] In the F_3-generation, increased number of pairs without offspring, reduced number of litter, increased number of litters with only stillbirths and underdeveloped pups were observed in the presence of increased mortalities of the dams. Jeter et al. (1954) found a decreased weight gain of the pups during lactation in Long Evans rats.[74] However, it was not clear whether these effects were a result of decreased milk production or due to direct exposure via the drinking water. Finally, in a poorly reported study, Howell et al. (1993) found developmental effects (aborted and resorbing fetuses) in the presence of severe maternal toxicity (death).[76] In two animal studies, sodium molybdate dihydrate did not cause maternal toxicity, nor fertility effects and malformations in the progeny. The compound was given via the diet at doses up to 40 mg molybdenum/kg bw/day during gestation days 6 and 20.[72,77]

In conclusion, the subcommittee is of the opinion that the study of Fungwe et al. (1990) gives some indications for effects on the development of the progeny. However, this study is not sufficient for a classification. The remaining studies do not support the findings of Fungwe et al. (1990) as the observed effects were found in the presence of maternal toxicity. No final conclusion can be made from the two studies in which no maternal and developmental effects were observed, since, for classification and labelling, this indicates that the chosen exposure levels were too low to induce adverse health effects. Therefore the subcommittee recommends not classifying molybdate compounds for effects on development due to a lack of appropriate data.

With respect to the effects of exposure to molybdenum trioxide, the subcommittee is of the opinion that a lack of appropriate data precludes the assessment of molybdenum trioxide for effects on development.

Effects on lactation

Aquilio et al. (1996) detected in human breast milk molybdenum levels of 6.8 µg/L.[29] Another study by Al-Saleh et al. (2004), levels of 13±1 µg/L in

maternal venous blood at delivery are reported (N=17).[90] This molybdenum concentration was below the calculated safe level of 25 µg per litre breast milk. Therefore, the subcommittee concludes that the available data do not indicate that a label for the effects on lactation is warranted and recommends no labelling.

Proposed classification for effects on fertility

For molybdate compounds: the subcommittee recommends classifying molybdate compounds in category 2 (*suspected human reproductive toxicant*), and labelling with H361f (*suspected of damaging fertility).*

For molybdenum trioxide: lack of appropriate data precludes the assessment of molybdenum trioxide for effects on fertility

Proposed classification for developmental toxicity

Lack of appropriate data precludes the assessment of molybdenum compounds (molybdate compounds and molybdenum trioxide) for effects on development

Proposed labelling for effects during lactation

Lack of appropriate data precludes the assessment of molybdenum compounds (molybdate compounds and molybdenum trioxide) for effects during lactation

The Subcommittee

- A.H. Piersma, *chairman*
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- D. Lindhout
  Professor of Medical Genetics, Paediatrician (not practising), Clinical Geneticist, University Medical Centre, Utrecht
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- J.T.J. Stouten, *scientific secretary*
  Health Council of the Netherlands, The Hague
- J.M. Rijnkels, *scientific secretary*
  Health Council of the Netherlands, Den Haag

Date last meeting: September 2013.

Notice on classification

The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and development as well as lactation of the above mentioned compound.

Classification for reproduction (fertility (F) and development (D)):	
Category 1	Known or presumed human reproductive toxicant (H360(F/D))
Category 1A	Known human reproductive toxicant
Category 1B	Presumed human reproductive toxicant
Category 2	Suspected human reproductive toxicant (H361(f/d))
No classification for effects on fertility or development	
Classification for lactation:	
	Effects on or via lactation (H362)
	No labelling for lactation

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC) 1272/2008). The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the subcommittee has agreed upon a number of additional considerations:

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects.
- Adverse effects in a reproductive study, occurring without reporting the parental or maternal toxicity, may lead to a classification other than category

1B, when the effects occur at dose levels which cause severe toxicity in *general* toxicity studies.

- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- The Committee does not only use guideline studies (studies performed according to OECD* standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

* Organisation for Economic Cooperation and Development.

Annex **H**

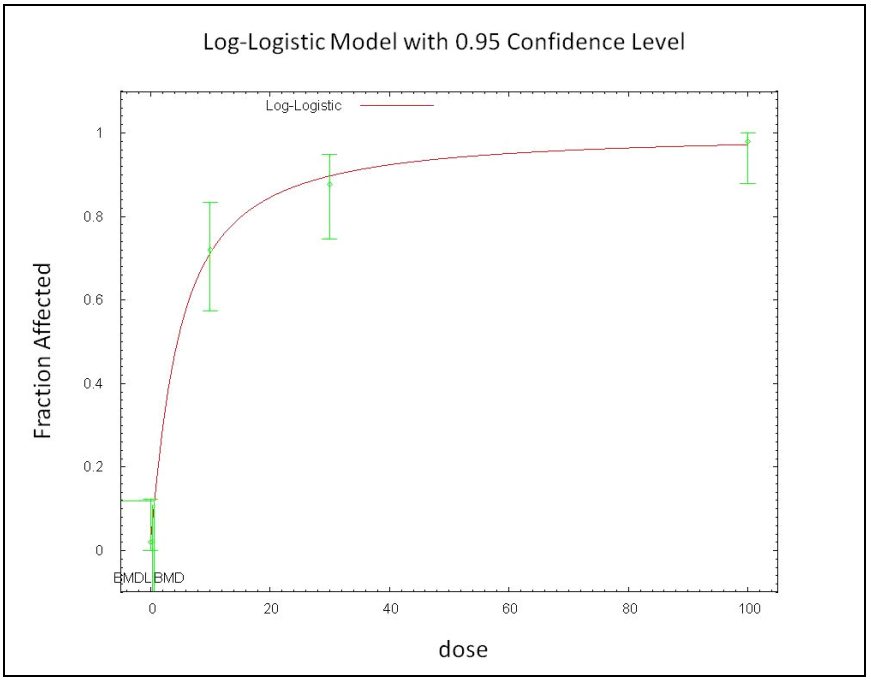
BMD-analysis: inhalation study on pathological respiratory tract effects by molybdenum trioxide

Software	: US EPA BMDS version 2.1.1.
Model type	: Dichotomous, restricted models.
BMR, risk type	: 10%, extra risk (default value for dichotomous (quantal) animal data).
BMDL	: Lowest 95% confidence interval of the BMD.
Model fitting	: Based on visual inspection of graphs, judgment on BMD-BMDL deviation (model accepted at a deviation of < factor 10), and calculated differences in log-likelihoods
Data source	: NTP (1997) and Chan et al. (1998).[43,56] Data only analysed using statistical difference ($p<0.05$) between exposed and control group.
Exposure	: 6 hours/day, 5 days/week for 105 weeks; inhalation of molybdenum trioxide.
Effects	: Pathological lesions in respiratory tract of rats and mice of both sexes.

	0 mg/m³	10 mg/m³	30 mg/m³	100 mg/m³	BMDL[a] mg/m³
Male F344/N rats (cases/group size)					
Lung: alveolus chronic inflammation	2/50	3/50	25/50*	47/50*	9.67
Larynx: epiglottis, squamous metaplasia	0/49	11/48*	16/49*	39/49*	3.33
Female F344/N rats (cases/group size)					
Lung: alveolus chronic inflammation	14/50	13/50	43/50*	49/50*	6.58
Nose: respiratory epithel. hyaline degeneration	1/48	13/49*	50/50*	50/50*	7.20
Larynx: epiglottis, squamous metaplasia	0/49	18/49*	29/49*	49/50*	1.87
Male B6C3F$_1$ mice (cases/group size)					
Lung: alveolar/bronchiolar epithelium metaplasia	0/50	32/50*	36/49*	49/50*	0.52
Larynx: epiglottis, squamous metaplasia	0/50	26/49*	37/48*	49/50*	0.70
Female B6C3F$_1$ mice (cases/group size)					
Lung: alveolar/bronchiolar epithelium metaplasia	2/50	26/50*	39/49*	46/49*	0.71
Lung: adenoma/carcinoma	3/50	6/50	8/49	15/49*	18.00
Larynx: epiglottis, squamous metaplasia	1/49	36/50*	43/49*	49/50*	0.29

* $p<0.01$.

[a] Model of choice: Loglogistic.



Graph BMD-analysis: larynx female B6C3F1$_1$ mice, squamous metaplasia epiglottis.

Annex I

BMD-analysis: diet study on body weight effects by sodium molybdate

Software	: US EPA BMDS version 2.1.1.
Model type	: Continuous, restricted constant variance models, lognormal distribution.
BMR, risk type	: 10% response, relative deviation (default for changes in body weight).
BMDL	: Lowest 95% confidence interval of the BMD.
Model fitting	: Based on visual inspection of graphs, judgment on model deviation (BMD-values of the models *Exponential5* and *Hill* must be close), and judgment on BMD-BMDL deviation (model accepted at a deviation of < factor 10).
Data source	: IMOA (2011).[53] Data only analysed using statistical difference ($p<0.05$) between exposed and control groups.
Exposure	: Daily for 90 days; oral administration in the diet of sodium molybdate dihydrate.
Effects	: Effects on body weight and body weight gain in male rats. Data given below concern weights and weight gains at the end of the exposure period.

	0 mg /kg bw	5 mg/kg bw	17 mg/kg bw	60 mg/kg bw	Lowest BMDL mg/kg bw	Model of choice[a]
Mean body weight (grams ± SD)						
	587.1 ± 50.3	583.9 ± 41.4	576.3 ± 47.9	498.5 ± 32.9*	26.0	Exp4
Mean body weight changes from baseline (grams ± SD)						
	246.3 ± 38.9	242.6 ± 37.6	240.1 ±33.9	164.4 ± 30.1*	10.9	Exp4

* $p<0.05$.

[a] Exp4 corresponds to Exponential Model 4. Model of choice based on lowest BMDL-value. Group size: 0, 5, 17, and 60 mg/kg bw, n = 20, 10, 10 and 19, respectively; concentration concerns mg molybdenum/kg bw.