MOLYBDENUM TRIOXIDE

1. Exposure Data

1.1 Identification

Chem. Abstr. Serv. Reg. No.: 1313-27-5

Chem. Abstr. Serv. Name: Molybdenum trioxide

IUPAC systematic name: Trioxomolybdenum (ECHA, 2016a)

Other common names: Molybdenum oxide, molybdenum (VI) oxide, molybdenum (VI) trioxide, molybdic acid anhydride, molybdic anhydride, molybdic oxide, molybdite

Molecular formula: MoO_3

Relative molecular mass: 143.94

Density: 4.69 g/cm^3 at 26 °C (HSDB, 2017)

Melting point: 795 °C (HSDB, 2017)

Boiling point: 1155 °C, sublimes (HSDB, 2017)

Solubility in water: 1.0 g/L at 20 °C (ECHA, 2016a). It is slightly soluble in water at room temperature, the saturated solution being acid (pH 2.5) (ECHA, 2016a).

Molybdenum trioxide (MoO_3) is a white solid at room temperature (HSDB, 2017).

Technical-grade molybdenum trioxide (see Section 1.2.1) typically contains 80% molybdenum trioxide, 6% molybdenum suboxides, 4% iron molybdates, 3% quartz, 1% calcium molybdate, 0.45% copper compounds, 0.03% lead compounds, and 0.012% arsenic compounds (Christensen et al., 2015).

1.2 Production and use

1.2.1 Production process

Molybdenum trioxide occurs naturally as the rare mineral molybdite (Anthony et al., 2001–2005), but is obtained commercially almost exclusively from molybdenite (molybdenum (IV) sulfide, MoS_2) (Sebenik et al., 2012). Molybdenite ore is crushed, ground, and passed through flotation cells to obtain about 90% molybdenum (IV) sulfide (Steifel, 2010). The remainder is mainly silica, with small amounts of aluminium, copper, and iron. Impure molybdenum trioxide, also called technical-grade or roasted molybdenum sulfide (CAS No. 86089-09-0), is obtained by roasting the molybdenum (IV) sulfide concentrate in air in a multiple-hearth furnace at a temperature of 600–650 °C (Sebenik et al., 2012). Pure molybdenum trioxide is obtained by sublimation or by wet chemical methods (Steifel, 2010). Other methods of molybdenum trioxide production exist. Hydrometallurgical routes, including solvent extraction, ion exchange, membrane-based separation, and precipitation,

have the advantage of producing molybdenum trioxide without emission of sulfur dioxide (Lasheen et al., 2015).

1.2.2 Production volume

World molybdenum (as Mo metal) mine production was estimated at 281 000 tonnes for 2014 (Polyak, 2016). Table 1.1 lists the mine production by country (more specific information about MoO_3 is not available). About half of the total amount of mine production is converted into and used as molybdenum trioxide (Christensen et al., 2015). National production volume of molybdenum trioxide in the USA was estimated at 83 290 tonnes for 2014 (EPA, 2016).

Molybdenum trioxide is a high production volume chemical. High production volume chemicals "are produced or imported at levels greater than 1,000 tonnes per year in at least one member country/region" of the Organisation for Economic Co-operation and Development (OECD, 2009).

1.2.3 Use

Technical-grade molybdenum trioxide is primarily and directly used in steel production. The rest is used in the synthesis of various molybdate salts (Stiefel, 2011).

In 2014 in the USA, metallurgical applications (corrosion inhibitor) accounted for ~88% of consumption. Christensen et al. (2015) estimated the world consumption of molybdenum trioxide to be divided between: ~80–90% for various steel applications; ~10% for catalysts (mainly for refineries); and ~5% for super alloys.

The lead REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) registrant for molybdenum trioxide lists the current uses for this chemical as: catalyst manufacturing, an intermediate in the manufacture of molybdenum chemicals, surface treatment substances, molybdenum metal, frits and enamels (blue dye), liquid industrial paints, pigments, water treatment chemicals, lubricant additives, lubricants and greases, and an intermediate for reduction to molybdenum dioxide in steel and alloy production and in steel and alloy powder production (CLIMAX, 2016).

Furthermore, recent research initiatives indicate that uses of molybdenum trioxide may increase in the future due to its interesting properties in new technologies, for example: solar energy harvesting and storing, and biocidal activity on material surfaces (Zollfrank et al., 2012; Lou et al., 2014). Some applications (catalyst, coatings, and ceramics) are facilitated by the use of molybdenum trioxide in the form of nanoparticles or nanotubes in combination with other molybdenum compounds (Jin et al., 2016).

Table 1.1 Mine production of molybdenum, by country, 2014

Country	Production (tonnes)
China	103 000
USA	68 200
Chile	48 770
Peru	17 018
Mexico	14 370
Canada	9 698
Armenia	7 100
Russian Federation	4 800
Islamic Republic of Iran	4 000
Mongolia	1 999
Turkey	1 300
Uzbekistan	530

Adapted from Polyak (2016)

1.3 Measurement and analysis

Molybdenum trioxide is measured by the analyte molybdenum in air, blood, tissue, urine, or water samples (Table 1.2). Air sampling to determine molybdenum can be performed using the National Institute for Occupational Safety and Health (NIOSH) Method 7300 or 7303 for elements by inductively coupled plasma.

Table 1.2 Analytical methods for molybdenum in different matrices

Sample matrix	Assay procedure	Limit of detection	Method/reference
Air	ICP-AES	0.8 ng/mL	NIOSH 7300, NIOSH 7303
Blood (plasma or whole blood)	ICP-AES	10 µg/10 mL	NIOSH 8005
Plasma	ICP-MS		Keyes & Turnlund (2002)
Tissue	ICP-AES	10 µg/g	NIOSH 8005
Urine	ICP-AES	2.0 µg/50 mL	NIOSH 8310
Water (drinking, surface, and domestic and industrial wastewaters)	ICP-AES	12 µg/L	EPA 200.7
Water	AAS	0.1 mg/L	Franson (1985)

AAS, atomic absorption spectrometry; AES, atomic emission spectrometry; ICP, inductively coupled plasma; MS, mass spectrometry

Molybdenum can be determined in other matrices by inductively coupled plasma mass spectrometry.

1.4 Occurrence and exposure

Molybdenum trioxide occurs naturally as the rare mineral molybdite. However, environmental levels of molybdenum trioxide have not been reported in the literature; it is therefore total elemental molybdenum that is discussed here.

1.4.1 Environmental occurrence

Environmental exposure to molybdenum is negligible for most people.

(a) Water/air

Most natural water worldwide contains low concentrations of molybdenum of < 2–3 µg/L. Around areas of molybdenum mining or other industrial manufacturing of molybdenum, concentration in water may reach up to 400 µg/L in surface water and up to 25 000 µg/L in groundwater (Barceloux & Barceloux, 1999). Molybdenum concentration in water can vary widely over short distances, but waters with an elevated pH will have increased solubility of molybdenum and increased leaching of molybdenum from soil to water (Runnells et al., 1977). Molybdenum in ambient air is typically very low, with concentrations in urban areas of 0.01–0.03 µg/m^3 and approximately 10 times lower in rural areas, except where molybdenum mining or manufacturing occurs (Barceloux & Barceloux, 1999). Molybdenum trioxide could be present in waste water, with the majority coming from industrial sites that use molybdenum trioxide in catalysts or alloys. However, in countries where recycling facilities exist, molybdenum is often recycled due to its economic value. For this reason, it is generally believed that molybdenum trioxide in wastewater streams is typically low in developed countries (Danish Ministry of the Environment, 2015). For the majority of people worldwide, ambient air and drinking-water exposures to molybdenum are negligible compared with dietary intake, especially for exposures to molybdenum trioxide (Lener & Bíbr, 1984).

(b) Soil

The typical range of molybdenum concentrations found in soil is 1–2 mg/kg (Barceloux & Barceloux, 1999). The concentration of molybdenum varies considerably with the type of soil, however (Runnells et al., 1977); sedimentary soils contain higher concentrations of molybdenum than acidic soils, with molybdenum at concentrations of > 0.7 mg/kg and < 0.2 mg/kg, respectively (Barceloux & Barceloux, 1999).

(c) Food

Diet is the major source of exposure to molybdenum for most people. Dietary analysis of 56 adults in Germany found molybdenum intake to be < 100 µg/day (Anke et al., 1991). Studies in the USA found a range of intakes over 120–240 µg/day for adults (Tsongas et al., 1980). Similarly, the European Food Safety Authority reported that dietary intake in European adults ranges over 58–57 µg/day, and the United States Institute of Medicine reported a range of 120–240 µg/day in the USA (Institute of Medicine, 2001; EFSA, 2013). Health Canada reported similar intakes in adults; during 1993–1999, average dietary intake of molybdenum for Canadians of all ages was estimated at 2.66 µg/kg body weight (bw) per day (Health Canada, 2011). Foods with the highest molybdenum content include legumes, leafy vegetables, beans, cereal grains, kidney, liver, and milk. Only small quantities are found in fruits, sugar-rich foods, and meat. The United States Institute of Medicine has established recommended dietary allowances, which is the average daily intake sufficient to meet nutrient requirements of healthy people, based on age and sex. These range from 2 µg/day in infants to 45 µg/day in adult men and women (Institute of Medicine, 2001). Molybdenum deficiency is extremely rare, as is molybdenum overdose due solely to dietary intake. A tolerable upper intake level for molybdenum was determined by the European Food Safety Authority to be 0.01 mg/kg bw per day, equivalent to 0.6 mg/person per day for adults (EFSA, 2006).

1.4.2 Exposure of the general population

The general population will typically only be exposed to molybdenum through diet, including drinking-water, with negligible exposure due to ambient air or soil. The United States National Health and Nutrition Examination Survey (NHANES) measures molybdenum in urine of the general USA population. In 484 people aged 18–55 years sampled for NHANES during 2011–2012, geometric mean urine molybdenum was 41.5 µg/L; no samples fell below the analytical limit of detection (Lewis & Meeker, 2015). The Canadian Health Measures Survey (CHMS) also measures for molybdenum in urine and blood in the general Canadian population. In all 5319 subjects aged 6–79 years measured during 2007–2009, the geometric mean urine molybdenum was 36.3 µg/L in urine and 0.68 µg/L in blood. In adults aged 20–79 years, the geometric mean urine and blood molybdenum were 32.9 µg/L and 0.67 µg/L, respectively (Health Canada, 2011). During 2012–2013 11 healthy men in China with no occupational history of working with metals gave multiple urine samples over a 3-month period. Mean molybdenum was 98.5 µg/L in 529 spot urine samples collected, with the first morning sample having a higher mean molybdenum concentration of 122.8 µg/L (Wang et al., 2016).

The molybdenum content in human breast-milk ranges from < 0.1 µg/L to > 60 µg/L, depending on days postpartum and mothers' diet. Infant formulas have more molybdenum than breast-milk (Gunshin et al., 1985; Casey & Neville, 1987; Yoshida et al., 2008; Mohd-Taufek et al., 2016).

1.4.3 Occupational exposures

See Table 1.3

Common occupations with exposure to molybdenum trioxide include mining and metallurgy works, steel foundries, and welding and other hot work processes using steel.

Exposure to respirable molybdenum dust was measured for 25 male workers in a molybdenite roasting plant in Denver, Colorado in the 1970s, at which stationary dust samples were collected from three locations. Results showed that the 8-hour time-weighted average molybdenum concentration ranged over 1.02–4.49 mg/m^3. All 25 workers gave a plasma

Table 1.3 Occurrence of molybdenum in facilities using molybdenum trioxide

Reference	Location, collection date	Occupation description	Sampling matrix, *n*	Exposure level[a]	Exposure range	Comments/additional data
Walravens et al. (1979)	USA, 1979	Roasting plant miners	Respirable air, *n* = 3	NR	1.02–4.49 mg/m³	Samples taken at three different locations in plant: base of roaster (1.02 mg/m³), first tier (1.58 mg/m³), and second tier (4.49 mg/m³) Total dust stationary samples collected at the first tier and second tier of the roasting plant 18 people not in the roasting plant
			Total dust, environmental, *n* = 2	NR	9.11–33.28 mg/m³	
			Plasma, *n* = 25	NR	9–365 µg/L	
		Student/research personnel	Urine, *n* = 14	1790 µg/L	120–11 000 µg/L	
			Urine, *n* = 18	53.66 µg/L	20–230 µg/L	
			Plasma, *n* = 24	NR	< LOD–34 µg/L	
Kucera et al. (2001)	NS	Stainless steel vessel production welders	Total dust, personal, *n* = 15, 8 h	2.25 µg/m³	0.27–9.7 µg/m³	Closed-face cassette with 0.8 µm pores
		Stainless steel vessel production drillers, cutters, assemblers	Total dust, personal, *n* =15, 8 h	0.34 µg/m³	0.14–0.60 µg/m³	
		Stainless steel vessel production polishers	Total dust, personal, *n* = 9, 8 h	1.86 µg/m³	0.03–4.2 µg/m³	
Huvinen et al. (2002)	Finland, 1999	Stainless steel production, steel melting shop	Air, personal, *n* = 6	Median 0.3 µg/m³	Maximum 2.3 µg/m³	Details on sampling method not specified

[a] Arithmetic mean unless indicated otherwise

LOD, limit of detection; NR, not reported; NS, not specified

sample, and 14 workers gave a urine sample. Plasma molybdenum concentrations ranged over 9–365 µg/L and urine molybdenum concentrations over 120–11 000 µg/L (Walravens et al., 1979). These urine values are greater than those found by NHANES and Health Canada in the general population (see Section 1.4.2).

Twenty stainless steel vessel production workers were monitored for exposure to molybdenum in dust in a study published in 2001. The stainless steel used in the plant contained an average of 2.0–2.5% molybdenum. Workers were divided into groups defined by occupational task: welding, polishing, or other (drilling, cutting, or assembling). Molybdenum exposure for each group had a mean value of 0.3–2 µg/m^3 over the range 0.03–9.7 µg/m^3 (see Table 1.3; Kucera et al., 2001).

Another study of occupational exposure published in 2002 took personal and area samples of molybdenum in a steel melting shop. From 6 personal samples and 17 stationary samples, the median molybdenum concentration was 0.3 µg/m^3 (maximum value: 2.3 µg/m^3) and 0.6 µg/m^3 (maximum value: 4 µg/m^3), respectively (Huvinen et al., 2002).

[The Working Group noted that air exposures to molybdenum were about three orders of magnitude higher at the Colorado roasting plant compared with the metal working shops. However, the samples at the roasting plant were acquired several decades earlier than those from the metalworking shops.]

1.5 Regulations and guidelines

A specific limit value for occupational exposure to molybdenum trioxide of 0.5 mg/m^3 as an 8-hour total weight average (TWA) concentration only exists in Finland. No values for short-term limit exist (GESTIS, 2017).

For insoluble molybdenum compounds in general, many countries have limit values ranging over 3–15 mg/m^3 as an 8-hour TWA concentration. Corresponding short-term limit values range over 10–60 mg/m^3. For soluble molybdenum compounds these ranges are 0.5–5 mg/m^3 (8-hour TWA) and 10–20 mg/m^3 (short-term limit value as Mo) (GESTIS, 2017).

Molybdenum trioxide has an official harmonized classification in the EU Classification and Labelling Regulation. In Regulation (EC) No. 1272/2008, it is classified as a Category 2 Carcinogen H351: "Suspected of causing cancer" as well as STOT SE 3: H335: "May cause respiratory irritation" and H319: "Causes serious eye irritation" (ECHA, 2016b).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Mouse

See Table 3.1

3.1.1 Inhalation

In a well-conducted good laboratory practice (GLP) study, groups of 50 male and 50 female B6C3F$_1$ mice (age, 6 weeks) were exposed by whole-body inhalation to molybdenum trioxide (purity, ~99%; mass median aerodynamic diameter, 1.3–1.8 µm) at concentrations of 0, 10, 30, or 100 mg/m^3 for 12 min (T_{90}) plus 6 hours per day, 5 days per week for up to 105 weeks on study (NTP, 1997; Chan et al., 1998). The body weights of the female mice were generally greater than those of the control group from week 11 until the end of the study. The survival of treated male and female mice was similar to that of controls. The incidence of metaplasia of the alveolar epithelium was significantly increased in all exposed groups of males and females. The incidences of

Table 3.1 Studies of carcinogenicity with molybdenum trioxide in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of lung tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 6 wk 105 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min (T90)/d, 5 d/wk 50, 50, 50, 50 36, 33, 25, 37	Bronchioloalveolar adenoma 9/50, 14/50, 10/49, 9/50 Bronchioloalveolar carcinoma 2/50, 16/50, 14/49, 10/50 Bronchioloalveolar adenoma or carcinoma (combined) 11/50, 27/50, 21/49, 18/50	NS $P < 0.001$ (low dose), $P < 0.001$ (mid-dose), $P = 0.017$ (high dose) $P = 0.001$ (low dose), $P = 0.020$ (mid-dose)	Principal strengths: GLP study; physiological exposure route; both sexes used Statistical test: logistic regression test
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6 wk 105 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 25, 31, 33, 35	Bronchioloalveolar adenoma 1/50, 4/50, 8/49, 9/49 Bronchioloalveolar carcinoma 2/50, 2/50, 0/49, 6/49 Bronchioloalveolar adenoma or carcinoma (combined) 3/50, 6/50, 8/49, 15/49	$P = 0.018$ (trend), $P = 0.036$ (mid-dose), $P = 0.016$ (high dose) $P = 0.024$ (trend) $P < 0.001$ (trend), $P = 0.003$ (high dose)	Principal strengths: GLP study; physiological exposure route; both sexes used Historical control incidence for NTP studies: adenoma, 61/939 (6.5 ± 3.2%) [range, 0–14%]; carcinoma, 38/939 (4.1 ± 3.2%) [range, 0–12%]; adenoma or carcinoma (combined), 97/939 (10.3 ± 3.7%) [range, 0–16%] Statistical test: logistic regression test
Full carcinogenicity Mouse, A/J (M+F combined) 6–8 wk 30 wk Stoner et al. (1976)	Intraperitoneally MoO_3, > 97% Saline 0, 950, 2735, 4750 mg/kg bw 19 times 20, 20, 20, 20 19, 13, 19, 15	Tumour [presumably adenomas] incidence 7/19, 4/13, 7/19, 10/15 Tumour multiplicity 0.42 ± 0.10, 0.30 ± 0.08, 0.50 ± 0.13, 1.13 ± 0.20*	[NS] *$P < 0.05$ (Student's *t* test)	Principal limitations: limited histopathological examination Equal number of M and F; incidences for M and F were combined

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence or multiplicity of lung tumours	Significance	Comments
Full carcinogenicity Rat, F344/N (M) 6 wk 106 wk NTP (1997)	Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m^3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 17, 10, 16, 17 Inhalation (whole-body exposure) MoO_3, ~99% Clean air 0, 10, 30, 100 mg/m3 6 h + 12 min/d, 5 d/wk 50, 50, 50, 50 28, 24, 24, 23	Bronchioloalveolar adenoma 0/50, 0/50, 0/50, 3/50 Bronchioloalveolar carcinoma 0/50, 1/50, 1/50, 1/50 Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 1/50, 1/50, 4/50 Bronchioloalveolar adenoma or carcinoma (combined) 0/50, 2/50, 0/50, 2/50	 $P = 0.017$ (trend) NS $P = 0.034$ (trend) NS	Principal strengths: GLP study; physiological exposure route; both sexes used Principal limitations: poor survival of exposed and control animals Historical control incidence at laboratory: adenoma, 16/347 (4.6 ± 4.0%) [range, 0–10%]; carcinoma, 4/347 (1.2 ± 1.1%) [range, 0–2%]; adenoma or carcinoma (combined), 20/347 (5.8 ± 3.7%) [range, 0–10%] Adjusted incidences: adenoma, 0.0, 0.0, 0.0, 14.8%; adenoma or carcinoma (combined), 0.0, 5.3, 4.3, 17.4% Terminal rate: adenoma, 0/17, 0/10, 0/16, 1/17; adenoma or carcinoma (combined), 0/17, 0/10, 0/16, 1/17 Statistical test: logistic regression test

bw, body weight; d, day(s); F, female; GLP, good laboratory practice; M, male; min, minute(s); MoO_3, molybdenum trioxide; NS, not significant; NTP, National Toxicology Program; wk, week(s)

carcinoma of the bronchioloalveolar were significantly increased in male mice (2 out of 50, 16 out of 50, 14 out of 49, and 10 out of 50) for all treated groups, and there was a significant positive trend in the incidence in females (2 out of 50, 2 out of 50, 0 out of 49, and 6 out of 49). The incidences of adenoma of the bronchioloalveolar were significantly increased in female mice (with a significant positive trend) exposed to 30 mg/m^3 and 100 mg/m^3 (1 out of 50, 4 out of 50, 8 out of 49, and 9 out of 49) and the incidences of adenoma or carcinoma (combined) of the bronchioloalveolar were significantly increased in female mice exposed to 100 mg/m^3 (3 out of 50, 6 out of 50, 8 out of 49, and 15 out of 49) and in male mice exposed to 10 mg/m^3 and 30 mg/m^3 (11 out of 50, 27 out of 50, 21 out of 49, and 18 out of 50). [The Working Group noted the strengths of the study: this was a GLP study, a physiological exposure route was employed, and both sexes were used.]

3.1.2 Intraperitoneal injection

Four groups of 20 A/J mice (equal numbers of male and female mice; age, 6–8 weeks) were given intraperitoneal injections of 0 (vehicle control), 950, 2735, or 4750 mg/kg bw (total doses) reagent-grade molybdenum trioxide (purity > 97%; impurities unspecified) in saline three times per week for a total of 19 injections (except saline controls: 24 injections). After 30 weeks, 13, 19, and 15 animals were still alive in the three treated groups. At that time, these animals and 19 surviving vehicle controls were killed and their lungs examined macroscopically for tumour induction; a few of the grossly visible nodules were examined microscopically to confirm the typical appearance of adenomas of the lung. The incidences of mice with lung tumours were 7 out of 19, 4 out of 13, 7 out of 19, and 10 out of 15 [no statistically significant differences], and the average number of lung tumours per mouse (multiplicity) was 0.42 ± 0.10, 0.30 ± 0.08, 0.50 ± 0.13, and 1.13 ± 0.20 (average ± standard error) for the 0, 950, 2735, or 4750 mg/kg bw groups, respectively. Lung tumour multiplicity in the 4750 mg/kg bw group was significantly ($P < 0.05$) higher than the vehicle control group (Stoner et al., 1976). [The Working Group noted the limitations of the study: the non-physiological route of exposure, the limited histopathological examination, and the combination of tumour incidences for male and female mice.]

3.2 Rat

See Table 3.1

3.2.1 Inhalation

In a well-conducted GLP study, groups of 50 male and 50 female Fischer 344/N rats (age, 6 weeks) were exposed by whole-body inhalation to molybdenum trioxide (purity, ~99%; mass median aerodynamic diameter, 1.3–1.8 μm) at concentrations of 0, 10, 30, or 100 mg/m^3 for 6 hours plus 12 min per day, 5 days per week for 106 weeks on study (NTP, 1997; Chan et al., 1998). Mean body weights of male and female exposed rats were similar to those of controls throughout the study. The survival of exposed and control rats was poor, but survival of male and female exposed rats was similar to those of their respective controls. The incidence of chronic inflammation of the alveolar was significantly increased in male and female treated rats. The incidences of adenoma of the bronchioloalveolar (0 out of 50, 0 out of 50, 0 out of 50, and 3 out of 50 for 0, 10, 30, and 100 mg/m^3, respectively) and of adenoma or carcinoma (combined) of the bronchioloalveolar (0 out of 50, 1 out of 50, 1 out of 50, and 4 out of 50) were increased in male rats with a significant positive trend ($P = 0.017$ and $P = 0.034$, respectively); these incidences were within historical control incidence ranges. The incidences of carcinoma of the bronchioloalveolar were 0 out of 50, 1 out of 50, 1 out of 50, and 1 out of 50 in male rats. No significant increase

in the incidence of lung neoplasms occurred in female rats. [The Working Group noted the strengths of the study: this was a GLP study, a physiological exposure route was employed, and both sexes were used. The Working Group also noted the poor survival of exposed and control male and female rats.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

4.1.1 Humans

No studies on molybdenum trioxide (MoO_3) in exposed humans were available to the Working Group.

Regarding elemental molybdenum (Mo), several publications from the same laboratory reported on toxicokinetics of radiolabelled elemental molybdenum following exposure to four healthy men. Turnlund and colleagues used a compartmental model based on isotope excretion patterns to determine molybdenum absorption, distribution, and elimination (Turnlund et al., 1995, 1998, 1999; Thompson & Turnlund, 1996; Novotny & Turnlund, 2006). Four healthy men were fed a low-molybdenum diet (22 µg/day or 0.23 µmol/day) for 102 days, followed by a high-molybdenum diet (467 µg/day or 4.9 µmol/day) for 18 days. Molybdenum was very efficiently absorbed, distributed, and excreted, primarily in the urine (Turnlund et al., 1995; Thompson & Turnlund, 1996).

4.1.2 Experimental systems

Exposure-dependent increases in blood molybdenum concentrations were seen in male and female F344/N rats and $B6C3F_1$ mice exposed to 0, 10, 30, or 100 mg/m³ molybdenum trioxide via inhalation for 106 and 105 weeks, respectively (NTP, 1997; Chan et al., 1998; see Section 3). Blood concentrations of molybdenum were greater in exposed male rats than in exposed female rats. [The Working Group noted that the reported effects on respiratory tract tissues of male rats and female mice suggest distribution of molybdenum to lungs, although this was not directly examined in these studies.]

Metabolism and excretion of molybdenum were not reported in either of these studies.

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for key characteristics of carcinogens (Smith et al., 2016), addressing whether molybdenum trioxide is genotoxic and induces inflammation. There were insufficient data for the evaluation of other key characteristics of human carcinogens.

4.2.1 Genetic and related effects

See Table 4.1

No data in exposed humans, human cells in vitro, or in experimental systems in vivo were available to the Working Group.

Molybdenum trioxide did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells in vitro (NTP, 1997). Molybdenum trioxide was not mutagenic in the five tested strains of *Salmonella typhimurium*. All tests were conducted with and without S9 metabolic activation enzymes (NTP, 1997).

4.2.2 Chronic inflammation

In a 106-week chronic inhalation study in male and female F344/N rats, molybdenum trioxide increased the incidence and severity of inflammation in the lung (NTP, 1997; Chan et al., 1998; Ozaki et al., 2002; see Section 3). This effect was not observed in mice.

Table 4.1 Genetic and related effects of molybdenum trioxide in experimental systems in vitro

Species	Tissue, cell line	End-point	Test	Results		Concentration (LEC or HIC)	Reference
				Without metabolic activation	With metabolic activation		
Chinese hamster	CHO cells	Chromosomal damage	Chromosomal aberrations	–	–	HIC, 10 µg/mL	NTP (1997)
Chinese hamster	CHO cells	Chromosomal damage	Sister-chromatid exchange	–	–	HIC, 10 µg/mL	NTP (1997)
Prokaryote (bacteria)	Null TA100, TA1535, TA1537, TA97, TA98	Mutation	Reverse mutation	–	–	HIC, 10 000 µg/plate	NTP (1997)

–, negative; CHO, Chinese hamster ovary; HIC, highest ineffective concentration; LEC, lowest effective concentration

4.2.3 Other mechanisms

Data on other key characteristics of carcinogens were sparse, and no such data were available to the Working Group from exposed humans or from experimental systems in vivo.

Molybdenum trioxide nanoplates were more cytotoxic to the invasive MCF-7 breast cancer cells than the MCF-7 parental cell line, with significant differences in cytotoxicity starting at 50 µg/mL (Anh Tran et al., 2014).

In a mouse germline stem cell model, molybdenum trioxide nanoparticles were more cytotoxic than soluble molybdenum salts. The nanoparticulate molybdenum exerted its cytotoxic effects via cellular metabolic activity, but only at higher doses (≥ 50 µg/mL); very low concentrations (5–10 µg/mL) induced membrane leakage (Braydich-Stolle et al., 2005).

Molybdenum trioxide gave positive results in the assay for cell transformation in the Syrian hamster embryo, requiring a dose of ≥ 75 µg/mL to demonstrate morphological transformation (Kerckaert et al., 1996).

Lewis et al. (1996) noted that molybdenum trioxide has been predicted to generate oxygen radicals due to its metal ion redox potential (Lewis et al., 1996).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

In a chronic (106-week) inhalation study in male F344/N rats, molybdenum trioxide exposure (100 mg/m^3 dose only) induced fibrosis and metaplasia in the lung (NTP, 1997; Ozaki et al., 2002).

5. Summary of Data Reported

5.1 Exposure data

Molybdenum trioxide (MoO_3) is a white solid with rare natural occurrence in the form of the mineral molybdite. It is obtained commercially almost exclusively from roasting molybdenite (molybdenum sulfide). Molybdenum trioxide is a high production volume chemical. Globally, more than 100 000 tonnes of molybdenum trioxide are estimated to be produced annually, the majority for direct use in steel production. Other significant uses include catalysts and super alloys, and upcoming developments include the harvesting and storing of solar energy, and biocidal activity

on material surfaces. Environmental exposures to molybdenum trioxide are negligible. Occupational exposures may occur mainly in mining and metallurgy works, steel foundries, and welding and other hot work processes using steel. Molybdenum air concentrations measured in a plant producing molybdenum trioxide in the 1970s ranged from 1.02 to 4.49 mg/m^3, and associated plasma and urine molybdenum concentrations were significantly higher than in the general population. In contrast, in two recent studies of metal workers, molybdenum air concentrations were all < 0.01 mg/m^3.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Two well-conducted carcinogenicity studies under GLP conditions are described in Sections 3.1.1 and 3.2.1: an inhalation study in male and female mice and an inhalation study in male and female rats, respectively. Section 3.1.2 describes an intraperitoneal injection study in male and female strain A mice.

In the inhalation study in mice, molybdenum trioxide significantly increased the incidence of carcinoma of the bronchioloalveolar in male mice (with a significant positive trend), the incidence of adenoma of the bronchioloalveolar in female mice (with a significant positive trend), and the incidence of adenoma or carcinoma (combined) of the bronchioloalveolar in female (with a significant positive trend) and male mice. There was also a positive trend in the incidence of carcinoma of the bronchioloalveolar in female mice. In the inhalation study in rats, there was no statistically significant increase in tumour incidence in male and female rats. In male rats, however, there was a significant positive trend in the incidence of adenoma and adenoma or carcinoma (combined) of the bronchioloalveolar; the incidences were within historical control ranges. In the intraperitoneal injection study in mice, molybdenum trioxide increased the multiplicity (but not the incidence) of lung tumours (presumably adenomas) in male and female mice combined.

5.4 Mechanistic and other relevant data

No toxicokinetic studies of molybdenum trioxide in humans or in experimental animals were available.

With respect to the key characteristics of human carcinogens, there is *weak* evidence that molybdenum trioxide is genotoxic or induces chronic inflammation. No data were available in exposed humans. Data on other key characteristics of carcinogens were sparse.

No in vivo genotoxicity assay data were available. In vitro, molybdenum trioxide was positive in an assay for cell transformation but was not genotoxic in Chinese hamster ovary cells or in several *Salmonella* strains.

Molybdenum trioxide increased the incidence and severity of chronic lung inflammation in a 2-year inhalation study in both male and female rats, but not in mice. An analysis of the male rats from this bioassay showed increased incidence of lung fibrosis and metaplasia.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of molybdenum trioxide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of molybdenum trioxide.

6.3 Overall evaluation

Molybdenum trioxide is *possibly carcinogenic to humans (Group 2B).*

References

Anh Tran T, Krishnamoorthy K, Song YW, Cho SK, Kim SJ (2014). Toxicity of nano molybdenum trioxide toward invasive breast cancer cells. *ACS Appl Mater Interfaces*, 6(4):2980–6. doi:10.1021/am405586d PMID:24417578

Anke M, Groppel B, Krause U, Arnhold W, Langer M (1991). Trace element intake (zinc, manganese, copper, molybdenum, iodine and nickel) of humans in Thuringia and Brandenburg of the Fed. Rep. of Germany. *J Trace Elem Electrolytes Health Dis*, 5(2):69–74. PMID:1821712

Anthony JW, Bideaux RA, Bladh KW, Nichols MC (2001–2005). Handbook of Mineralogy. Tucson (AZ), USA: Mineral data publishing. Online version, Mineralogical Society of America, Chantilly, VA. Available from: http://www.handbookofmineralogy.org/pdfs/molybdite.pdf, accessed 17 August 2016.

Barceloux DG, Barceloux D (1999). Molybdenum. *J Toxicol Clin Toxicol*, 37(2):231–7. doi:10.1081/CLT-100102422 PMID:10382558

Braydich-Stolle L, Hussain S, Schlager JJ, Hofmann MC (2005). In vitro cytotoxicity of nanoparticles in mammalian germline stem cells. *Toxicol Sci*, 88(2):412–9. doi:10.1093/toxsci/kfi256 PMID:16014736

Casey CE, Neville MC (1987). Studies in human lactation 3: molybdenum and nickel in human milk during the first month of lactation. *Am J Clin Nutr*, 45(5):921–6. doi:10.1093/ajcn/45.5.921 PMID:3578094

Chan PC, Herbert RA, Roycroft JH, Haseman JK, Grumbein SL, Miller RA et al. (1998). Lung tumor induction by inhalation exposure to molybdenum trioxide in rats and mice. *Toxicol Sci*, 45(1):58–65. doi:10.1093/toxsci/45.1.58 PMID:9848111

Christensen FM, Warming M, Kjølholt J, Lau Heckmann L-H, Nilsson NH (2015). Survey of molybdenum trioxide. Environmental project No. 1716. Copenhagen, Denmark: Danish Environmental Protection Agency; Available from: http://mst.dk/service/publikationer/publikationsarkiv/2015/jul/survey-of-molybdenum-trioxide/

CLIMAX (2016). Chemical safety report: molybdenum trioxide. Rotterdam, The Netherlands: Climax Molybdenum BV. Available from: http://www.molybdenumconsortium.org/assets/files/Uses/MoTriox-2ndUpdateFeb2016-IdentifiedUses.pdf, accessed 15 December 2016.

Danish Ministry of the Environment (2015). Survey of molybdenum trioxide. Environmental project No. 1716, 2015. Available from: http://mst.dk/service/publikationer/publikationsarkiv/2015/jul/survey-of-molybdenum-trioxide/

ECHA (2016a). Molybdenum trioxide. Helsinki, Finland: European Chemicals Agency. Available from: https://www.echa.europa.eu/en/web/guest/registration-dossier/-/registered-dossier/15499/1, accessed 11 October 2016, Registration dossier.

ECHA (2016b). Harmonised classification - Annex VI of Regulation (EC) No. 1272/2008 (CLP Regulation). Available from: https://www.echa.europa.eu/fr/web/guest/information-on-chemicals/cl-inventory-database/-/discli/details/68763

EFSA (2006). Tolerable upper intake levels for vitamins and minerals. Scientific Committee on Food, Scientific Panel on Dietetic Products, Nutrition and Allergies, European Food Safety Authority, February 2006. Available from: http://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndatolerableuil.pdf

EFSA (2013). Scientific opinion on dietary reference values for molybdenum. *EFSA J.*, 11(8):3333 doi:10.2903/j.efsa.2013.3333

EPA (2016). ChemView [online database]. Washington (DC), USA: United States Environmental Protection Agency, Office of Pollution Prevention and Toxics. Available from: https://chemview.epa.gov/chemview, accessed 8 March 2018.

Franson MA (1985). Standard methods for the examination of water and wastewater.p. 174. [cited 2016 October 10]. Available from: Available from https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@rn+@rel+1313-27-5

GESTIS (2017). GESTIS Substance Database. IFA (Institut fur Arbeitsschutz). Available from: http://limitvalue.ifa.dguv.de/, accessed 17 January 2017.

Gunshin H, Yoshikawa M, Doudou T, Kato N (1985). Trace elements in human milk, cow's milk, and infant formula. *Agric Biol Chem*, 49(1):21–6.

Health Canada (2011). Dietary intakes of contaminants & other chemicals for different age-sex groups of Canadians. Canadian Total Diet Study. Available from: http://www.hc-sc.gc.ca/fn-an/surveill/total-diet/intake-apport/index-eng.php accessed 23 October 2016.

HSDB (2017). Hazardous Substances Data Bank. [online database]. TOXNET toxicology data network. Bethesda

(MD), USA: United States National Library of Medicine. Available from: https://toxnet.nlm.nih.gov/

Huvinen M, Uitti J, Oksa P, Palmroos P, Laippala P (2002). Respiratory health effects of long-term exposure to different chromium species in stainless steel production. *Occup Med (Lond)*, 52(4):203–12. doi:10.1093/occmed/52.4.203 PMID:12091586

Institute of Medicine (2001). DRI. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc: a report of the panel on micronutrients and of interpretation and uses of dietary reference intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington (DC) USA: National Academy Press.

Jin B, Zhou X, Huang L, Lickleder M, Yang M, Schmuki P (2016). Aligned MoOx/MoS2 core-shell nanotubular structures with a high density of reactive sites based on self-ordered anodic molybdenum oxide nanotubes. *Angew Chem Int Ed Engl*, 55(40):12252–6. doi:10.1002/anie.201605551 PMID:27599478

Kerckaert GA, LeBoeuf RA, Isfort RJ (1996). Use of the Syrian hamster embryo cell transformation assay for determining the carcinogenic potential of heavy metal compounds. *Fundam Appl Toxicol*, 34(1):67–72. doi:10.1006/faat.1996.0176 PMID:8937893

Keyes WR, Turnlund JR (2002). Determination of molybdenum and enriched Mo stable isotope concentrations in human blood plasma by isotope dilution ICP-MS. *J Anal At Spectrom*, 17(9):1153–6. doi:10.1039/b202250h

Kucera J, Bencko V, Pápayová A, Saligová D, Tejral J, Borská L (2001). Monitoring of occupational exposure in manufacturing of stainless steel constructions. Part I: Chromium, iron, manganese, molybdenum, nickel and vanadium in the workplace air of stainless steel welders. *Cent Eur J Public Health*, 9(4):171–5. PMID:11787242

Lasheen TA, El-Ahmady ME, Hassib HB, Helal AS (2015). Molybdenum metallurgy review: Hydrometallurgical routes to recovery of molybdenum from ores and mineral raw materials. *Miner Process Extr Metall Rev*, 36(3):145–73. doi:10.1080/08827508.2013.868347

Lener J, Bíbr B (1984). Effects of molybdenum on the organism (a review). *J Hyg Epidemiol Microbiol Immunol*, 28(4):405–19. PMID:6396329

Lewis DF, Ioannides C, Parke DV (1996). COMPACT and molecular structure in toxicity assessment: a prospective evaluation of 30 chemicals currently being tested for rodent carcinogenicity by the NCI/NTP. *Environ Health Perspect*, 104:Suppl 5: 1011–6. doi:10.1289/ehp.96104s51011 PMID:8933049

Lewis RC, Meeker JD (2015). Biomarkers of exposure to molybdenum and other metals in relation to testosterone among men from the United States National Health and Nutrition Examination Survey 2011-2012. *Fertil Steril*, 103(1):172–8. doi:10.1016/j.fertnstert.2014.09.020 PMID:25439796

Lou SN, Ng YH, Ng C, Scott J, Amal R (2014). Harvesting, storing and utilising solar energy using MoO3: modulating structural distortion through pH adjustment. *ChemSusChem*, 7(7):1934–41. doi:10.1002/cssc.201400047 PMID:24811956

Mohd-Taufek N, Cartwright D, Davies M, Hewavitharana AK, Koorts P, Shaw PN et al. (2016). The simultaneous analysis of eight essential trace elements in human milk by ICP-MS. *Food Anal Methods*, 9(7):2068–75. doi:10.1007/s12161-015-0396-z

National Toxicology Program(1997). NTP toxicology and carcinogenesis studies of molybdenum trioxide (CAS No. 1313-27-5) in F344 rats and B6C3F1 mice (inhalation studies). *Natl Toxicol Program Tech Rep Ser*, 462:1–269. PMID:12587014

Novotny JA, Turnlund JR (2006). Molybdenum kinetics in men differ during molybdenum depletion and repletion. *J Nutr*, 136(4):953–7. doi:10.1093/jn/136.4.953 PMID:16549456

OECD (2009). The 2007 OECD List of High Production Volume Chemicals. ENV/JM/MONO40. OECD Environment, Health and Safety Publications Series on Testing and Assessment Number 112. Environment Directorate Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Paris: Organisation for Economic Co-operation and Development.

Ozaki K, Haseman JK, Hailey JR, Maronpot RR, Nyska A (2002). Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat–the National Toxicology Program experience. *Toxicol Pathol*, 30(2):263–70. doi:10.1080/019262302753559605 PMID:11950170

Polyak DE (2016). Molybdenum [advance release]. 2014 Minerals Yearbook. Washington (DC), USA: United States Geological Survey.

Runnells DD, Kaback DS, Thurman EM (1977). Geochemistry molybdenum 237 and sampling of molybdenum in sediments, soils, and plants in Colorado. In: Chappell WR, Peterson KK editors. Molybdenum in the environment. Volume 2. New York, USA: Elsevier Science Publishing Co.

Sebenik RF, Burkin AR, Dorfler RR, Laferty JM, Leichtfried G, Meyer-Grünow H et al. (2012). Molybdenum and molybdenum compounds. Ullmann's encyclopedia of industrial chemistry. Volume 23. Weinheim: Wiley-VCH.

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:26600562

Steifel EI (2010). Molybdenum and molybdenum alloys. Kirk-Othmer encyclopedia of chemical technology. Hoboken (NY), USA: John Wiley & Sons.

Stiefel EI (2011). Molybdenum compounds. Kirk-Othmer encyclopedia of chemical technology. Hoboken (NY), USA: John Wiley & Sons.

Stoner GD, Shimkin MB, Troxell MC, Thompson TL, Terry LS (1976). Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res*, 36(5):1744–7. PMID:1268831

Thompson KH, Turnlund JR (1996). Kinetic model of molybdenum metabolism developed from dual stable isotope excretion in men consuming a low molybdenum diet. *J Nutr*, 126(4):963–72. doi:10.1093/jn/126.4.963 PMID:8613900

Tsongas TA, Meglen RR, Walravens PA, Chappell WR (1980). Molybdenum in the diet: an estimate of average daily intake in the United States. *Am J Clin Nutr*, 33(5):1103–7. doi:10.1093/ajcn/33.5.1103 PMID:7369160

Turnlund JR, Keyes WR, Peiffer GL (1995). Molybdenum absorption, excretion, and retention studied with stable isotopes in young men at five intakes of dietary molybdenum. *Am J Clin Nutr*, 62(4):790–6. doi:10.1093/ajcn/62.4.790 PMID:7572711

Turnlund JR, Thompson KH, Scott KC (1998). Key features of copper versus molybdenum metabolism models in humans. *Adv Exp Med Biol*, 445:271–81. doi:10.1007/978-1-4899-1959-5_17 PMID:9781395

Turnlund JR, Weaver CM, Kim SK, Keyes WR, Gizaw Y, Thompson KH et al. (1999). Molybdenum absorption and utilization in humans from soy and kale intrinsically labeled with stable isotopes of molybdenum. *Am J Clin Nutr*, 69(6):1217–23. doi:10.1093/ajcn/69.6.1217 PMID:10357742

Walravens PA, Moure-Eraso R, Solomons CC, Chappell WR, Bentley G (1979). Biochemical abnormalities in workers exposed to molybdenum dust. *Arch Environ Health*, 34(5):302–8. doi:10.1080/00039896.1979.10667421 PMID:496425

Wang YX, Feng W, Zeng Q, Sun Y, Wang P, You L et al. (2016). Variability of metal levels in spot, first morning, and 24-hour urine samples over a 3-month period in healthy adult Chinese men. *Environ Health Perspect*, 124(4):468–76. PMID:26372665

Yoshida M, Takada A, Hirose J, Endô M, Fukuwatari T, Shibata K (2008). Molybdenum and chromium concentrations in breast milk from Japanese women. *Biosci Biotechnol Biochem*, 72(8):2247–50. doi:10.1271/bbb.80283 PMID:18685182

Zollfrank C, Gutbrod K, Wechsler P, Guggenbichler JP (2012). Antimicrobial activity of transition metal acid MoO(3) prevents microbial growth on material surfaces. *Mater Sci Eng C*, 32(1):47–54. doi:10.1016/j.msec.2011.09.010 PMID:23177771