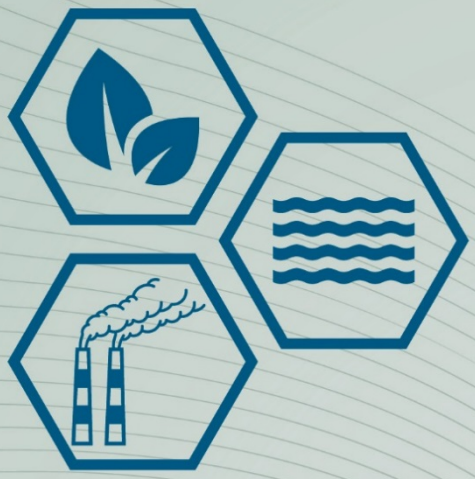

# Toxicological Profile for Molybdenum

**Draft for Public Comment**

**April 2017**

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

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# UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

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# FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

# QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

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***Primary Chapters/Sections of Interest***

**Chapter 1: Public Health Statement**: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

**Chapter 2: Relevance to Public Health**: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

**Chapter 3: Health Effects**: Specific health effects of a given hazardous compound are reported by type of health effect (e.g.,death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
***NOTE***: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

**Pediatrics**: Four new sections have been added to each Toxicological Profile to address child health issues:

| | |
|---|---|
| **Chapter 1** | **How Can (Chemical X) Affect Children?** |
| **Chapter 1** | **How Can Families Reduce the Risk of Exposure to (Chemical X)?** |
| **Section 3.8** | **Children's Susceptibility** |
| **Section 6.6** | **Exposures of Children** |

**Other Sections of Interest:**

| | |
|---|---|
| **Section 3.9** | **Biomarkers of Exposure and Effect** |
| **Section 3.12** | **Methods for Reducing Toxic Effects** |

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***ATSDR Information Center***

***Phone:*** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
***Internet***: http://www.atsdr.cdc.gov

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

*Managing Hazardous Materials Incidents* is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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***Other Agencies and Organizations***

*The National Center for Environmental Health* (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

*The National Institute for Occupational Safety and Health* (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

*The National Institute of Environmental Health Sciences* (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

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***Clinical Resources (Publicly Available Information)***

*The Association of Occupational and Environmental Clinics* (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

*The American College of Occupational and Environmental Medicine* (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

*The American College of Medical Toxicology* (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

*The Pediatric Environmental Health Specialty Units* (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

*The American Association of Poison Control Centers* (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

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## THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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# PEER REVIEW

A peer review panel was assembled for molybdenum. The panel consisted of the following members:

1. John Meeker, Sc.D., C.I.H., Professor, Environmental Health Sciences, Associate Dean for Research, School of Public Health, University of Michigan, Ann Arbor, Michigan;

2. Alexander V. Lyubimov, M.D., Ph.D., D.A.B.T., Toxicology Research Laboratory, Chicago, Illinois; and

3. Dagobert Heijerick, ARCHE consulting, Gent, Belgium.

These experts collectively have knowledge of molybdenum's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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# 1. PUBLIC HEALTH STATEMENT FOR MOLYBDENUM

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on molybdenum, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found molybdenum in at least 86 of the 1,832 current or former NPL sites. The total number of NPL sites evaluated for molybdenum is not known. But the possibility remains that as more sites are evaluated, the sites where molybdenum is found may increase. This information is important because these future sites may be sources of exposure, and exposure to molybdenum may be harmful.

If you are exposed to molybdenum, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

## WHAT IS MOLYBDENUM?

Molybdenum is a chemical element with the symbol Mo. Pure molybdenum exists as a dark-gray or black powder with a metallic luster or as a silvery-white mass. It does not occur naturally in the pure metallic form. It is principally found as oxide or sulfide compounds. Therefore, almost all exposure is to a molybdenum compound rather than the actual metal alone. Important naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite. Molybdenum has a very high melting point and it is used widely in industry to make steel alloys.

Molybdenum occurs naturally in all plants and animals. Low levels of molybdenum are required for good health in humans and animals.

## WHAT HAPPENS TO MOLYBDENUM WHEN IT ENTERS THE ENVIRONMENT?

Molybdenum can enter the environment through releases from mining, milling, and smelting operations and coal-fired power plants. The primary source of molybdenum in air is from coal combustion.

Molybdenum released to the air will settle to the ground by gravity or in rain and snow. Molybdenum can also be directly released into surface water. When molybdenum is released into soil or water, it can become attached to the organic material and other components (such as clay, sand, etc.) in the top layers of the soil or in the water and may not move far from where it is released. The soil conditions, especially the acidity of the soil, will influence the binding of molybdenum to soil and sediment. Molybdenum does not break down in the environment.

## HOW MIGHT I BE EXPOSED TO MOLYBDENUM?

Molybdenum is common in the environment. The primary way that you may be exposed to molybdenum is by eating food containing molybdenum. Grains, legumes, nuts, and dairy products have the highest levels of molybdenum. You may also be exposed to molybdenum in some nutritional supplements. You may be exposed to small amounts of molybdenum by breathing air, by drinking water, and by skin contact with soil and water. You may be exposed to higher levels of molybdenum in drinking water if you live near industries using molybdenum and the industries release molybdenum into the waterways.

## HOW CAN MOLYBDENUM ENTER AND LEAVE MY BODY?

Molybdenum can enter your body when you breathe air, drink water, or eat food containing molybdenum. When you breathe air containing molybdenum, molybdenum particles can be deposited in your lungs. Some of these particles can be coughed up and swallowed. Particles deposited deeper in the lungs are likely to pass through the lining of the lungs and enter the bloodstream. Some of the molybdenum in the lungs may stay there for years. At least half of ingested molybdenum will enter the bloodstream. The amount of molybdenum absorbed depends on what other food and beverages are ingested. We do not have any information on whether molybdenum can enter the body through the skin. Molybdenum in the blood will be distributed throughout the body, with the highest amounts found in the liver and kidneys. Molybdenum leaves your body in urine and feces, mostly in urine. Generally, the amount of molybdenum in your body remains constant (the amount that enters your body equals the amount that leaves). More information on how molybdenum enters and leaves the body is presented in Chapter 3.

## HOW CAN MOLYBDENUM AFFECT MY HEALTH?

Molybdenum is essential for good health. An intake of 45 micrograms of molybdenum per day (μg/day) is recommended for adults. On average, adults in the United States ingest 76–109 μg molybdenum per day.

Exposure to high levels of molybdenum can be harmful. Long-term exposure of rats and mice to molybdenum dust in the air can cause damage to the nasal cavity, epiglottis, and lungs. Studies in animals suggested that ingesting large amounts of molybdenum, at least 1,000 times higher than needed for health may damage the male and female reproductive system and might cause kidney and liver damage.

A study in mice provides some evidence that exposure to inhaled molybdenum can result in lung cancer. Molybdenum has not been classified as to carcinogenicity by the Department of Health and Human Services (HHS), the International Agency for Research on Cancer (IARC), or EPA.

More detailed information on the health effects of molybdenum in humans and animals can be found in Chapter 3.

## HOW CAN MOLYBDENUM AFFECT CHILDREN?

This section discusses potential health effects of molybdenum exposure in humans from when they're first conceived to 18 years of age.

Children need small amounts of molybdenum to maintain good health. It is likely that the adverse health effects observed in adults exposed to higher than normal levels of molybdenum would also be observed in children. We do not know if children would be more susceptible to the toxicity of molybdenum than adults. We do not have enough information to determine whether molybdenum can cause birth defects or affect growth. Studies in humans and laboratory animals show that molybdenum is transferred from the mother to the fetus. Molybdenum has also been found in breast milk.

## HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO MOLYBDENUM?

If your doctor finds that you have been exposed to significant amounts of molybdenum, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

Molybdenum is part of the natural environment and you need some molybdenum in your diet to maintain good health. Families can be exposed to more molybdenum than is needed for health if they live near natural or industrial sources of molybdenum, such as mining sites. If you live in an area with high levels of molybdenum in drinking water, you may consider using bottled drinking water.

If you are exposed to molybdenum at work, you can wear protective equipment and can remove contaminated clothing before going home.

## ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO MOLYBDENUM?

Molybdenum is normally found in all tissues of the body, as well as in blood, urine, and feces. High levels of molybdenum in the blood or urine can show that you have been exposed to higher than normal levels of molybdenum. Measuring blood molybdenum levels may only tell you if you have been very recently exposed to molybdenum. Urinary molybdenum levels are more likely to give information on long-term exposure to molybdenum. Tests to measure molybdenum levels in the body are not usually available at a doctor's office because they require special equipment. Although these tests can show that you have been exposed to higher than normal molybdenum levels, they cannot be used to predict how much molybdenum you have been exposed to or whether the exposure will result in an adverse health effect. More detailed information on the measurement of molybdenum is provided in Chapters 3 and 7.

## WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for

toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The Institute of Medicine has made recommendation of the amount of molybdenum that is needed for good health; these values are called Recommended Dietary Allowances (RDAs). The RDAs are specific for different age groups:

- 17 μg/day for children aged 1–3 years
- 22 μg/day for children aged 4–8 years
- 34 μg/day for children aged 9–13 years
- 43 μg/day for teens aged 14–18 years
- 45 μg/day for adults
- 50 μg/day for pregnant and nursing women

EPA has determined that exposure to drinking water containing 0.08 milligrams per liter (mg/L) is not expected to cause effects that are harmful to children exposed for 1 or 10 days. Lifetime exposure to drinking water containing 0.04 mg/L is not likely to cause adverse health effects.

OSHA has set a limit of 5 milligrams per cubic meter ($mg/m^3$) for soluble molybdenum compounds and 15 $mg/m^3$ for insoluble molybdenum compounds and total dust in workroom air to protect workers during an 8-hour work shift (40-hour work week). NIOSH has not established a guideline for exposure to molybdenum to protect workers exposed up to 10 hours per workday. However, NIOSH has established a level of 5,000 $mg/m^3$ for insoluble molybdenum compounds and 1,000 $mg/m^3$ for soluble molybdenum

compounds that it considers immediately dangerous and likely to cause death or immediate or delayed permanent adverse health effects, or to prevent escape.

Further information on regulations and guidelines pertaining to molybdenum is provided in Chapter 8.

## WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

# 2. RELEVANCE TO PUBLIC HEALTH

## 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MOLYBDENUM IN THE UNITED STATES

Molybdenum (Mo) is a naturally occurring trace element that can be found extensively in nature. Molybdenum is a metal that exists as a dark-gray or black powder with a metallic luster or as a silvery-white mass. It does not occur naturally in the pure metallic form, but principally as oxide or sulfide compounds. Therefore, almost all exposure is to a molybdenum compound rather than the actual metal. Important naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite.

Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans. It is used widely in industry for metallurgical applications; some of these applications include high temperature furnaces, as a support wire for tungsten filaments in incandescent light bulbs, and as a component of steel used in solar panels and wind turbines.

Molybdenum is more abundant in areas of natural mineral deposits and can be found in all environmental media. Higher concentrations in air, water, and soil can be found near industrial operations due to contamination. Molybdenum concentrations in ambient air have been reported to range from below detection limits to 0.03 $mg/m^3$. Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 $\mu g/m^3$, are higher than those found in rural areas, 0.001–0.0032 $\mu g/m^3$. It has been reported that concentrations of molybdenum in surface waters are generally <1.0 µg/L and drinking water and groundwaters contain about 1.0 µg/L. Near industrial sources, surface water molybdenum concentrations can reach 200–400 µg/L and groundwater concentrations can reach 25,000 µg/L. Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations, far exceeding the U.S. Geological Survey (USGS) health-based screening level of 40 µg/L. Globally, most soils contain molybdenum at concentrations between 0.6 and 3.5 ppm, although total concentrations in soils can vary widely depending on geological composition or industrial contamination. The average concentration of soils is generally 1–2 ppm. In the United States, it has been reported that the median concentration of molybdenum in soils is 1.2–1.3 ppm, with a range of 0.1–40 ppm.

The exposure to molybdenum to the general population is almost entirely through food. Foods derived from above-ground plants, such as legumes, leafy vegetables, and cauliflower, generally have a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains,

leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet. Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum. The primary source of dietary molybdenum intake among children in the United States is milk. Exposure to molybdenum in an industrial setting such as mining can be significant.

## 2.2 SUMMARY OF HEALTH EFFECTS

Molybdenum, as a component of pterin-based cofactor, is an essential element. Historically, three molybdenum cofactor-containing enzymes have been identified: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. These enzymes are involved in the degradation of sulfur-containing amino acids and sulfatides, purine degradation pathway catalyzing the oxidation of hypoxanthine to xanthine and of xanthine to uric acid, and oxidation of aromatic and nonaromatic heterocycles and aldehydes to carboxylic acids. Within the last 10 years, a fourth enzyme, mitochondrial amidoxime reducing component (mARC), has been identified in mammals. Clear signs of molybdenum deficiency have not been found in healthy humans. However, a deficiency in molybdenum cofactor has been observed in individuals with a severe metabolic defect. The lack of molybdenum cofactor and subsequent deficiencies in molybdoenzymes is manifested in central nervous system effects. The effects that typically occur shortly after birth include intractable seizures and feeding difficulties; the patients develop severe psychomotor retardation due to progressive cerebral atrophy and ventricular dilatation. The nutritional requirements for molybdenum are based on maintaining molybdenum balance; the Institute of Medicine has established the following age-specific RDAs:

- 17 μg/day for 1–3 year olds,
- 22 μg/day for 4–8 year olds,
- 34 μg/day for 9–13 year olds,
- 43 μg/day for 14–18 year olds,
- 45 μg/day (0.64 μg/kg/day) for adults, and
- 50 μg/day in pregnant and lactating women.

A small number of studies have investigated the toxicity of molybdenum following inhalation exposure. Decreases in lung function, dyspnea, and cough were reported in workers exposed to fine or ultrafine molybdenum trioxide dust. Another study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides did not have alterations in lung function. However, this study did

find an increase in serum uric acid levels. In studies of rats and mice exposed to molybdenum trioxide for 2 years, hyaline degeneration of the nasal epithelium, squamous metaplasia of the epiglottis, and chronic inflammation (rats only) were observed. However, no effects were observed following a 13-week exposure to similar concentrations. No other alterations were observed in the intermediate- or chronic-duration studies.

The oral toxicity of molybdenum has been well-established in ruminants, particularly cows and sheep. The toxicity is likely due to an interaction between molybdenum and sulfate in the rumen, resulting in the formation of thiomolybdates. In the absence of adequate copper in the rumen, the thiomolybdate is absorbed through the rumen or small intestine and can bind to copper-containing compounds such as ceruloplasmin and cytochrome oxidase, resulting in symptoms resembling copper deficiency (a condition often referred to as molybdenosis). The observed effects can include decreases in weight gain, alterations in hair/wool texture and pigmentation, delayed puberty, and reduced conception rates. Molybdenum also interacts with copper in monogastric animals; however, the mode of interaction differs between the species. Exposure to molybdenum results in decreases in blood and liver copper levels in ruminants, which is in contrast to the higher relative levels of liver and kidney copper in rats fed a copper-deficient diet, as compared to those fed a copper-adequate diet. Exposure to a molybdenum excess and copper-deficient diet also resulted in higher relative levels of liver molybdenum and lower relative levels of kidney molybdenum. Exposure of rats to thiomolybdate compounds can result in effects that mimic copper deficiency. These data suggest that the findings in ruminants do not appear to be relevant to humans or monogastric animals. Additionally, studies in which laboratory animals were fed a copper-deficient diet may not be relevant to evaluating the risk of molybdenum toxicity to the general population with adequate copper intake. A human study showed that a 24-day exposure to high molybdenum levels in the diet (1,490 µg/day, approximately 21 mg/kg/day) did not result in any significant alterations in copper metabolism. In the United States, the average copper intake is 1.0–1.6 mg/day and the copper recommended dietary allowance is 0.9 mg/day.

A small number of studies have evaluated the toxicity of molybdenum in humans following oral exposure. An increased occurrence of gout and increased blood uric acid levels were observed in residents living in an area of high molybdenum levels in the soil; no alterations in urinary uric acid levels were found in a 10-day experimental study in men. Several studies have used the National Health and Nutrition Examination Survey (NHANES) dataset to evaluate potential associations between urinary molybdenum levels and several diseases; statistically significant associations were found for the occurrence of high blood pressure, self-reported liver conditions, and decreased triiodothyronine or

thyroxine. Although the studies did not specifically evaluate copper intake, it is likely to be adequate based on a NAS finding that copper intake in the United States is greater than or equal to the dietary requirement. Other population studies have found significant associations between blood molybdenum levels and sperm concentration and morphology or testosterone levels and between urinary molybdenum levels and the psychomotor index in infants. Although the observational epidemiology studies have found statistically significant associations, they do not establish causality and it is possible that the effects are not due to molybdenum exposure.

A number of studies have examined the oral toxicity in laboratory animals. Studies in which the basal diet provided an adequate amount of copper have identified a number of end points including hepatic effects, renal effects, reproductive effects, and possibly developmental effects. Based on the available animal data, the reproductive effects appear to be the most sensitive targets. Consistent with the findings in an epidemiology study, decreases in sperm motility and concentration and increases in sperm morphological changes have been observed in rats exposed to ≥4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate or sodium molybdate. Degeneration of the seminiferous tubules was also observed at similar molybdenum doses. Effects have also been observed in the female reproductive system (oocyte morphological alterations, abnormal rate of ovulation, and irregularities in the estrous cycle) at ≥1.5 mg molybdenum/kg/day in rats. Mixed results have been observed in animal developmental toxicity studies. Decreases in the number of live fetuses and fetal growth were observed in rats administered 14 mg molybdenum/kg as sodium molybdate; however, no developmental effects were observed in rats at 4.4 or 38 mg/kg/day as ammonium tetrathiomolybdate or sodium molybdate, respectively. Several studies have reported renal effects in rats exposed to ≥60 mg/kg/day. The effects included hyperplasia of the renal proximal tubules, degeneration, increases in total lipid levels in the kidney, and diuresis and creatinuria. The liver effects, which consisted of decreases in glycogen content, increases in aminotransferase activities, and increases in lipid content, have been observed at higher doses (≥300 mg/kg/day) that are often associated with body weight losses. No hepatic effects have been observed at lower (≤60 mg/kg/day) doses.

## 2.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 2-1, an inhalation MRL has been derived for chronic-duration exposure to molybdenum and oral MRLs have been derived for acute- and intermediate-duration exposure to molybdenum. The chronic-duration inhalation MRL is based on squamous metaplasia of the epiglottis in female mice exposed to molybdenum trioxide 6 hours/day, 5 days/week for 2 years (NTP 1997). Acute-

and intermediate-duration inhalation MRLs were not derived because the available studies did not identify adverse effects in rats or mice exposed for 14 days or 13 weeks (NTP 1997); the acute-duration study did identify a no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect levels (LOAELs) for decreases in body weight gain, but this was not considered a primary effect. The acute- and intermediate-duration oral MRLs for molybdenum were based on reproductive effects in female mice and rats, respectively. The data were considered inadequate for derivation of a chronic-duration oral MRL for molybdenum. Refer to Section 3.6.2 and Appendix A for detailed information regarding MRL derivation for molybdenum.

## Table 2-1. Minimal Risk Levels (MRLs) for Molybdenum[a]

| Exposure duration | MRL | Critical effect | Point of departure | Uncertainty factor | Reference |
|---|---|---|---|---|---|
| Inhalation exposure | | | | | |
| Acute | Insufficient data for derivation of an MRL | | | | |
| Intermediate | Insufficient data for derivation of an MRL | | | | |
| Chronic | 0.0004 mg Mo/m$^3$ | Squamous metaplasia in female mice exposed to ≥6.7 mg Mo/m$^3$ | $BMCL_{HEC}$ of 0.012 mg Mo/m$^3$ | 30 | NTP 1997 |
| Oral exposure | | | | | |
| Acute | 0.05 Mg Mo/kg/day | Increase rate of abnormal MII oocytes in mice | NOAEL of 5.3 mg Mo/kg/day | 100 | Zhang et al. 2013 |
| Intermediate | 0.008 mg Mo/kg/day | Increased estrous cycle length in rats | NOAEL of 0.76 mg Mo/kg/day | 100 | Fungwe et al. 1990 |
| Chronic | Insufficient data for derivation of an MRL | | | | |

[a]The respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level

# 3. HEALTH EFFECTS

## 3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of molybdenum. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

## 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not

the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

### 3.2.1 Inhalation Exposure

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.1.1 Death

No deaths were reported in rats or mice exposed to ≤200 mg molybdenum/$m^3$ for 14 days (NTP 1997) or ≤67 mg molybdenum/$m^3$ for 90 days or 2 years (NTP 1997).

#### 3.2.1.2 Systemic Effects

No information was located regarding cardiovascular, gastrointestinal, hematological, muscular/skeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans following inhalation exposure to molybdenum. No information was located regarding dermal or ocular effects in animals following inhalation exposure to molybdenum.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

**Respiratory Effects.** Limited data are available on the toxicity of molybdenum to the respiratory tract of humans. A study of workers exposed to molybdenum trioxide and other oxides at a molybdenite

## Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

| Figure key[a] | Species (strain) No./group | Exposure duration/ concentrations | Parameters monitored | System | NOAEL ($mg/m^3$) | Less serious LOAEL ($mg/m^3$) | Serious LOAEL ($mg/m^3$) | Results | Reference/comments |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| **Systemic** | | | | | | | | | |
| 1 | Rat<br>5M, 5F<br>(F344/N) | 6 hours/day;<br>5 days/week;<br>14 days<br>0, 2, 6.7, 20, 67, 200 mg Mo/$m^3$ | CS, BW, HP | Resp<br>Bd Wt | 200 | 67 | 200 | No histological alterations were observed in the nasal cavity. Decreased body weight gain in males exposed to 67 mg/$m^3$ (10%) and females exposed to 200 mg/$m^3$ (13%); weight loss was observed in males exposed to 200 mg/$m^3$. | NTP 1997 (molybdenum trioxide) |
| 2 | Mouse<br>5M, 5F<br>(B6C3F1) | 6 hours/day;<br>5 days/week;<br>14 days<br>0, 2, 6.7, 20, 67, 200 mg Mo/$m^3$ | CS, BW, HP | Resp<br>Bd Wt | 200 | | 200 | No histological alterations were observed in the nasal cavity. Body weight loss in males and decrease in body weight gain in females. | NTP 1997 (molybdenum trioxide) |
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| **Systemic** | | | | | | | | | |
| 3 | Rat<br>10M, 10F<br>(F344/N) | 6.5 hours/day;<br>5 days/week;<br>13 weeks<br>0, 0.67, 2, 6.7, 20, 67mg Mo/$m^3$ | CS, BW,OW, HP | Resp<br>Cardio<br>Gastro<br>Hemato<br>Musc/skel<br>Hepatic<br>Renal<br>Endocr<br>Bd Wt | 67<br>67<br>67<br>67<br>67<br>67<br>67<br>67<br>67 | | | No alterations in organ weights, hematology or clinical chemistry parameters, or histological alterations were found. | NTP 1997 (molybdenum trioxide) |
| 4 | Mouse<br>10M, 10F<br>(B6C3F1) | 6.5 hours/day;<br>5 days/week;<br>13 weeks<br>0, 0.67, 2, 6.7, 20, 67mg Mo/$m^3$ | CS, BW,OW, HP | Resp<br>Cardio<br>Gastro<br>Hemato<br>Musc/skel<br>Hepatic<br>Renal<br>Endocr<br>Bd Wt | 67<br>67<br>67<br>67<br>67<br>67<br>67<br>67<br>67 | | | No alterations in organ weights, hematology or clinical chemistry parameters, or histological alterations were found. | NTP 1997 (molybdenum trioxide) |

## Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

| Figure key[a] | Species (strain) No./group | Exposure duration/ concentrations | Parameters monitored | System | NOAEL ($mg/m^3$) | Less serious LOAEL ($mg/m^3$) | Serious LOAEL ($mg/m^3$) | Results | Reference/comments |
|---|---|---|---|---|---|---|---|---|---|
| **Reproductive** | | | | | | | | | |
| 5 | Rat 10M, 10F (F344/N) | 6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/$m^3$ | CS, BW,OW, HP | | 67 | | | No significant alterations in sperm counts or motility were found | NTP 1997 (molybdenum trioxide) |
| 6 | Mouse 10M, 10F (B6C3F1) | 6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/$m^3$ | CS, BW,OW, HP | | 67 | | | No significant alterations in sperm counts or motility were found | NTP 1997 (molybdenum trioxide) |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| **Systemic** | | | | | | | | | |
| 7 | Rat 50M, 50F (F344/N) | 6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/$m^3$ | CS, BW, HP | Resp<br>Cardio<br>Gastro<br>Musc/skel<br>Hepatic<br>Renal<br>Endocr<br>Bd Wt | <br>67<br>67<br>67<br>67<br>67<br>67<br>67 | 6.7 | | Concentration-related increasing incidence of hyaline degeneration of nasal respiratory and olfactory epithelium (females only), squamous metaplasia of the epiglottis, and chronic lung inflammation (only significant at 20 and 67 $mg/m^3$ concentrations) | NTP 1997 (molybdenum trioxide) |
| 8 | Mouse 50M, 50F (B6C3F1) | 6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/$m^3$ | CS, BW, HP | Resp<br>Cardio<br>Gastro<br>Musc/skel<br>Hepatic<br>Renal<br>Endocr<br>Bd Wt | <br>67<br>67<br>67<br>67<br>67<br>67<br>67 | 6.7 | | Concentration-related increasing incidence of squamous metaplasia of the epiglottis, histiocytic cellular infiltration in the lungs, and alveolar epithelial metaplasia were observed at 6.7, 20, and 67 $mg/m^3$. Other respiratory effects were nasal supprative inflammation in males at 20 or 67 $mg/m^3$ and hyaline degeneration of nasal respiratory and olfactory epithelium (females only) at 67 $mg/m^3$. | NTP 1997 (molybdenum trioxide) |

## Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

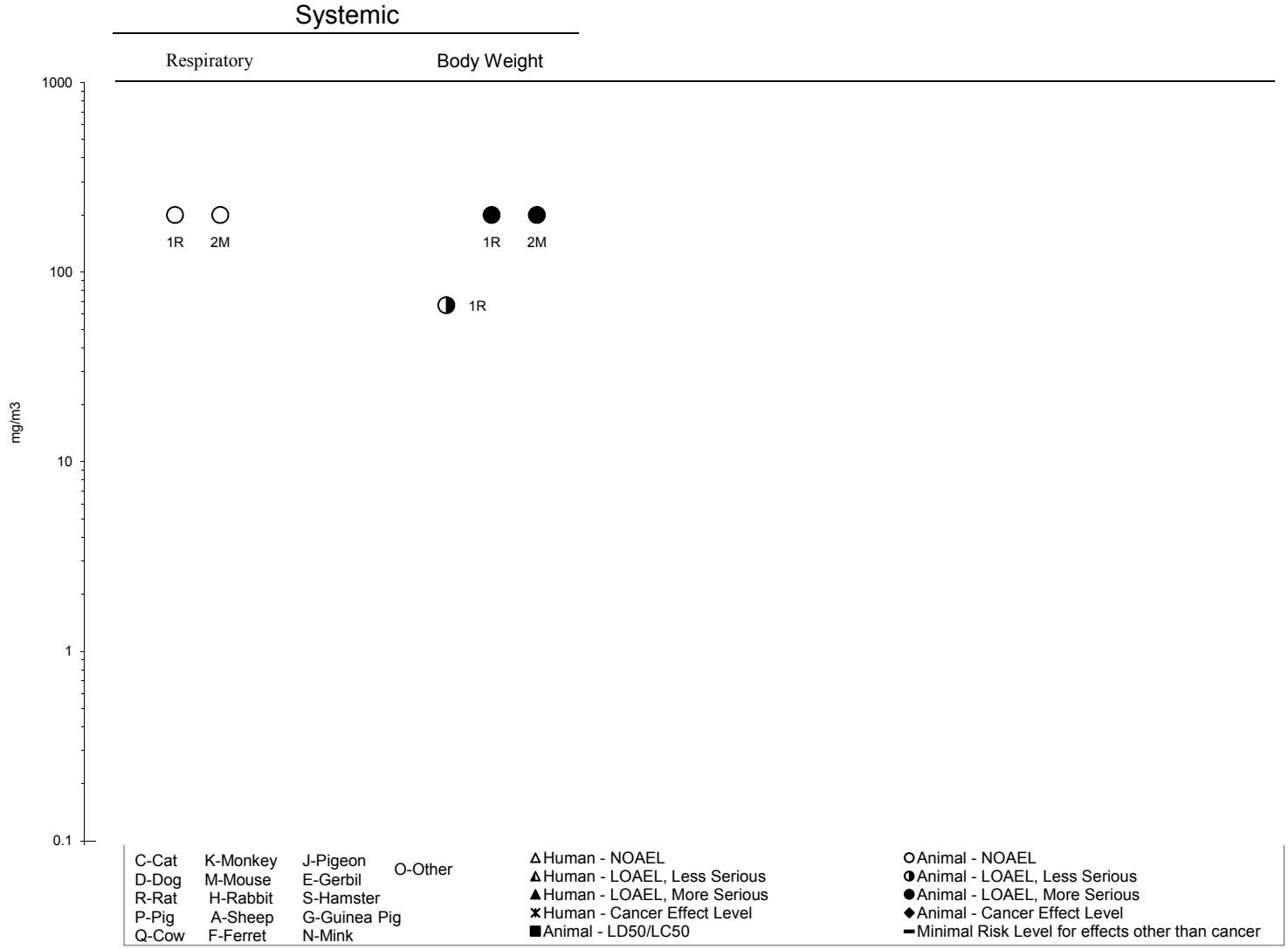
| Figure key[a] | Species (strain) No./group | Exposure duration/ concentrations | Parameters monitored | System | NOAEL ($mg/m^3$) | Less serious LOAEL ($mg/m^3$) | Serious LOAEL ($mg/m^3$) | Results | Reference/comments |
|---|---|---|---|---|---|---|---|---|---|
| **Cancer** | | | | | | | | | |
| 9 | Mouse 50M, 50F (B6C3F1) | 6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/$m^3$ | CS, BW, HP | | | | 6.7 | Increased incidences of alveolar/bronchiolar carcinoma in males at ≥6.7 mg/$m^3$; increased incidence of alveolar/bronchiolar adenoma in females at ≥20 mg/$m^3$. An increase in alveolar/bronchiolar adenoma or carcinoma were also observed in male mice exposed to 6.7 or 20 mg/$m^3$. | NTP 1997 (molybdenum trioxide) |

[a]The number corresponds to entries in Figure 3-1.

BC = biochemistry; BW = body weight; Cardio = cardiovascular; CI = confidence interval; CS = clinical signs; d = day(s); Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GC = gas chromatography; GN = gross necropsy; HE = hematology; Hemato = hematology; HP = histopathology; hr = hour(s); $LC_{50}$ = lethal concentration, 50% kill; LE = lethality; M = male(s); min = minute(s); MRL = Minimal Risk Level; NS = not specified; OP = ophthalmology; OW = organ weight; $RD_{50}$ = concentration resulting in a 50% reduction in respiratory rate; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)

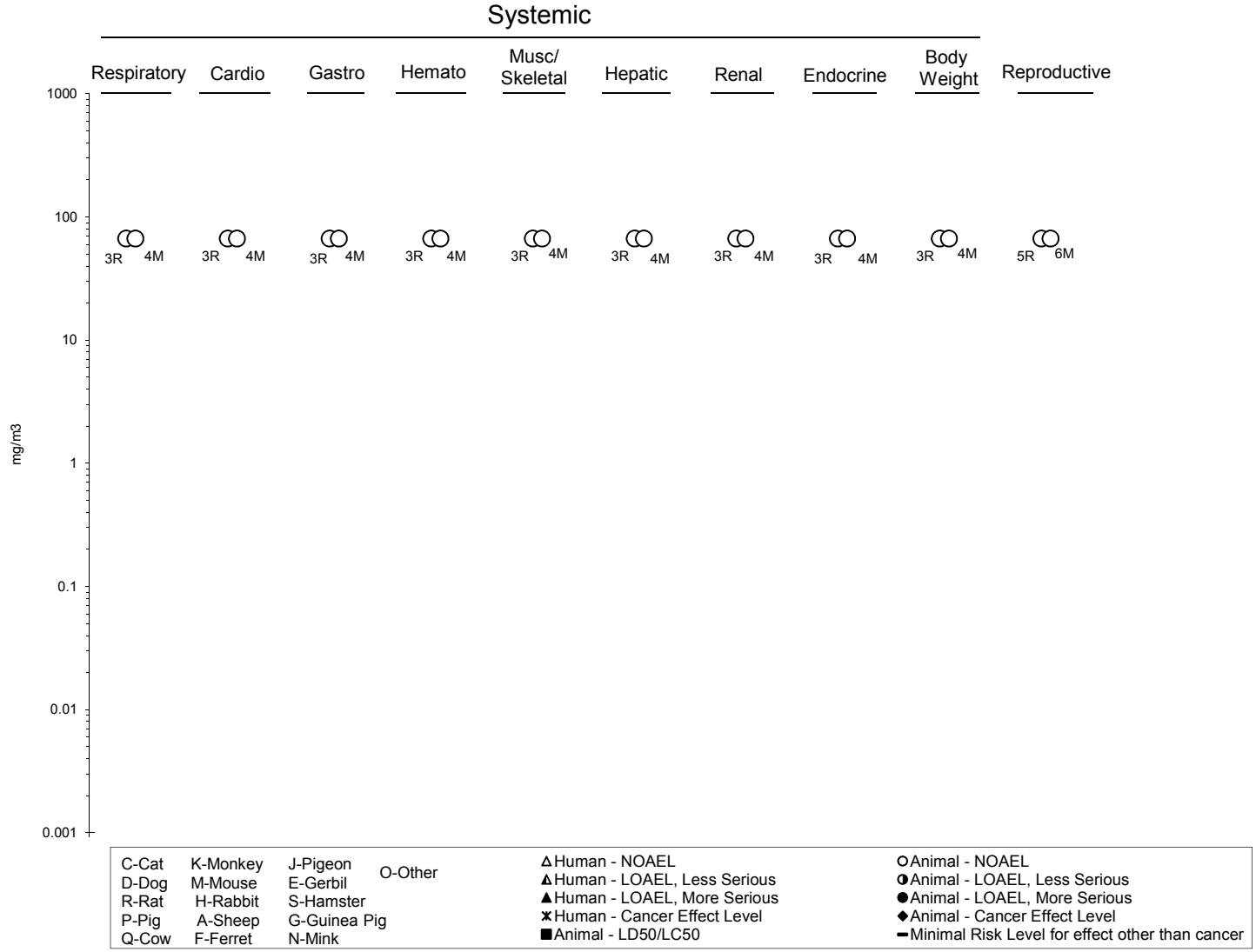
## Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation

Acute (≤ 14 days)



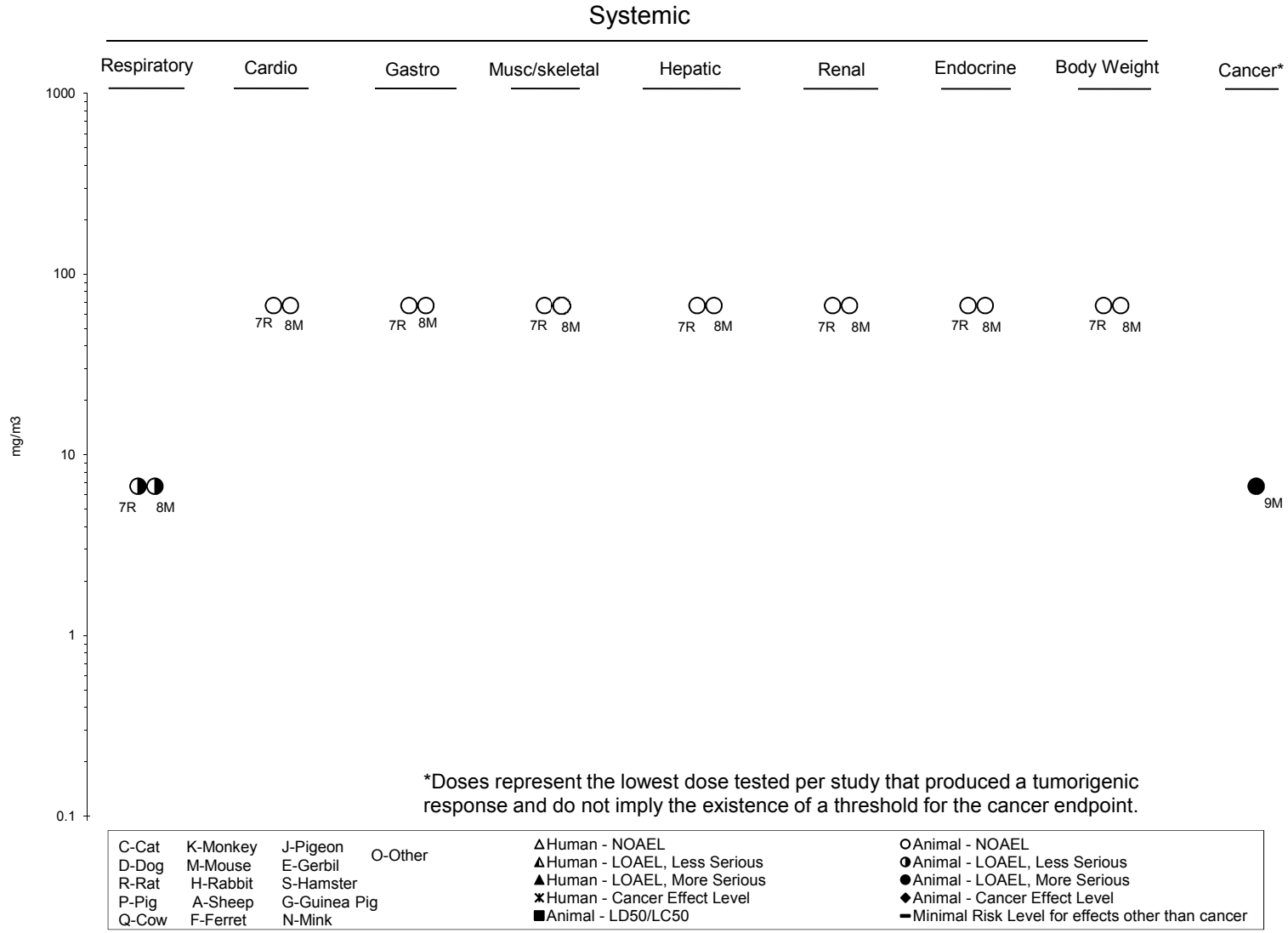
## Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation *(Continued)*

Intermediate (15-364 days)



## Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation *(Continued)*

Chronic (≥365 days)



roasting plant reported normal lung function test results in 20/25 workers (Walravens et al. 1979). Some alterations in lung function (forced expiratory volume in 1 second, $FEV_1$) was observed in the remaining five workers; the decrease in $FEV_1$ was characterized as mild in three of the workers and "more marked" in two workers, which may be indicative of mild obstructive lung disease. The study did not provide lung function data for a reference group. The estimated 8-hour time-weighted average (TWA) molybdenum concentration in total dust was 9.46 mg molybdenum/$m^3$; the molybdenum content of the respirable dust ranged from 1.02 to 4.49 mg molybdenum/$m^3$. Another study of workers exposed to fine and ultrafine molybdenum trioxide dust reported dyspnea and cough in symptomatic workers (Ott et al. 2004). Radiographic abnormalities were noted in the lungs of most of the symptomatic workers and in half of the asymptomatic workers, although none of the radiographs showed evidence of interstitial lung disease. Significant alterations in lung function (increased predicted $FEV_1$ and forced vital capacity) were also observed in the workers, as compared to a control group. In symptomatic workers, alterations in bronchioalveolar lavage cytology suggestive of subclinical alveolitis were noted. This study (Ott et al. 2004) has several limitations including the lack of monitoring data, minimal information on the control group, which does not appear to be comprised of workers at this facility, and differences in the mean and ranges of ages of the different groups (40.0 years [range of 24–58 years], 30.5 years [22–45 years], and 30.0 years [14–72 years] in the symptomatic workers, asymptomatic workers, and controls, respectively), which were not adjusted for in the statistical analyses.

The database on the respiratory toxicity of molybdenum in laboratory animals is comprised of acute-, intermediate-, and chronic-duration studies conducted by the National Toxicology Program (NTP 1997). No histological alterations were observed in the nasal cavity of rats and mice exposed to 200 mg molybdenum/$m^3$ as molybdenum trioxide for 14 days (NTP 1997); no other regions of the respiratory tract were examined. Similarly, no histological alterations were observed in the respiratory tract of rats or mice exposed to ≤67 mg molybdenum/$m^3$ as molybdenum trioxide for 13 weeks (NTP 1997). In contrast, chronic exposure has resulted in lesions in the nose, larynx, and lungs in rats and mice exposed to molybdenum trioxide for 2 years (NTP 1997). In the nose, hyaline degeneration of the respiratory and olfactory epitheliums were observed in rats exposed to ≥6.7 mg molybdenum/$m^3$ and in mice exposed to 67 mg molybdenum/$m^3$; other nasal lesions observed in mice included suppurative inflammation at ≥20 mg molybdenum/$m^3$ and olfactory epithelial atrophy at 67 mg molybdenum/$m^3$. Squamous metaplasia of the epiglottis was observed in rats and mice exposed to ≥6.7 mg molybdenum/$m^3$. In the lungs, chronic inflammation was observed in rats exposed to ≥20 mg molybdenum/$m^3$ and alveolar epithelial metaplasia and histiocytic cellular infiltration were observed at ≥6.7 mg molybdenum/$m^3$.

**Cardiovascular Effects.** No histological alterations were observed in the hearts of rats or mice exposed to molybdenum trioxide concentrations as high as 67 mg molybdenum/$m^3$ for 13 weeks or 2 years (NTP 1997).

**Gastrointestinal Effects.** Intermediate- or chronic-duration exposure to ≤67 mg molybdenum/$m^3$ as molybdenum trioxide did not result in histological alterations in the gastrointestinal tract (NTP 1997).

**Hematological Effects.** No significant alterations in hematological parameters were observed in rats or mice following exposure to molybdenum trioxide concentrations as high as 67 mg molybdenum/$m^3$ for 13 weeks (NTP 1997).

**Musculoskeletal Effects.** No histological alterations were observed in the bone of rats or mice exposed to 6.7–67 mg molybdenum/$m^3$ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997). Chronic molybdenum exposure also did not affect femoral bone density or curvature in groups of 10 rats exposed to concentrations as high as 67 mg molybdenum/$m^3$ (NTP 1997).

**Hepatic Effects.** No significant alterations in serum clinical chemistry parameters or liver weights were observed in rats or mice exposed to molybdenum trioxide concentrations as high as 67 mg molybdenum/$m^3$ for 13 weeks (NTP 1997). No significant alterations in the incidence of hepatic lesions were observed following 13 weeks or 2 years of exposure (NTP 1997).

**Renal Effects.** Intermediate- or chronic-duration inhalation exposure to molybdenum trioxide (highest concentration tested was 67 mg molybdenum/$m^3$) did not result in histological alterations in the kidney of rats or mice (NTP 1997).

**Endocrine Effects.** Based on histopathology findings, the adrenal, pituitary, pancreas, parathyroid, and thyroid glands were not affected by exposure of rats and mice to ≤67 mg molybdenum/$m^3$ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997).

**Body Weight Effects.** Decreases in body weight gain and weight loss were observed in rats and mice exposed to molybdenum trioxide for 14 days (NTP 1997). Terminal body weights were 10% lower in male rats exposed to 67 mg molybdenum/$m^3$ than in the controls, and weight loss was observed in male rats and mice exposed to 200 mg molybdenum/$m^3$. In female rats and mice exposed to 200 mg molybdenum/$m^3$, the terminal body weights were 13 and 10%, respectively, lower than the control

groups. No significant alterations in body weight gain were observed in rats or mice exposed to molybdenum trioxide concentrations as high as 67 mg molybdenum/$m^3$ for 13 weeks or 2 years (NTP 1997).

**Other Systemic Effects.** Slight, but significant increases in serum uric acid levels were observed in molybdenite roasting facility workers exposed to a TWA concentration of 9.47 mg molybdenum/$m^3$ as molybdenum trioxide and other oxides (Walravens et al. 1979). The serum uric acid levels were 5.90 mg/dL in the exposed workers and 5.01 mg/dL in the controls; these levels are within the normal range. No significant associations between serum molybdenum levels and serum uric acid levels were found, and none of the workers reported gout-like symptoms.

#### 3.2.1.3 Immunological and Lymphoreticular Effects

No studies have examined immune function following inhalation exposure to molybdenum. Intermediate- and chronic-duration studies in rats and mice did not report histological alterations in the thymus or spleen at molybdenum trioxide levels as high as 67 mg molybdenum/$m^3$ (NTP 1997).

#### 3.2.1.4 Neurological Effects

No histological alterations were observed in the brain of rats and mice exposed to ≤67 mg molybdenum/$m^3$ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997); the study did not evaluate neurological function.

#### 3.2.1.5 Reproductive Effects

Following a 13-week exposure to molybdenum trioxide, no alterations in sperm count or motility were observed in rats or mice at concentrations as high as 67 mg molybdenum/$m^3$ (NTP 1997). No histological alterations were observed in male or female reproductive tissues following exposure to ≤67 mg molybdenum/$m^3$ for 13 weeks or 2 years (NTP 1997).

#### 3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following inhalation exposure to molybdenum.

#### 3.2.1.7 Cancer

In a case-control study examining the potential association between lung cancer and exposure to 16 potential carcinogens, Droste et al. (1999) did not find a significant increase in lung cancer among workers who self-reported exposure to molybdenum. However, an increased risk of lung cancer was found in workers who self-reported working in industries that could involve exposure to molybdenum (odds ratio of 2.1, 95% confidence interval of 1.2–3.7); the job most often related to molybdenum exposure was processing of stainless steel in the manufacture of metal goods, which could also involve exposure to other carcinogens including chromium, nickel, and arsenic. Limitations of this study, including self-reported exposure and the potential exposure to other lung carcinogens, preclude its use in assessing the potential carcinogenicity of molybdenum.

In the 2-year NTP rat study (NTP 1997), an increase in the combined incidence of alveolar/bronchiolar adenoma or carcinoma was observed in male rats exposed to 67 mg molybdenum/$m^3$; however, the incidence was within the range of historical controls and NTP considered this to be equivocal evidence of carcinogenic activity. No other concentration-related increases in neoplastic lesions were observed in the rats. In mice, there were significant increases in the incidences of alveolar/bronchiolar carcinoma in males at ≥6.7 mg molybdenum/$m^3$, alveolar/bronchiolar adenoma or carcinoma in males at 6.7 and 20 mg molybdenum/$m^3$, alveolar/bronchiolar adenoma in females at 20 and 67 mg molybdenum/$m^3$, and alveolar/bronchiolar adenoma or carcinoma in females at 67 mg molybdenum/$m^3$ (NTP 1997). NTP (1997) concluded that the male and female mouse data provided some evidence of molybdenum carcinogenicity.

### 3.2.2 Oral Exposure

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

A number of studies have examined the oral toxicity of molybdenum; most were conducted in laboratory animals and most had a limited scope (examined one or two potential targets); the studies evaluated the toxicity of several molybdenum compounds, predominantly sodium molybdate, ammonium heptamolybdate, and ammonium tetrathiomolybdate. Studies have also been conducted in ruminants, particularly cows and sheep; however, these species are not considered suitable models for humans due to differences in interactions between molybdenum, copper, and sulfate in the rumen (see Section 3.5.2 for more information). Studies in rats provide evidence that copper status, particularly the copper content of

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| **Systemic** | | | | | | | | | |
| 1 | Human<br>4 M | 10 days (F);<br>0.00237, 0.00771, 0.022 mg/kg/day | UR | Other | 0.022 | | | No alterations in urinary uric acid levels | Deosthale and Gopalan 1974 (ammonium molybdate) |
| 2 | Rat (Sprague Dawley)<br>22 M | PND 4-17;<br>0 or 50 mg/kg/day | BW, HP | Musc/Skel<br>Bd Wt | <br>50 | 50 | | Increased buccal and sulcal enamel lesions following pre-eruptive exposure to molybdenum and administration of a caries promoting diet. | Hunt and Navia 1975 (sodium molybdate) |
| 3 | Rabbit (New Zealand White)<br>5 F | 14 day (F);<br>0, 1.2 mg/kg/day | BW, HP | Hepatic<br>Renal<br>Bd Wt | <br>1.2<br>1.2 | 1.2 | | A 60% increase in serum triglyceride levels was found; no significant alterations in liver or kidney histopathology were found. | Bersenyi et al. 2008 (ammonium heptamolybdate) |
| 4 | Rabbit (New Zealand White)<br>5 M | 14 day (F);<br>0, 0.58 mg/kg/day | BW, HP | Hepatic<br>Renal<br>Bd Wt | 0.58<br>0.58<br>0.58 | | | No histological alterations in the liver or kidneys or alterations in serum clinical chemistry parameters were observed. The molybdenum in the diet came from carrots grown in molybdenum rich soil. | Bersenyi et al. 2008 (ammonium heptamolybdate) |
| **Reproductive** | | | | | | | | | |
| 5 | Mouse (ICR)<br>25 F | 14 days (W);<br>0, 1.3, 2.6, 5.3, and 11 mg/kg/day | HP | | 5.3[b] | 11 | | Significant increase in the rate of abnormal MII oocytes and decrease in ovarian weights were observed at 11 mg/kg/day. Ovarian hyperemia was observed at 5.3 and 11 mg/kg/day (incidence and statistical significance were not reported). | Zhang et al. 2013 (sodium molybdate) |
| 6 | Mouse (ICR)<br>10 M | 14 days;<br>0, 3, 6, 12, 25, and 49 mg/kg/day | OF | | 12 | 25 | | Significant decreases in relative epididymis weight, sperm concentration, and sperm motility and increase in rate of sperm abnormalities. | Zhai et al. 2013 (sodium molybdate) |
| 7 | Rabbit (New Zealand White)<br>5 F | 14 days (F);<br>0, 1.2 mg/kg/day | BW, HP | | 1.2 | | | No histological alterations were observed in the ovaries. | Bersenyi et al. 2008 (ammonium heptamolybdate) |

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|
| 8 | Rabbit (New Zealand White)<br>5 M | 14 days (F);<br>0, 0.58 mg/kg/day | BW, HP | | | 0.58 | | Reduction in germ cells and mature spermatocytes (incidence andr statistical significance were not reported) | Bersenyi et al. 2008 (ammonium heptamolybdate) |
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| **Systemic** | | | | | | | | | |
| 9 | Rat (Sprague Dawley)<br>7 M | 8 weeks (GW);<br>0, 40, 80 mg/kg/day | BW, OW, UR | Renal<br>Bd Wt | 40<br>40 | 80<br>80 | | Increases in diuresis and creatinuria, decreases in creatinine clearance, increases in urinary kallikrein (distal tubule enzyme) levels, and increases in relative and absolute kidney weights. Decrease in body weight gain; terminal body weight was 26% lower than in controls | Bompart et al. 1990 (ammonium heptamolybdate) |
| 10 | Rat<br>3-6M, 2-3F (Sprague Dawley) | 6 weeks (F); 0 or 70 mg/kg/day | BW, HE | Hemato | 70 | | | No alterations in mean hemoglobin levels were found. | Gray and Daniel 1954 (sodium molybdate) |
| 11 | Rat (CD)<br>25M, 25F | 59-61 days (males)<br>22-35 days (females (GW); 0, 0.4, 1.5, 4.4 mg/kg/day | BW, HE | Hemato<br>Bd Wt | 1.5<br>1.5 | 4.4<br>4.4 | | Decreases in body weight gain in males starting at day 50. Decreases in erythrocyte count, hemoglobin concentration, and hematocrit in males. | Lyubimov et al. 2004 (ammonium tetrathiomolybdate) |
| 12 | Rat (Wistar)<br>4M | 5 weeks;<br>0 or 74 mg/kg/day | BW, EA | Bd Wt | | 74 | | 36% decrease in body weight gain | Mills et al. 1958 (sodium molybdate) |
| 13 | Rat (Sprague Dawley)<br>10M, 10F | 90 days (F); 0, 5, 17, or 60 mg/kg/day | CS, BW, BC, HE, FI, GN, HP, OW | Resp<br>Cardio<br>Gastro<br>Hemato<br>Renal<br>Endocr<br>Ocular<br>Bd Wt | 60<br>60<br>60<br>60<br>17<br>60<br>60<br>17 | <br><br><br><br>60<br><br><br>60 | | 15.2% lower terminal body weight in males; slight diffuse hyperplasia in the renal proximal tubules in 2/10 female rats exposed to 60 mg/kg/day. | Murray et al. 2013 (sodium molybdate) |

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|
| 14 | Rat (Druckery) 10M | 5 days/week 60 days (GW); 0, 4.7, 14, 24 mg/kg | BW | Bd Wt | 24 | | | No significant alterations in body weight gain were observed | Pandey and Singh 2002 (sodium molybdate) |
| 15 | Rat (Wistar) 6M | 9 weeks (W); 0 or 100 mg/kg/day | BW, BI, OW | Cardio<br>Bd Wt<br>Metab | 100<br>100<br>100 | | | Slight decrease (approximately 4%) in systolic blood pressure. No significant alterations in blood triglyceride, glucose, or insulin levels. | Peredo et al. 2013 (sodium molybdate) |
| 16 | Rat (Wistat) 10M or 5M, 5F | 4-5 weeks (F); 0 or 110 mg/kg/day | BW, EA | Bd Wt | | 110 | | 46-48% decrease in body weight gain; no feed intake data were provided. | Van Reen and Williams 1956 (sodium molybdate) |
| 17 | Rat (NMRI-D) 17-18 NR | 5 weeks; 0, 2, 4, and 8 mg/kg/day | HP | Musc/Skel | 8 | | | No significant alterations in the number of carious teeth and the severity of carious lesions | Van Reen et al. 1962 (sodium molybdate) |
| 18 | Rat (Wistar) 8 (sex not reported | 6 weeks; 0, or 85 mg/kg/day | BW, EA | Bd Wt | 85 | | | No alteration in body weight gain was observed and there was no effect on the ability to acetylated p-aminobenzoic acid. An increase in liver alkaline phosphatase levels was observed. Feed intake of control group was matched to molybdenum group. | Williams and Van Reen 1956 (sodium molybdate) |
| 19 | Rat (Wistar) 8 (sex not reported) | 6 weeks; 0, 90, 144, and 185 mg/kg/day | BW, EA | Bd Wt | | 90 | | Decreases in body weight gain of 22, 44, and 60% were observed in the 90, 144, and 185 mg/kg/day groups; decreases in feed intake were also observed in these groups. | Williams and Van Reen 1956 (sodium molybdate) |
| 20 | Rat (Sprague Dawley) 10F | 8 weeks (W); 0,0.015, 0.076, 0.15, 0.30, 0.76, and 1.5 mg/kg/day | BW, EA, OW | Bd Wt | 1.5 | | | No significant differences in terminal body weights were observed. | Yang and Yang 1989 (sodium molybdate) |

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|
| 21 | Rabbit (Dutch) 2-5 M,F | 30-84 days (F); 0, 7.1, 25, 54, 120, 240 mg/kg/day | CS, LE, BW, HE | Hemato<br>Dermal<br>Bd Wt | 25<br>25<br>25 | 54<br>54 | <br><br>120 | Weight loss was observed in the 120 and 240 mg/kg/day groups. Anemia was observed in 2/5, 5/5, and 4/5 rabbits in the 54, 120, and 240 mg/kg/day groups and in no rabbits at lower doses. Alopecia was observed in 4/5 and 4/5 rabbits in the 54 and 120 mg/kg/day groups; not observed at lower doses or in the 240 mg/kg/day group. | Arrington and Davis 1953 (sodium molybdate) |
| **Reproductive Effects** | | | | | | | | | |
| 22 | Rat (Sprague Dawley) 21F | 8 weeks (W); 0, 0.76, 1.5, 7.6, and 15 mg/kg/day | BW, WI, OF | | 0.76[c] | 1.5 | | Prolonged estrus phase (6-12 hours) of the estrous cycle observed at ≥1.5 mg/kg/day. No effect on fertility was observed. | Fungwe et al. 1990 (sodium molybdate) |
| 23 | Rat (Long Evans) 4M, 4F | At least 8 weeks (F); 0 or 7 mg/kg/day | BW, HE | | 7 | | | All rats produced litters; rats were maintained on a high copper diet.. | Jeter and Davis 1954 (sodium molybdate) |
| 24 | Rat (CD) 25M, 25F | 59-61 days (males) 22-35 days (females) (GW); 0, 0.4, 1.5, 4.4 mg/kg/day | OF, HP | | 1.5 | 4.4 | | Decreases in sperm motility and sperm count, and increased sperm morphological alterations; histological alterations in spermatogenesis in 25/25 males. No alterations in female reproductive parameters. | Lyubimov et al. 2004 (ammonium tetrathiomolybdate) |
| 25 | Rat (Sprague Dawley) 10M, 10F | 90 days (F); 0, 5, 17, or 60 mg/kg/day | CS, BW, BC, HE, FI, GN, HP, OW | | 17 | 60 | | Significant decrease in the percentage of progressively motile sperm; no alterations in overall percentage of motile sperm, spermatid or sperm counts, or sperm morphology. No alterations in vaginal cytology, estrus cycle, or histopathology of male or female reproductive organs | Murray et al. 2013 (sodium molybdate) |

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|
| 26 | Rat (Druckery) 10M | 5 days/week 60 days (GW); 0, 4.7, 14, 24 mg/kg | | | 4.7 | 14 | | Decreases in sperm count and sperm motility and increases in sperm abnormalities were observed at 14 mg/kg and higher. Degeneration of seminiferous tubules were observed in the testesat 24 mg/kg (incidence and statistical significance were not reported. | Pandey and Singh 2002 (sodium molybdate) |
| 27 | Rat (Druckery) 20M | 5 days/week 60 days (GW); 0 or 14 mg/kg | DX, FX | | | 14 | | Decrease in fertility (60% versus 80% in controls) and increased pre-implantation losses | Pandey and Singh 2002 (sodium molybdate) |
| **Developmental Effects** | | | | | | | | | |
| 28 | Rat (long Evans) 4M, 4F | At least 14 weeks (F); 0 or 7 mg/kg/day | BW, HE | | 7 | | | All rats produced litters and there were no alterations in birth weight or average weight at weaning. | Jeter and Davis 1954 (sodium molybdate). |
| 29 | Rat (CD) 25M, 25F | 59-61 days (males) 22-35 days (females) (GW); 0, 0.4, 1.5, 4.4 mg/kg/day | DX | | 4.4 | | | No effects on resorptions, pre- or post-implantation losses or viable fetuses | Lyubimov et al. 2004 (ammonium tetrathiomolybdate) |
| 30 | Rat (Sprague Dawley) 25F | GD6-20 (F); 0, 2.8, 9.8, 20.0, and 37.5 mg/kg/day | DX | | 37.5 | | | No effects on resorptions, post-implantation losses, fetal body weights, or occurrence of fetal malformations. | Murray et al. 2014 (sodium molybdate) |
| 31 | Rat (Druckery) 20M | 5 days/week 60 days (GW); 0 or 14 mg/kg | DX, FX | | | 14 | | Increased post-implantation losses, increased resorptions, decreased number of live fetuses, and decreases in fetal weight and crown-rump length. Males mated with unexposed females | Pandey and Singh 2002 (sodium molybdate) |

## Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

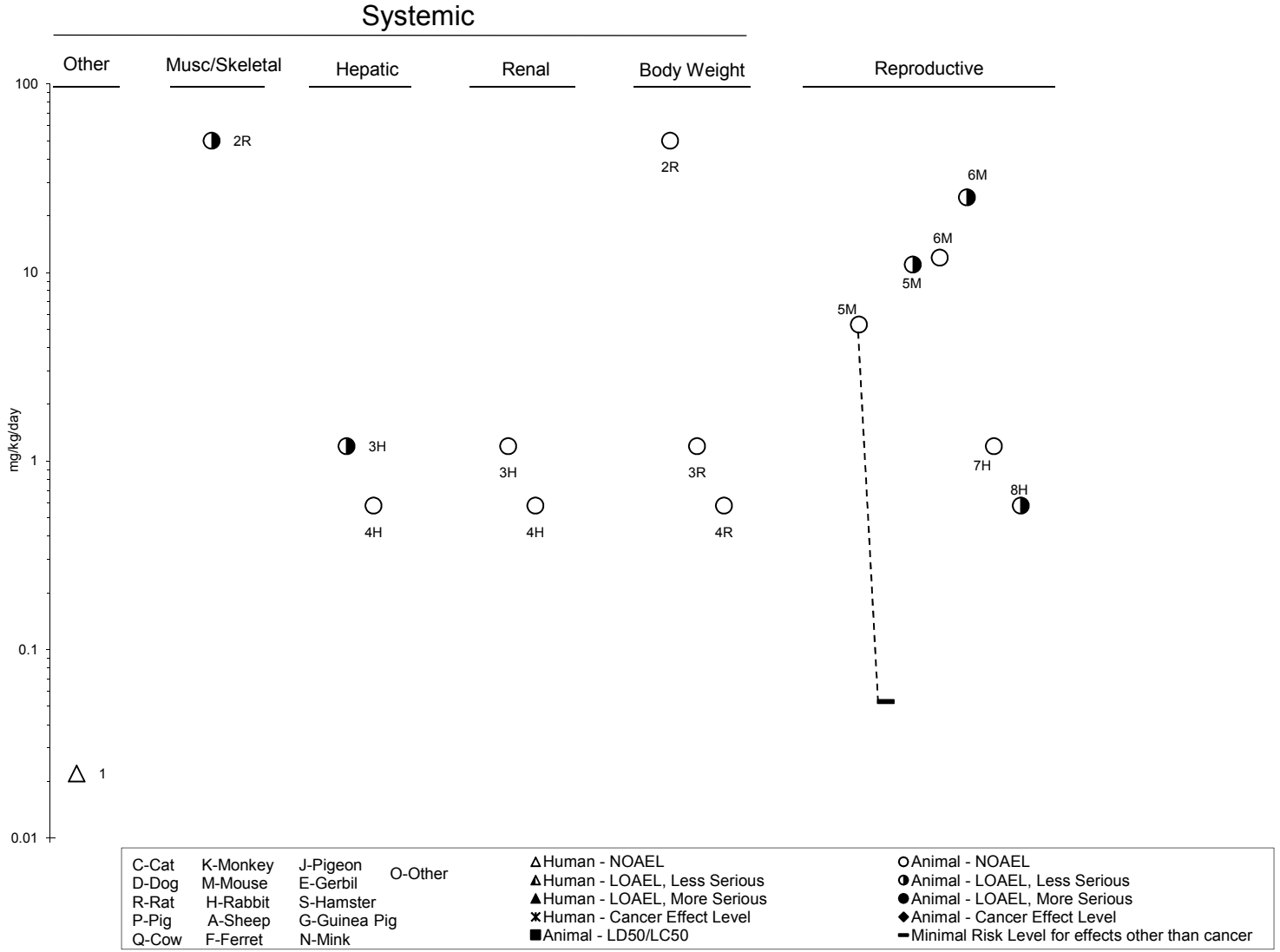
| Figure key[a] | Species (strain) No./group | Exposure parameters/ concentrations | Parameters monitored | System | NOAEL (mg/kg/day) | Less serious LOAEL (mg/kg/day) | Serious LOAEL (mg/kg/day) | Results | Reference (compound) |
|---|---|---|---|---|---|---|---|---|---|

[a]The number corresponds to entries in Figure 3-2.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.053 m molybdenum/kg/day based on the NOAEL of 5.3 mg molybdenum/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate-duration oral MRL of 0.0076 mg molybdenum/kg/day based on the NOAEL of 0.76 mg molybdenum/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

BC = biochemistry; BW = body weight; Cardio = cardiovascular; CS = clinical signs; d = day(s); DX = developmental; EA = enzyme activity; Endocr = endocrine; F = female(s); F = food; FI = feed intake; FX = function testing; Gastro = gastrointestinal; GN = gross necropsy; GW = gavage in water; HE = hematology; Hemato = hematology; HP = histopathology; hr = hour(s; MRL = Minimal Risk Level; NS = not specified; Musc/Skel = mucsculoskeletal; OP = ophthalmology; OW = organ weight; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)

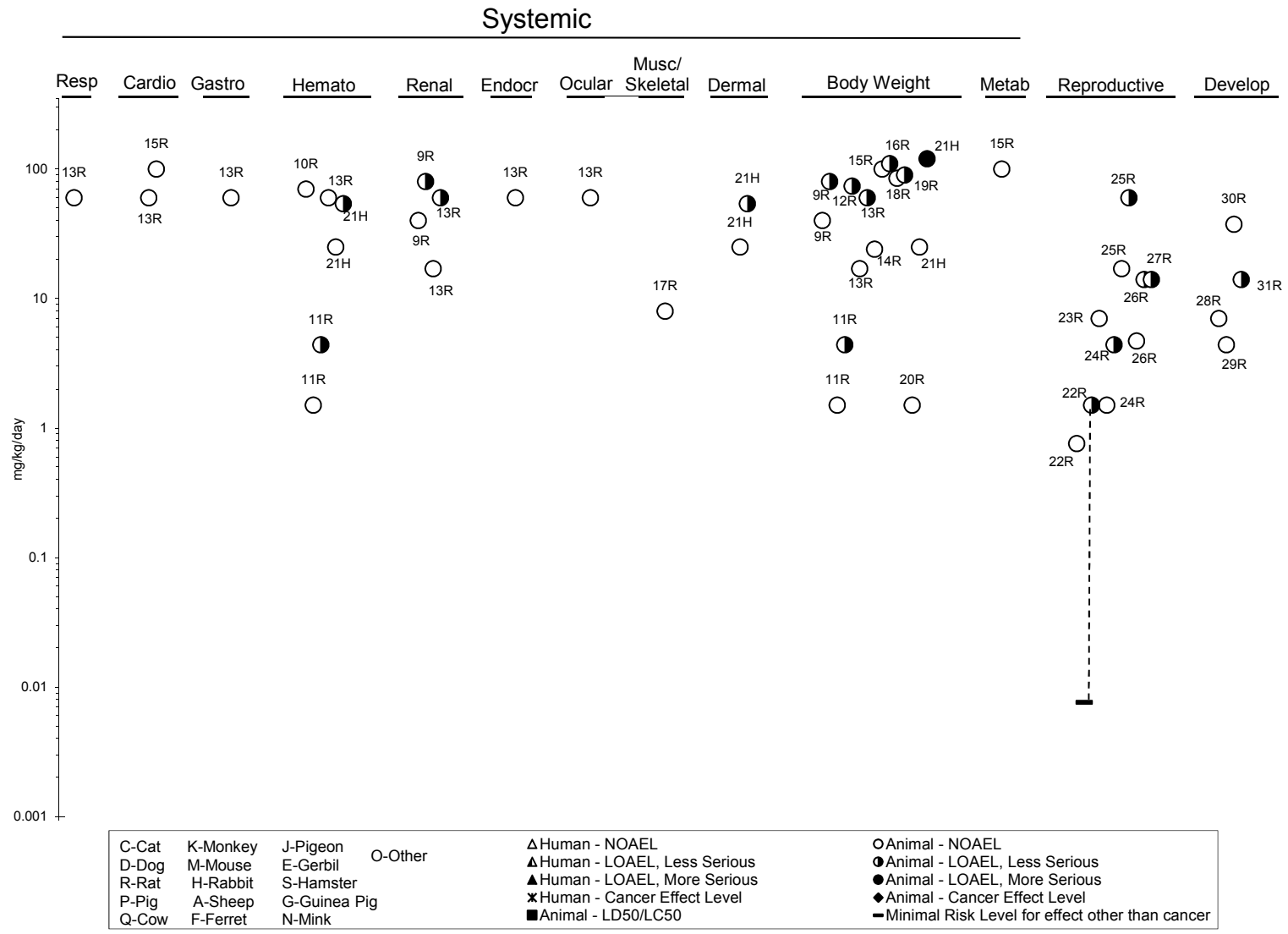
## Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral

Acute (≤ 14 days)



## Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral *(Continued)*

Intermediate (15-364 days)



the diet, can influence the toxicokinetics of molybdenum and possibly its toxicity. The current recommended dietary copper concentrations of 5, 6, and 3 ppm have been set for rats, mice, and rabbits, respectively (NAS 1977, 1995); for rats and mice, a copper dietary level of 8 ppm has been established to support gestation and lactation (NAS 1995). Administration of 150 and/or 500 mg/kg molybdenum in the diet for up to 6 weeks to rats fed a copper-deficient or copper-adequate diet resulted in profound differences in the distribution of copper and molybdenum in the plasma, liver, and kidneys (Nederbragt 1980, 1982). For example, at a molybdenum dietary concentration of 150 mg/kg, molybdenum levels in the liver and kidneys were 3.5 and 9 times higher, respectively, in the copper-adequate rats as compared to 6 and 4 times higher in the copper-deficient rats. Additionally, the relative increase in copper levels in the liver and kidneys was greater in the rats fed the copper-deficient diet, as compared to those fed the copper-adequate diet. Administration of tetrathiomolybdate compounds, as compared to molybdate compounds, results in more dramatic shifts in copper levels in rats fed copper adequate diets (Mills et al. 1981a). Since it is not known whether the differences in the distribution of copper and molybdenum influence the molybdenum toxicity, studies in which the laboratory animals were fed a basal diet with inadequate copper levels are clearly identified in the text, are discussed separately from studies in which there was adequate dietary copper levels, and are not included in the LSE table or figure. Additionally, laboratory animal studies in which the diet provided an inadequate amount of copper are not likely to be a good model for the U.S. population since the median copper intake of adults in the United States exceeds the nutritional requirement (RDA) for copper (NAS 2001).

#### 3.2.2.1 Death

Several oral studies have reported deaths in rabbits exposed to molybdenum. Mortality rates of 42–100% were observed in rabbits exposed to 59–120 mg molybdenum/kg/day for intermediate durations (Arrington and Davis 1953; Robinson et al. 1969; Valli et al. 1969; Widjajakusuma et al. 1973). Although the causes of death were not reported, anorexia, body weight loss, and anemia were observed in most of the studies at the lethal concentrations, suggesting that the deaths may be related to a functional copper deficiency. The copper content of the diet was adequate in the Arrington and Davis (1953) study and was not reported in the Widjajakusuma et al. (1973), Robinson et al. (1969), and Valli et al. (1969) studies. No deaths have been reported in rat studies (e.g., Lyubimov et al. 2004; Murray et al. 2013, 2014; Pandey and Singh 2002).

### 3.2.2.2 Systemic Effects

**Respiratory Effects.** Only one animal study examined the respiratory tract following oral exposure to molybdenum. No lesions were observed in the lungs of rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2013).

**Cardiovascular Effects.** Using the NHANES dataset (2009–2012), Shiue and Hristova (2014) found a significant positive association between urinary molybdenum levels and high blood pressure among adults after adjusting for potential confounders (adjusted odds ratio of 1.45; 95% confidence interval of 1.04–2.02). The investigators estimated that molybdenum accounted for 6.3% of the variance in the population risk and significant associations were also found for other metals including cesium, lead, platinum, antimony, arsenic, and tungsten and industrial pollutants including phthalates, bisphenol A, and parabens. In a population-based study examining the possible association between municipal water constituents and cardiovascular mortality in residents of 94 large cities in the United States, Schroeder and Kraemer (1974) found a weak negative correlation between arteriosclerotic heart disease deaths and molybdenum levels among white males, but not white females or nonwhite males or females. The mean concentration of molybdenum in the municipal water samples was 1.25 µg/L (0.00003 mg molybdenum/kg/day, assuming a water intake of 2 L/day and body weight of 70 kg) with a range of 0–16 µg/L. These studies appear to provide conflicting results, with one study suggesting a beneficial effect of increased molybdenum (Schroeder and Kraemer 1974) and the other a detrimental effect (Shiue and Hristova 2014). However, a number of etiological factors contribute to the overall risk of both diseases and the contribution of molybdenum to the overall risk was low in both studies.

No alterations in heart weight or histopathology were observed in rats ingesting ≤60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2013). Peredo et al. (2013) reported a slight decrease (approximately 4%) in systolic blood pressure in rats exposed to 100 mg molybdenum/kg/day as sodium molybdate in drinking water for 9 weeks; this slight decrease in blood pressure was not considered biologically relevant.

**Gastrointestinal Effects.** No histological alterations were observed in the gastrointestinal tract of rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2013). In contrast, Fell et al. (1979) reported soft feces and diarrhea and a number of histological alterations in the gastrointestinal tract of rats exposed for up to 21 days to 0.5 mg molybdenum/kg/day as ammonium tetrathiomolybdate in the diet (diet provided an inadequate amount of copper). The

alterations included shortening of the gastric pits with a reduction in the amount of mucin in the stomach, an increase in the crypt to villus ratio in the small intestine due to a lengthening of the crypts, edema of the lamina propria in the ileum, and submucosal edema of the cecum resulting in a thickening of the cecum but no effect on the brush border. However, the investigators did not provide incidence data, which limits the assessment of these alterations.

**Hematological Effects.** In general, the hematological system does not appear to be a target of molybdenum toxicity when the basal diet contains adequate levels of copper. In rats exposed to sodium molybdate or ammonium heptamolybdate, the highest NOAEL values for hematological alterations ranged from 3.35 to 150 mg molybdenum/kg/day for intermediate-duration exposure (Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Hunt and Navia 1973; Jeter and Davis 1954; Johnson et al. 1969; Murray et al. 2013). One study reported decreases in erythrocyte counts, hemoglobin, and hematocrit in rats exposed to 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate administered via gavage for 59–61 days (Lyubimov et al. 2004). Although the basal diet contained the NRC's recommended amount of copper (NAS 1995), hematological effects were not observed in rats exposed to the same molybdenum dose receiving a diet containing additional copper (110 ppm), suggesting that the hematological effects may have been secondary to a molybdenum-induced copper deficiency (anemia is a sign of copper deficiency). In young rabbits, exposure to 54 mg molybdenum/kg/day as sodium molybdate in the diet resulted in anemia (Arrington and Davis 1953). Even though the reported copper concentration in the diet exceeded the more recently recommended standard of 3 ppm (NAS 1977), administration of additional copper resulted in increases in hemoglobin levels. In a similar study using mature rabbits, anemia was observed in one of two rabbits exposed to 30 mg molybdenum/kg/day as sodium molybdate in the diet (Arrington and Davis 1953). Decreases in hemoglobin levels and packed cell volume were also observed in two other rabbit studies (Valli et al. 1969; Widjajakusuma et al. 1973) in which rabbits were exposed to 77 or 59 mg molybdenum/kg/day in the diet for approximately 4 weeks. Mortality was observed in both studies and neither study reported the copper levels of the basal diet; Valli et al. (1969) did note that the rabbits were fed a diet with a low copper content. In pigs, no hematological alterations were observed following dietary exposure to 20–100 ppm molybdenum as sodium molybdate or ammonium heptamolybdate in the diet for at least 8 weeks (Gipp et al. 1967; Kline et al. 1973); the studies did not provide sufficient information to allow for an estimation of the molybdenum dose.

**Musculoskeletal Effects.** A number of animal studies have examined the effect of molybdenum on bone growth and strength and on the promotion of dental caries. Musculoskeletal effects were observed

in two studies in which the diet contained at least the recommended level of copper. In a study by Johnson et al. (1969) in which rats were exposed to 150 mg molybdenum/kg/day as sodium molybdate in the diet for 6 weeks (the basal diet contained copper levels that were 3 times higher than the recommended amount), decreases in femur breaking strength (22% less than controls) and tail ring rupture strength (32% less than controls) were observed. Young rabbits exposed to ≥54 mg molybdenum/kg/day as sodium molybdate for 30–84 days exhibited a front limb abnormality characterized by weakness progressing to an inability to "maintain weight and legs spread outward" (Arrington and Davis 1953). This was not observed in mature rabbits exposed to ≤120 mg molybdenum/kg/day as sodium molybdate for at least 54 days (Arrington and Davis 1953). The investigators noted that in three of the seven affected animals, one or both feet bent inward at the carpus joint, the articular surface of the radius was exposed, and the tendon slipped out of normal position. It should also be noted that increases in mortality were also observed in the young rabbits exposed to 54 mg molybdenum/kg/day, and in two of the rabbits with limb abnormalities, administration of additionally copper did not reverse the skeletal effect, although there was improvement of other effects including anemia and body weight gain.

In an acute-duration study, femurs were significantly shorter in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate or ammonium tetrathiomolybdate for 13 days (Parry et al. 1993). No alterations in the width of the growth plate or the bone composition (dry matter content, ash content, or percentage of calcium or phosphorus) were found. Similar findings were found in a 26-day study conducted by Parry et al. (1993); significant decreases in femur length were noted in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate or ammonium tetrathiomolybdate in the diet. Although no direct comparisons were made between the two molybdenum groups, the magnitude of the decrease in femur length, as compared to the controls, was greater in the tetrathiomolybdate group. Increases in growth plate width were also observed in the rats exposed to ammonium tetrathiomolybdate, but not in rats exposed to ammonium heptamolybdate. In both experiments, the rats were fed a basal diet with inadequate copper levels (60% of the recommended concentration); in the ammonium tetrathiomolybdate study, plasma and liver copper levels indicated that the animals were extremely copper deficient. Spence et al. (1980) examined the development of widening of the epiphyseal growth plate over time in rats exposed to 1 mg molybdenum/kg/day as ammonium tetrathiomolybdate in the diet for 2–21 days. The study found cartilaginous dysplasia at the epiphyseal growth plate with impaired or arrested endochondral ossification, increases in periosteal osteogenesis and production of large amounts of disorganized bone, resorption of most trabecular bone, hemorrhaging within and tearing of tendons and ligaments, rotation and slipping of the distal epiphysis in

the femur without fracture, and impaired fibrogenesis at ligamentous attachments to bone. A thickening and widening of the epiphyseal growth plate was observed in the distal femur and proximal and in the epiphyses of the humeral head, distal radius, and ulna; these effects were observed within the first 2 weeks of the study. Other morphological alterations in the bone were observed after 7 days of exposure; these included loss of alignment of hypertrophic cells at the periphery of the epiphyseal cartilage and localized increases in cell numbers. In rats allowed to recover for 39 days following the 21-day exposure period, osteogenesis and fibrogenesis returned to normal, and remodeling and growth returned (although some abnormal cartilage and bone were present). As with the Parry et al. (1993) study, the rats in the Spence et al. (1980) study were fed a basal diet containing an inadequate amount of copper (60% of the recommended level). Fejery et al. (1983) found an increase in femur breaking strength in rats exposed to 0.17 or 1.7 mg molybdenum/kg/day (copper content of the diet was not reported), which was considered a beneficial effect; at 17 mg molybdenum/kg/day, breaking strength was similar to controls. However, if the rats were maintained on a protein-deficient diet, decreases in breaking strength were observed at 1.7 and 17 mg molybdenum/kg/day. In rabbits exposed to a lethal concentration of sodium molybdate (77 mg molybdenum/kg/day) in the diet for 4 weeks, fractures of the humeral bone epiphyses were observed in 50% of the animals (Valli et al. 1969). Other effects included longitudinal widening of the epiphyseal cartilage, marked reduction in trabecular bone, irregularly arranged spicules, and irregular metaphyseal calcification. In addition, the investigators noted that there was marked muscular degeneration in the pelvic limbs in 25% of the rabbits. The copper content of the basal diet was not reported in this study, although the investigators noted that the diet had a low copper content.

Alterations in tooth enamel and caries formation have also been observed in laboratory animals exposed to molybdenum. In rat pups administered 50 mg molybdenum/kg/day as sodium molybdate via gavage on postnatal days (PNDs) 4–17 (prior to tooth eruption) and fed a caries-promoting diet on PNDs 18–35, a 25% increase in buccal enamel lesion and 85 and 12.5% increases in lesions penetrating to the buccal and sulcal dentine-enamel junctions, respectively, were observed in the mandibular molars (Hunt and Navia 1975). Fejery et al. (1983) reported biphasic alterations in incisor tooth enamel microhardness in rats exposed to sodium molybdate in drinking water for 6 weeks (the copper content of the basal diet was not reported). At 1.7 mg molybdenum/kg/day, there were increases in microhardness (6–7% increases in surface and deep enamel microhardness), which was considered a beneficial effect. However, at 17 mg molybdenum/kg/day, tooth surface and deep enamel microhardness was decreased by 14.5 and 7.5%, respectively. The study also examined the possible effect of a low protein diet (3% in the low-protein groups compared to 18% in the protein-adequate groups) and found that the beneficial effect of 1.7 mg

molybdenum/kg/day did not occur in the rats in the low-protein diet; a 4–5% reduction in microhardness was found at 1.7 mg/kg/day. Van Reen et al. (1962) did not find increases in dental caries in weanling NMRI-D rats (a caries susceptible strain) exposed to 8 mg molybdenum/kg/day as sodium molybdate for 5 weeks (the basal diet provided adequate copper levels).

**Hepatic Effects.** There are limited data on the hepatotoxicity of molybdenum in humans. Using the NHANES 2007–2008 data, Mendy et al. (2012) found a significant association between urinary molybdenum levels and the risk of having a self-reported liver condition (odds ratio of 3.09; 95% confidence interval of 1.24–7.73). The geometric mean urinary molybdenum level of the population was 43.8 μg/g creatinine (95% confidence interval of 42.61–45.19); the investigators did not report the urinary concentration associated with the increased risk of liver conditions. This study does not establish causality between molybdenum exposure and liver damage, and significant associations were also found between uranium and cesium levels and liver conditions.

The liver does not appear to be a sensitive target of molybdenum toxicity in laboratory animals, although effects have been observed at higher doses. No histological alterations were observed in livers of rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days (Bersenyi et al. 2008), rabbits exposed to 0.58 mg molybdenum/kg/day from carrots grown in ammonium heptamolybdate rich soil, or rats exposed to 60 mg molybdenum/kg/day in the diet for 90 days (Murray et al. 2013); these are the only studies that included histological examination of the liver. The Bersenyi et al. (2008) female rabbit study did not find alterations in serum alanine or aspartate aminotransferases levels, γ-glutamyl transferase, alkaline phosphatase, or cholesterol levels; however, a 60% increase in serum triglyceride levels was found at 1.2 mg molybdenum/kg/day. In contrast, the Murray et al. (2013) study examined similar serum clinical chemistry parameters (including triglyceride levels) and did not find any significant alterations. A series of studies conducted by Rana and associates have also reported some liver alterations in rats exposed to 300–490 mg molybdenum/kg/day as ammonium molybdate. The reported alterations included increases in total lipid levels (Rana et al. 1980; Rana and Kumar 1980b, 1980c), decreases in "total carbohydrate" (Rana and Kumar 1980c), decreases in glycogen content (Rana et al. 1985), and increases in serum alanine aminotransferase and aspartate aminotransferase activities (Rana and Chauhan 2000). The addition of 100 mg/kg body weight/day copper to the basal diet (approximately 5 ppm) appeared to reverse the effects of molybdenum on hepatic lipid and carbohydrate levels (Rana and Kumar 1980c). There was low confidence in these studies due to the poor reporting of the study design (including route of oral administration, whether the dose was reported in terms of molybdenum or ammonium molybdate, and copper content of the diet), the lack of histological

examination of the liver, and the reported body weight losses (Rana et al. 1980; Rana and Chauhan 2000); body weight was not assessed in every study.

**Renal Effects.** The available data from laboratory animal studies suggest that the kidney may be a target of molybdenum toxicity. Most of these studies involved exposure to ammonium molybdate or ammonium heptamolybdate and it is possible that the renal effects may be due to the ammonium ion rather than the molybdate. In the only available acute-duration study, no histological alterations were observed in the kidneys of female rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days (Bersenyi et al. 2008) or male rabbits exposed to 0.58 mg molybdenum/kg/day from carrots grown in ammonium heptamolybdate-rich soil for 14 days (Bersenyi et al. 2008). Murray et al. (2013) reported a slight diffuse hyperplasia in the renal proximal tubules in 2/10 female rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days; no renal lesions were observed in females exposed to 60 mg molybdenum/kg/day for 90 days and allowed to recover for 60 days. No alterations were observed in the male rats. Although the incidence was low, the investigators considered it to be treatment-related because it is an uncommon finding in female rats of this age. Degenerative changes in the kidneys were noted in male rats exposed to 240 mg molybdenum/kg/day as ammonium molybdate (Bandyopadhyay et al. 1981). It should be noted that the food intake in the molybdenum group was paired to another group of rats fed a low-protein diet and exposed to molybdenum; the basal diet likely provided adequate copper levels. No other studies included histological examination of the kidneys.

Several studies reported alterations in serum and urinary parameters that could be suggestive of altered renal function. Diuresis and creatinuria and a decrease in creatinine clearance were observed in rats administered via gavage 80 mg molybdenum/kg/day as ammonium heptamolybdate for 8 weeks (Bompart et al. 1990). The study did not find significant alterations in urinary protein or glucose levels. Studies by Rana and associates have reported increases in total lipid levels in the kidneys (Rana et al. 1980; Rana and Kumar 1980c), decreases in "total carbohydrate" levels in the kidney (Rana and Kumar 1980c), increases in serum urea and urinary albumin levels (Rana and Kumar 1983), and increases in urine specific gravity (Rana and Kumar 1983) in rats exposed to high doses of ammonium molybdate (300–490 mg molybdenum/kg/day). The addition of copper (approximately 5 ppm) to the basal diet appeared to reverse the increased lipid and decreased carbohydrate levels (Rana and Kumar 1980c). As noted in the hepatic effects section, there is low confidence in these studies and the results should be interpreted cautiously.

**Endocrine Effects.** The possible association between molybdenum and thyroid effects was investigated in adults (subjects did not report having thyroid disease, thyroid cancer, or taking thyroid medication on a medical questionnaire completed at the blood sampling) using the NHANES 2007–2008 data set (Yorita Christensen 2013). Significant associations between decreased levels of triidothyronine (free and total) and thyroxine (free) and higher urinary molybdenum levels were found. Although the study found associations, these data are inadequate for establishing causality. A study of men at a fertility clinic found a significant inverse relationship between blood molybdenum levels and prolactin levels (Meeker et al. 2009); the men were categorized into three groups based on blood molybdenum levels (<70$^{th}$ percentile, 70$^{th}$–85$^{th}$ percentile, and >85$^{th}$ percentile). The study did not find a significant association with thyroid stimulating hormone and blood molybdenum levels.

In animal studies, increases in serum cortisol, prolactin, and follicle stimulating hormone levels were found in male rats administered 240 mg molybdenum/kg/day as ammonium molybdate for 4 weeks (Bandyopadhyay et al. 1981); as noted in the renal effects section, food intake was matched to a low-protein molybdenum group. Murray et al. (2013) did not find increases in histological alterations in the adrenal glands, pituitary gland, or thyroid of rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days. Several thyroid effects were reported in rabbits exposed to 59 mg molybdenum/kg/day as sodium molybdate in the diet for 25–31 days (Widjajakusuma et al. 1973). The investigators did not report the copper content of the diet; it is likely to be low based on the severe decreases in body weight, hematological parameters, and increased mortality. The effects included decreases in thyroxine secretion rates; decreases in follicle size (height and diameter); atrophy of the follicular epithelium, colloids, and stroma; and degenerative alterations in the follicular epithelium and interfollicular connective tissue. With the exception of the degenerative changes, similar, but less prominent, thyroid effects were also observed in pair-fed controls, suggesting that the resulted decreases in food intake and body weight contributed to the thyroid toxicity.

**Dermal Effects.** There are limited data on the dermal toxicity of molybdenum following oral exposure. In the first study of weanling rabbits (Arrington and Davis 1953), alopecia and slight dermatosis were observed in four of five rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate in the diet for 84 days; no dermal effects were observed at 25 mg molybdenum/kg/day. In another study by this group, alopecia and slight dermatosis were observed in one of two mature rabbits exposed to 30 mg molybdenum/kg/day as sodium molybdate. Anemia was also observed at these doses. In the study of weanling rabbits, administration of additional copper resulted in a return to a normal hair coat, suggesting that copper insufficiency, possibly molybdenum induced, was a contributing factor to the

dermal toxicity. Johnson et al. (1969) reported decreases (25% lower than controls) in skin rupture strength in rats exposed to 150 mg molybdenum/kg/day as sodium molybdate in the diet for 6 weeks.

**Ocular Effects.** No ocular lesions were observed in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2013); no other studies examined ocular end points.

**Body Weight Effects.** A large number of animal studies have reported alterations in body weight following acute- or intermediate-duration exposure to molybdenum. Large differences in terminal body weights between controls and molybdenum-exposed groups and weight loss have been reported in many studies in which the basal diet did not provide adequate levels of copper (Brinkman and Miller 1961; Fell et al. 1983; Johnson and Miller 1961; Ostrom et al. 1961; Sasmal et al. 1968; Van Reen 1959). In one study, exposure to 500 mg molybdenum/kg/day as sodium molybdate resulted in weight loss in rats (Sasmal et al. 1968); no alterations in weight loss were observed at 50 or 100 mg molybdenum/kg/day. The weight loss began early in the study; the animals weighed about 35% less than at the start of the study after 1 week of exposure. In another study by this group (Sasmal et al. 1968), exposure to 50 mg molybdenum/kg/day as ammonium molybdate resulted in weight loss. Although the study suggests differences between the two molybdenum compounds, the very low copper content of the diet (no additional copper was added to the purified diet) precludes extrapolating these data to other conditions. In another study comparing molybdenum compounds, a 10-day dietary exposure to 0.6 mg molybdenum/kg/day as ammonium tetrathiomolybdate resulted in a 10% decrease in body weight in rats; however, no alterations in body weight gain were observed in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate under the same exposure conditions (Parry et al. 1993). The copper content of the diet was 3 ppm, which is lower than the recommendation of 5 ppm in the diet (NAS 1995).

Decreases in body weight gain have been observed in studies in which the basal diet provided a nutritionally adequate level of copper (Arrington and Davis; 1953; Bompart et al. 1990; Jeter and Davis 1954; Johnson 1969; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956). Studies in rats in which the basal diet contained at least twice the amount of copper recommended by the NAS (1995) reported significant decreases in body weight gain at 60–110 mg molybendum/kg/day as sodium molybdate or ammonium heptamolybdate in intermediate-duration studies (Bompart et al. 1990; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956; Williams and Van Reen 1956). The magnitude of the decrease in body weight gain appeared to be related to the dose, with approximately 15% decreases observed at 60 mg molybdenum/kg/day and 48% decreases observed at 110 mg

molybdenum/kg/day. Administration of ammonium tetrathiomolybdate resulted in a very low LOAEL of 4.4 mg molybdenum/kg/day for decreases in body weight gain (Lyubimov et al. 2004); there are insufficient data to assess whether this is evidence of differences between molybdenum compounds. Decreases in food intake have also been reported in dietary exposure studies (Murray et al. 2013; Williams and Van Reen 1956) and a gavage study (Lyubimov et al. 2004). Williams and Van Reen (1956) found that when the control group food intake was matched to the molybdenum group, body weight was not adversely affected after 5 weeks of exposure to 85 mg molybdenum/kg/day as sodium molybdate. However, when the control group had *ad libitum* access to food, exposure to 90 mg molybdenum/kg/day as sodium molybdate resulted in a 22% decrease in body weight gain. In contrast, Murray et al. (2013) found a decrease in food conversion efficiency suggesting that factors other than the reduction in feed intake resulted in the decreased body weight gain. Similarly, in a study by Johnson and Miller (1961) in which the basal diet contained 3.2 ppm copper, large differences (50–60% less) in food intake were observed between the control group and the group exposed to 20 ppm molybdenum/kg/day as sodium molybdate. However, when the control intake was matched to the molybdenum group's intake, significant decreases in body weight gain were still observed.

**Metabolic Effects.** The potential of molybdenum to induce metabolic alterations has not been fully investigated. Two studies in rats did not find significant alterations in serum glucose levels following intermediate-duration exposure to 60 or 100 mg molybdenum/kg/day (Murray et al. 2013; Peredo et al. 2013); additionally, serum insulin levels were not altered by exposure to 100 mg molybdenum/kg/day (Peredo et al. 2013). Prakash (1989) reported decreases in glycogen levels in the hind limb muscles of rats administered 490 mg molybdenum/kg/day as ammonium molybdate via gavage for 30 days. The significance of this effect is difficult to determine since the study did not provide information on body weight gain.

**Other Systemic Effects.** Koval'skiy et al. (1961) reported a significant increase in blood uric acid levels and symptoms of gout in residents living in an area of Armenia with high levels of molybdenum in the soil and food, as compared to residents living outside of this area. The mean uric acid levels in a subset of the examined population (n=52) was 6.2 mg/dL, as compared to levels in five control subjects who had a mean level of 3.8 mg/dL; the mean uric acid levels were 8.1 mg/dL among the subjects with gout symptoms and 5.3 mg/dL among the exposed subjects without symptoms. The investigators reported that copper intakes (5–10 mg/day) were lower in the high molybdenum area as compared to copper intake for residents outside of this area (10–15 mg/day). It was also noted that gout-like symptoms have not been observed in other high molybdenum areas that have higher copper intakes

(Koval'skiy et al. 1961). Interpretation of the result of this study is limited by the small control group, as compared to the exposed group; lack of information on the selection of controls, particularly if they were matched to the exposed group; and lack of information on diet and alcohol exposure, which could influence uric acid levels. Based on the levels of molybdenum in the foodstuff, the investigators estimated a daily dose of 10–15 mg (0.14–0.21 mg/kg/day assuming a 70-kg body weight). Deosthale and Gopalan (1974) did not find significant increases in urinary uric acid levels in four subjects exposed to a low molybdenum diet for 10 days followed by a high molybdenum diet with an ammonium molybdate supplement for 7 days (TWA molybdenum intake was 0.014 mg molybdenum/kg/day), as compared to uric acid levels when the subjects were fed a low molybdenum diet. A series of studies in Colorado investigated uric acid levels in communities with high molybdenum levels in the drinking water from mine tailings pollution (EPA 1979). Comparisons between subjects living in areas with high molybdenum in the drinking water (80–200 μg/L; approximately 0.002–0.006 mg/kg/day) to those living in areas with lower levels (<40 μg/L; <0.001 mg/kg/day) did not result in any significant differences in serum uric acid levels or urinary molybdenum levels. Another study (EPA 1979) noted that serum uric acid levels were within the normal range in students with an estimated molybdenum intake of 500 μg/day (0.007 mg/kg/day) (EPA 1979). A third study found significant increases in uric acid levels in residents with low molybdenum (20 μg/L; 0.0006 mg/kg/day) levels in the water and in residents with high molybdenum levels (150–200 μg/L; 0.004–0.006 mg/kg/day) in the drinking water; as compared to residents with drinking water levels of 0–50 μg/L (0–0.001 mg/kg/day). The inconsistencies in the results could be explained by the lack of control of several variables including age, sex, alcohol intake, dietary habits, and altitude.

Murray et al. (2013) found a statistically significant decrease in serum uric acid levels in female rats exposed to ≥5 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days; no alterations were observed in male rats exposed to up to 60 mg molybdenum/kg/day. Other statistically significant alterations in serum clinical chemistry parameters noted in the Murray et al. (2013) study include decreases in total protein and calcium at 60 mg molybdenum/kg/day in males and decreases in serum creatinine at ≥5 mg molybdenum/kg/day in females. The investigators noted that the changes in serum clinical chemistry (including uric acid levels) were not considered treatment-related because the alterations were of small magnitude, not dose-related, due to outliers in the controls, and/or were consistent with normal variability. Quantitative data for the serum clinical chemistry parameters were not provided in the published paper.

### 3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans and animals following oral exposure to molybdenum.

### 3.2.2.4 Neurological Effects

There are limited data on the neurotoxicity of molybendum; no human or animal studies were designed to assess sensitive neurological end points. No overt signs of neurotoxicity were observed in laboratory animal studies (e.g., Murray et al. 2013); Murray et al. (2013) did not report any histological alterations in the brain.

### 3.2.2.5 Reproductive Effects

There are limited data on reproductive effects of molybdenum in humans. The available studies have evaluated correlations between ambient molybdate exposure and reproductive health measures, including semen quality (Meeker et al. 2008) and sex hormone levels (Meeker et al. 2010). Meeker et al. (2008) reported a negative significant association between higher molybdenum blood levels (>85$^{th}$ percentile, based on molybdenum levels in blood) and sperm concentration (adjusted odds ratio of 3.48, 95% confidence interval of 1.12–10.8) after adjustment for potential confounders and other metal exposures. No significant associations were found for sperm morphology (adjusted odds ratio of 2.61, 95% confidence interval of 0.97–7.0) or sperm motility (adjusted odds ratio of 2.24, 95% confidence interval of 0.77–6.49). In another study, Meeker et al. (2010) reported a negative correlation between higher molybdenum blood levels (≥70$^{th}$ percentile) and testosterone and free androgen index (molar ratio of total testosterone sex hormone-binding globulin) levels. The men in these studies, who were recruited from Michigan infertility clinics and were not all considered to be infertile (i.e., their partners may have been infertile), were only exposed to molybdenum from their surroundings. A significant negative association between a biomarker of molybdenum exposure (urinary levels) and serum testosterone levels was also observed in a study of males participating in NHANES (2011–2012) (Lewis and Meeker 2015). The study found a 3.82% decrease in serum testosterone levels when urinary molybdenum levels doubled (after adjustment for age, body mass index [BMI], income, race, and smoking). Although these studies found statistically significant associations, they do not establish causality and the alterations in reproductive parameters may be due to multiple factors rather than only to molybdenum exposure.

Several studies have evaluated the reproductive toxicity in male laboratory animals. Decreases in sperm motility and concentration and increases in sperm morphological changes were observed in rats administered via gavage 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate for 59–61 days (Lyubimov et al. 2004) or 14 mg molybdenum/kg/day as sodium molybdate for 60 days (Pandey and Singh 2002), and in mice exposed to 25 mg molybdenum/kg/day as sodium molybdate in the drinking water for 14 days (Zhai et al. 2013). These studies also found decreases in epididymis, seminal vesicle, and/or prostate gland weights (Lyubimov et al. 2004; Pandey and Singh 2002; Zhai et al. 2013). Degeneration of the seminiferous tubules was found in rats at 7 mg molybdenum/kg/day as sodium molybdate, which was administered in the diet from weaning age through sexual maturity (Jeter and Davis 1954); although this study provided an adequate amount of copper, there was evidence of copper deficiency (achromotrichia) at ≥7 mg molybdenum/kg/day. Degeneration of the seminiferous tubules was also reported by Pandey and Singh (2002) for intermediate-duration (60 days) exposures in rats administered molybdenum at doses up to 24 mg molybdenum/kg/day (sodium molybdate); however, the dose(s) producing the effects are unclear and incidence data were not reported. Lyubimov et al. (2004) reported delayed spermiation, increased sperm and seminal fluid concentration, and increased sloughing of epididymal tail epithelial cells at 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate. Although the basal diet in the Lyubimov et al. (2004) study provided 11 ppm of copper, which is above the NAS (1995) recommended amount for rats (5 ppm), dietary copper supplementation (110 ppm) prevented testicular toxicity. It is likely that the tetrathiomolybdate interfered with the absorption of dietary copper, resulting in a secondary effect of copper insufficiency. In contrast to these findings, Murray et al. (2013) did not find any alterations in spermatid, sperm counts, sperm motility, or sperm morphology in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet. Although the study found no alterations in the percentage of motile sperm, a significant decrease in the percentage of progressively motile sperm was observed at 60 mg molybdenum/kg/day (59.0% compared to 69.4% in controls). The investigators noted that the decrease was likely attributable to the control group having a value that approached the upper end of the range for historical controls (mean of 59.8%). Given the results of the Lyubimov et al. (2004), Pandey and Singh (2002), and Zhai et al. (2013) studies, the 60 mg molybdenum/kg/day dose level was considered a LOAEL for male reproductive effects. It should be noted that the basal diet in this study exceeded the NAS (1995) recommendation; the copper content was 14.23 ppm.

Effects have also been observed in female laboratory animals. An increase in the rate of M II oocyte morphological abnormalities and decreases in relative ovarian weights were observed in mice exposed to 11 mg molybdenum/kg/day as sodium molybdate in drinking water for 14 days (Zhang et al. 2013). The

investigators also reported ovarian hyperemia in mice exposed to 5.3 and 11 mg molybdenum/kg/day; however, the incidence and statistical significance were not reported. Irregularities in the estrous cycle were reported in rats administered 1.5 mg molybdenum/kg/day in the drinking water from weaning through sexual maturity (Fungwe et al. 1990). Murray et al. (2013) did not find any alterations in vaginal cytology or estrus cycle in female rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate and Bersenyi et al. (2008) did not find histological alterations in the ovaries of rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days.

Several intermediate-duration studies evaluated fertility. No alterations in fertility were observed in female rats exposed to ≤15 mg molybdenum/kg/day as sodium molybdate in drinking water (Fungwe et al. 1990) or in male and female rats exposed to 7 mg molybdenum/kg/day as sodium molybdate in the diet when a high copper diet was administered (Jeter and Davis 1954). In contrast, Pandey and Singh (2002) reported decreases in fertility in males exposed to 14 mg molybdenum/kg/day and mated to unexposed females. Another study conducted by Jeter and Davis (1954) in which rats were exposed to 7 mg molybdenum/kg/day from weaning to maturity also found impaired male fertility; in this study, there is some indication that the diet did not provide an adequate level of copper.

#### 3.2.2.6 Developmental Effects

There are limited data on the developmental effects of molybdenum in humans from two population studies. Vazquez-Salas et al. (2014) found an association between third trimester maternal urinary molybdenum levels (mean level of 54.0 µg/g creatinine) and infant psychomotor development indices, including gross and fine motor coordination, during the first 30 months of life in a study of women in Mexico participating in a prospective study of neurodevelopment in children. A doubling of creatinine corrected urinary molybdenum levels resulted in significant decreases in psychomotor development index scores. No association was found between maternal urinary molybdenum levels during pregnancy (mean levels ranged from 45.6 to 54.6 µg/g creatinine during the first, second, and third trimesters) and newborn body weight or infant mental development indices (sensory ability, memory, learning, problem solving, and verbal ability). Shirai et al. (2010) found no association between maternal urinary molybdenum levels and newborn body weight, length, or head circumference in women in Japan with mean urinary molybdenum levels of 79.0 µg/g creatinine. As noted elsewhere in this document, these observational epidemiology studies do not establish causality between molybdenum and developmental effects, and other factors are likely to have contributed to the risk.

Several studies have examined the effect of molybdenum on development in laboratory animals. No developmental effects were reported in three studies of rats exposed to molybdenum in the presence of adequate copper concentrations in the basal diet (Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014). Murray et al. (2014) reported no effects on litter size, embryofetal survival, sex ratio, fetal body weight, or fetal malformations and variations in rats exposed to 38 mg molybdenum/kg/day as sodium molybdate in the diet on gestation days 6–20. Similarly, Lyubimov et al. (2004) found no effects on litter size or fetal survival in rats administered molybdenum daily via gavage at 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate for 59–61 days (for 29 days prior to mating, during mating, and thereafter until sacrifice) in males or for 22–35 days (for 15 days prior to mating, during mating, and during gestation days 0–6) in females. No alterations in birth weights were observed in the offspring of male and female rats exposed to 7 mg molybdenum/kg/day as sodium molybdate for at least 14 weeks (Jeter and Davis 1954). However, a fourth study found decreases in the number of live fetuses, fetal crown-rump length, and fetal body weight in the offspring of male rats administered 14 mg molybdenum/kg as sodium molybdate via gavage for 60 days prior to mating to untreated females (Pandey and Singh 2002). The copper content of the commercial diet was not reported, but was assumed to be adequate. Two studies only available as abstracts provide additional information on the potential developmental toxicity of molybdenum. Lyubimov et al. (2002) found no developmental effects in rats exposed to 6 mg/kg/day as tetrathiomolybdate on gestation days 6–17. Exposure on gestation days 7–20, resulted in an increase in carpal/tarsal flexure in the offspring of dams exposed to 20 mg/kg/day ammonium tetrathiomolybdate (Lyubimov et al. 2003). Although neither study provided information on the copper content of the diet, it is assumed to be adequate based on Lyubimov et al. (2004).

Developmental effects have also been reported in studies in which the copper content of the diets were lower than the NAS recommended standard of 8 ppm for pregnant rats (NAS 1995). Fungwe et al. (1990) reported increases in fetal resorptions and decreases in litter weights in female rats exposed to 1.3 mg molybdenum/kg/day as sodium molybdate in the drinking water for 8 weeks prior to mating through gestation day 21; the copper content in the basal diet was 6.3 ppm. Decreased maternal body weight gain was also observed at doses resulting in developmental toxicity. Decreased weaning weights were observed in the offspring of rats exposed to ≥2 mg molybdenum/kg/day as sodium molybdate; the copper content of the diet was 5 ppm (Jeter and Davis 1954).

#### 3.2.2.7 Cancer

No studies were located regarding cancer in humans and animals following oral exposure to molybdenum.

### 3.2.3 Dermal Exposure

#### 3.2.3.1 Death

No studies were located regarding death in humans and animals following dermal exposure to molybdenum.

#### 3.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans and animals following dermal exposure to molybdenum.

#### 3.2.3.3 Immunological and Lymphoreticular Effects

There are limited data on the immunotoxicity of molybdenum in humans. Studies of patients with stainless steel stents (which contain nickel, chromate, and molybdenum) or in patients prior to hip or knee replacements found a low rate of positive results in patch tests with molybdenum (Koster et al. 2000; Menezes et al. 2004; Zeng et al. 2014). In patients with stainless steel stents, 3% had a positive delayed-type contact hypersensitivity reaction to molybdenum chloride (Koster et al. 2000). In the other studies, exposure to an unspecified molybdenum compound did not result in any positive hypersensitivity results.

Guinea pigs showed contact sensitization to a topical challenge with molybdenum pentachloride after induction via intradermal injection with 0.03% molybdenum and topical exposure to 5.2% molybdenum and an epicutaneous challenge with ≥0.35% molybdenum as molybdenum pentachloride (Boman et al. 1979). Similarly, guinea pigs were sensitized to 3.2% molybdenum as sodium molybdate following intradermal (3.2% molybdenum) or topical (8% molybdenum) induction (Boman et al. 1979).

#### 3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans and animals following dermal exposure to molybdenum.

#### 3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals following dermal exposure to molybdenum.

#### 3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following dermal exposure to molybdenum.

#### 3.2.3.7 Cancer

No studies were located regarding cancer in humans and animals following dermal exposure to molybdenum.

### 3.3 GENOTOXICITY

No studies were available regarding genotoxic effects of molybdenum compounds in humans following environmental or occupational exposure to these compounds. The genotoxicity of molybdenum compounds has been studied mostly in *in vitro* assays utilizing prokaryotic organisms and in mammalian cells. Limited information is available regarding the *in vivo* genotoxicity of molybdenum.

As shown in Table 3-3, sodium molybdate induced a modest, but statistically significant, increase in micronucleated bone marrow cells (polychromatic erythrocytes, PCE) from male C57BL/6J mice following two intraperitoneal injections of 200 or 400 mg/kg sodium molybdate on two consecutive days (Titenko-Holland et al. 1998). The increase in micronucleated cells per 1,000 PCE or in micronuclei per 1,000 PCE were about half of those produced by colchicine, the positive control. The same group of investigators reported that sodium molybdate induced a positive response in the dominant lethal assay in mice. In these experiments, male C57BL/6J mice were treated with 200 or 400 mg/kg sodium molybdate and were mated with non-treated female C3H/J mice at various times after dosing. Sodium molybdate

## Table 3-3. Genotoxicity of Molybdenum Compounds *In Vivo*

| Species | Compound | End point | Results | Reference |
|---|---|---|---|---|
| Mouse (male C57BL/6J) | Sodium molybdate | Micronuclei in bone marrow cells | (+) | Titenko-Holland et al. 1998 |
| Mouse (male C57BL/6J) | Sodium molybdate | Dominant lethal assay | (+) | Titenko-Holland et al. 1998 |
| *Drosophila melanogaster* wing spot test | Molybdenum chloride | Gene mutation | + | Ogawa et al. 1994 |

+ = positive result; (+) = weakly positive result

did not significantly affect pregnancy rate, but induced a significant dose-related increase in post-implantation loss, which was attributed to an effect on post-meiotic male germ cells.

Assessment of the activity of molybdenum chloride in the *Drosophila melanogaster* wing spot test showed that the compound induced spots with one or two mutant hairs (small spots) (Ogawa et al. 1994). Almost all of the spots detected were mutant clones expressing the *mwh* phenotype which, according to the investigators, suggested a nonlethal genetic change such as gene mutation or mitotic recombination occurring at a late developmental stage, or a semi-lethal change such as partial aneuploidy for a chromosomal region containing the *mwh* locus.

Table 3-4 summarizes studies of genotoxic effects of molybdenum compounds in *in vitro* systems. Results of gene mutation and DNA tests performed in prokaryotic organisms, almost all conducted without metabolic activation, were mixed, but negative results outnumbered positive results. It is worth noting the positive results reported for potassium molybdate and ammonium molybdate in the DNA repair assay (Nishioka 1975). The investigator speculated that because molybdenum has a valence of +6 in both compounds, molybdate is an oxidizing agent and the positive effect might reflect an oxidation capacity.

The few studies that tested molybdenum compounds in mammalian cells provided mixed results (Table 3-4). Different results were reported by NTP (1997) and Gibson et al. (1997) in experiments with molybdenum trioxide: negative in the former study for chromosomal aberrations, and positive in the latter for micronuclei formation. Aside from the differences in end point tested, it should be noted that NTP (1997) tested concentrations of molybdenum trioxide of up to 10 µg/mL, whereas Gibson et al. (1997) tested concentrations of molybdenum trioxide ranging from 250 to 750 µg/mL. Titenko-Holland et al. (1998) reported positive results for micronuclei formation in human peripheral lymphocytes incubated with sodium or ammonium molybdate. However, because blood was collected from only two donors, the results should be interpreted with caution.

In summary, the limited information regarding effects *in vivo* of molybdenum compounds is insufficient to infer possible outcomes of exposure in human populations. *In vitro* studies in prokaryotic organisms provided mixed results, but there is suggestive evidence that molybdenum valence +6, as in molybdate compounds ($MoO_4^{-2}$), could induce genotoxicity due to its oxidative capacity. Too few studies were available regarding effects of molybdenum compounds in mammalian cells *in vitro* to draw a meaningful

## Table 3-4. Genotoxicity of Molybdenum Compounds *In Vitro*

| Species (test system) | Compound | End point | Results | | Reference |
|---|---|---|---|---|---|
| | | | With activation | Without activation | |
| Prokaryotic organisms: | | | | | |
| *Salmonella typhimurium*, TA98, TA100, TA1535, TA1537, 1538 | Ammonium molybdate | Gene mutation | No data | – | Arlauskas et al. 1985 |
| *S. typhimurium*, TA97, TA98, TA100, TA 1535, TA1537 | Molybdenum trioxide | Gene mutation | – | – | NTP 1997; Zeiger et al. 1992 |
| *Saccharmyces cerevistiae* D3 | Sodium molybdate | Gene conversion and mutation | No data | – | Singh 1983 |
| *Escherichia coli*, WP2uvrA$^-$ | Ammonium molybdate | Reverse gene mutation | No data | – | Arlauskas et al. 1985 |
| *E. coli,* 2 WP2 strains | Ammonium molybdate | Reverse gene mutation | No data | + | Nishioka 1975 |
| *E. coli*, CM571 | Ammonium molybdate | Reverse gene mutation | No data | – | Nishioka 1975 |
| *E. coli* PQ37 | Molybdenum chloride | DNA damage | No data | – | Olivier and Marzin 1987 |
| *E. coli* WP2$_s$(λ) | Sodium molybdate | DNA damage | No data | (+) | Rossman et al. 1984 |
| *E. coli* WP2$_s$(λ) | Sodium molybdate | DNA damage | No data | (+) | Rossman et al. 1991 |
| *Bacillus subtilis,* H17 and M45 | Molybdic acid | DNA repair assay | No data | – | Kanematsu et al. 1980 |
| *B. subtilis* H17 and M45 | Molybdenum disulfide | DNA repair assay | No data | – | Kanematsu et al. 1980 |
| *B. subtilis* H17 and M45 | Molybdenum chloride | DNA repair assay | No data | – | Nishioka 1975 |
| *B. subtilis* H17 and M45 | Potassium molybdate | DNA repair assay | No data | + | Nishioka 1975 |
| *B. subtilis* H17 and M45 | Ammonium molybdate | DNA repair assay | No data | + | Nishioka 1975 |
| *Photobacterium fischeri* | Sodium molybdate | Direct mutation | No data | – | Ulitzur and Barak 1988 |
| Mammalian cells: | | | | | |
| Human peripheral lymphocytes | Sodium molybdate | Micronucleus assay | No data | (+) | Titenko-Holland et al. 1998 |
| Human peripheral lymphocytes | Ammonium molybdate | Micronucleus assay | No data | + | Titenko-Holland et al. 1998 |

## Table 3-4. Genotoxicity of Molybdenum Compounds *In Vitro*

| Species (test system) | Compound | End point | Results | | Reference |
|---|---|---|---|---|---|
| | | | With activation | Without activation | |
| Syrian hamster embryo (SHE) cells | Molybdenum trioxide | Micronucleus assay | No data | + | Gibson et al. 1997 |
| Chinese hamster ovary (CHO) cells | Molybdenum trioxide | Chromosomal aberrations | – | – | NTP 1997 |
| CHO cells | Molybdenum trioxide | Sister chromatid exchanges | – | – | NTP 1997 |

+ = positive result; (+) = weakly positive result; – = negative result; ± = equivocal result

conclusion, although two studies found positive results and a third study found weak positive results in the micronuclei assay.

## 3.4 TOXICOKINETICS

### 3.4.1 Absorption

#### 3.4.1.1 Inhalation Exposure

Inhaled molybdenum particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption into blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, liver, kidney). The above processes apply to all forms of deposited molybdenum, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size, solubility). Particles having diameters >5 μm are deposited primarily in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract (Bailey et al. 2007; ICRP 1994). Smaller particles (≤5 μm) are deposited primarily in the pulmonary region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by absorption, lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow.

Dissolved molybdenum is absorbed into blood. The rate of absorption will depend on solubility. ICRP (2012) assigns molybdenum sulfide, oxides, and hydroxides to a "slow" classification in their absorption, which equates to an expected terminal absorption half-time of approximately 19 years (Baily et al. 2007; ICRP 1994). More soluble forms of molybdenum, such as molybdenum trioxide ($Mo^{VI}O_3$), would be expected to undergo more rapid dissolution and absorption.

Quantitative estimates of absorption following inhalation exposure to molybdenum in humans or animals were not identified. Evidence for absorption of molybdenum trioxide is available from inhalation studies on molybdenum trioxide conducted in rodents (Fairhall et al. 1945; NTP 1997). Fairhall et al. (1945) showed distribution to several tissues following inhalation exposure of guinea pigs to molybdenum trioxide. In rats and mice exposed to inhaled molybdenum trioxide (6.7–67 mg molybdenum/$m^3$, 6 hours/day, 5 days/week for 2 years), exposure-dependent increases in blood molybdenum were observed (NTP 1997). The respectively blood molybdenum levels in the 0, 6.7, 20, and 67 mg

molybdenum/$m^3$ groups were 0.221, 0.800, 1.774, and 6.036 μg/g in male rats, 0.059, 0.355, 0.655, and 2.411 μg/g in female rats, 0.102, 0.208, and 0.770 μg/g in male mice (no data were available for controls), and 0.043, 0.066, 0.198, and 0.523 μg/g for female mice.

#### 3.4.1.2 Oral Exposure

Absorption of ingested molybdenum has been studied in human adults and infants (Cantone et al. 1993, 1997; Engle et al. 1967; Giussani et al. 1998, 2006, 2007; Novotny and Turnlund 2006, 2007; Robinson et al. 1993; Sievers et al. 2001a, 2001b; Turnlund et al. 1995a, 1995b; Werner et al. 1998; Yoshida et al. 2006). These studies fall into two general categories: mass balance studies and bioavailability studies. Mass balance studies estimate the absorption fraction from measurements of the difference between the ingested dose of molybdenum and fecal excretion (the difference being net absorption). Bioavailability studies estimate the absorption fraction from measurements of the plasma concentration of molybdenum following the oral dose. These methods provide estimates of net absorption in that absorbed molybdenum that is excreted into the gastrointestinal tract (e.g., biliary excretion) may not be accurately quantified from mass balance or bioavailability estimates. However, both approaches have been facilitated by the use of stable isotopes of molybdenum ($^{95}$Mo, $^{96}$Mo), which allow measurement of plasma and excretion kinetics following concurrent intravenous and oral dosing. The use of stable isotopes also allows measurement of the administered molybdenum in plasma and excreta, distinct from background sources of molybdenum derived from other sources and preexisting body stores. By incorporating elimination kinetics data into mathematical models that include parameters representing absorption and fecal excretion of absorbed molybdenum, the absorption fraction can be estimated. In most reported stable isotope studies, the exact form of molybdenum administered was not reported. However, typically, the isotope dosing material was prepared from an acid dissolution of metallic molybdenum ($Mo^{[0]}$). The resulting material dissolved in water most likely was a mixture of soluble molybdate anion ($Mo^{[VI]}O_4^{2-}$) and other soluble molybdenum oxide hydrates.

Balance and bioavailability studies conducted in humans have shown that the fraction of ingested molybdenum that is absorbed depends on numerous factors, including molybdenum dose level, fasting, diet, and nutritional status. Absorption was estimated to be 80–100% in replete fasted adults who ingested molybdenum dissolved in water or in a beverage (Giussani et al. 2006; Novotny and Turnlund 2006, 2007; Turnlund et al. 1995a). Absorption was 80–100% following a single dose of 20–40 μg Mo/kg dissolved in water and decreased with increasing dose level; absorption was 60% after a dose of 60 μg Mo/kg (Giussani et al. 2006). Absorption was lower when molybdenum was ingested with a meal

(40–60%), when dissolved in black tea (20%), or when incorporated into vegetables cultivated with $^{96}Mo$ (30–60%), compared to when ingested without a meal (80–100%) (Giussani et al. 2006; Werner et al. 1998). Absorption was lower when molybdenum was incorporated into the diet (83%) compared to when it was administered in a beverage (90–94%) (Novotny and Turnlund 2007). Absorption appears to be affected by dietary molybdenum intake and molybdenum nutritional status. The absorption fraction was 90% in adults fed a diet containing 22 µg/day (approximately 0.3 µg Mo/kg/day), compared to 94% when fed a diet containing 467 µg Mo/day (approximately 7 µg Mo/kg/day) (Novotny and Turnlund 2007). Absorption in infants (gestational age 30–39 weeks) was 96–99% when a stable isotope of molybdenum was mixed with breast milk or infant formula (Sievers et al. 2001a, 2001b).

Long-term diet mass balance studies, without the aid of stable isotopes, have been conducted in adults and children (Engel et al. 1967; Robinson et al. 1973; Tipton et al. 1966). Because these studies cannot distinguish between the ingested dose of molybdenum and molybdenum excreted from body stores, these studies will underestimate the absorption fraction. A 50-week balance study conducted in two adult males (age 23 and 25 years) found absorption to range from 60 to 80% (Tipton et al. 1966). A 3-week balance study conducted in women (age 19–21 years) found absorption to range from 40 to 70% (Robinson et al. 1973). An 8-day balance study conducted in women (age 18–23 years) found absorption to range from 72 to 84% (Yoshida et al. 2006). Balance studies (18–30 days) conducted in female children (age 6–10 years) estimated the absorption fraction from diet to range from 67 to 85% (Engel et al. 1967).

Measurements of the time course of plasma molybdenum following oral doses of molybdenum indicate that absorption is relatively rapid, with peak concentrations in plasma attained within 100 minutes of dosing (Giusanni et al. 2006; Novotny and Turnlund 2007).

Studies of absorption and elimination kinetics conducted in swine provide estimates of absorption of ingested molybdenum. Based on cumulative urinary and fecal excretion measurements in swine dosed with a stable isotope of molybdenum, absorption was estimated to be between 80 and 90% (Bell et al. 1964). Studies conducted in rats have shown that tetrathiomolybdate ($Mo^{VI}S_4^{2-}$) is more poorly absorbed when ingested in the diet; approximately 21% was absorbed when the copper content of the diet was 8 ppm (Mills et al. 1981b).

#### 3.4.1.3 Dermal Exposure

Studies evaluating the absorption of molybdenum following dermal exposure were not identified.

### 3.4.2 Distribution

#### 3.4.2.1 Inhalation Exposure

Very little information on the distribution on molybdenum following inhalation exposure is available. Following exposure of guinea pigs to inhaled molybdenum trioxide (150–300 mg/m$^3$, 1 hour/day, 5 days/week for 5 weeks), molybdenum was distributed to the lungs, liver, kidneys, and bone (Fairhall et al. 1945). Tissue levels decreased by approximately 20% in the 2-week postexposure period.

#### 3.4.2.2 Oral Exposure

Absorbed molybdenum distributes to various tissues. Human autopsy studies have found that the kidney and liver have the highest amounts of molybdenum (Iyengar et al. 1978; Schroeder et al. 1970; Sorensen and Archambault, 1963; Sumino et al. 1975; Tipton and Cook 1963; Tipton et al. 1965; Yoo et al. 2002; Zeisler et al. 1988). Based on a review of these data, Giussani (2008) estimated liver and kidney molybdenum concentrations to be approximately 0.5–1.5 µg Mo/g wet in liver (700–2,700 µg) and 0.2–0.4 µg Mo/g wet in kidney (55–120 µg). Coughtrey and Thorne (1983) reported relatively high concentrations (56 µg Mo/g) in bone, based on their recalculation of measurements of molybdenum in bone ash reported in Nusbaum et al. (1965) and Iyengar et al. (1978). However, these results are not supported by other studies (previously cited) and have been attributed to overestimation of tissue concentrations measured by arc emission spectrometry in the Nusbaum et al. (1965) and Iyengar et al. (1978) studies (Giussani 2008).

Results of studies in rats and guinea pigs exposed to oral molybdenum show that molybdenum is widely distributed (Bibr et al. 1977; Howell et al. 1993; Murray et al. 2014; Pandey et al. 2002). Generally, the highest molybdenum tissue concentration is observed in the kidney. Molybdenum also is distributed to liver, spleen, brain, lung, heart, bone, muscle, testis, epididymis, seminal vesicles, prostate, blood cells, and plasma. Studies conducted in rats have shown that molybdenum absorbed following ingestion of tetrathiomolybdate from the diet distributes to the kidneys and liver (Mills et al. 1981a).

***Maternal-Fetal Transfer.*** Results of studies in humans and animals show that molybdenum is distributed to the fetus. In humans, maternal and fetal cord blood levels obtained from 33 maternal-fetal pairs at parturition show similar molybdenum levels (maternal: 1.44±0.75 µg/L, mean±standard deviation [SD]; fetal: 1.44±0.89 µg/L) (Bougle et al. 1989). Molybdenum concentrations in venous cord blood (flowing from the placenta to the fetus; 0.7±0.2 µg/L, mean±SD) were slightly higher than in arterial cord blood (flowing from the fetus to the placenta; 0.6±0.2 µg/L), indicating fetal retention of molybdenum (Krachler et al. 1999).

Gestational exposure of rats to ammonium molybdate and thiomolybdate shows distribution of molybdenum to fetal liver, kidney, bone, and brain (Howell et al. 1993). Levels in liver, kidney, and bone were similar, with lower levels in brain. In rats, dose-dependent increases in placental and maternal liver content of molybdenum were observed following gestational exposure to molybdenum (sodium molybdate) in drinking water (5–100 mg Mo/L; equivalent to approximately 0.76–15 mg/kg/day, based on intermediate exposure to nonpregnant female rats) over the full dose range (Fungwe et al. 1989). However, neonatal whole-body levels of molybdenum reached a plateau at drinking water concentrations ≥50 mg/L (Fungwe et al. 1989). Results suggest that molybdenum levels in the fetus reach steady state more rapidly than in dams.

***Maternal-Infant Transfer.*** Several studies have measured molybdenum in breast milk (Anderson 1992; Aquilio et al. 1996; Biego et al. 1998; Bougle et al. 1988; Casey and Neville 1987; Dang et al. 1984; Friel et al. 1999; Krachler et al. 1998; Wappelhorst et al. 2002); the mean concentrations ranged from 0.02 to 24 µg/L. Breast milk concentrations are highest at the start of breast feeding and then decline (EFSA 2013). In the only study comparing maternal intake to breast milk levels, Wappelhorst et al. (2002) did not find a correlation between breast milk concentrations of molybdenum (mean concentration of 72 µg/L) and maternal molybdenum intake (mean intake of 132 µg/day).

#### 3.4.2.3 Dermal Exposure

Studies evaluating the distribution of molybdenum following dermal exposure were not identified.

### 3.4.3 Metabolism

Molybdenum exists in several valence states and may undergo oxidation and reduction. Although molybdenum can exist in biological systems in several different valence states (3+, 4+, 5+, and 6+), the primary form of molybdenum that interacts with enzyme systems is $Mo^{[VI]}$, as the molybdate anion

($Mo^{[VI]}O_2^{2-}$) (Nakanishi et al. 2013). After molybdate is taken into a cell, it is incorporated into a molybdopterin to form molybdenum cofactor (Moco). Moco is a sulfur-molybdate complex that forms the prosthetic group in molybdenum-dependent enzymes (Mendel and Kruse 2012; Schwarz et al. 2009). Given that Moco is extremely sensitive to oxidation, it is believed that it is bound to a Moco binding protein in the cell (Mendel and Kruse 2012). This stored Moco would be readily available to meet the cell's demand for molybdenum enzymes. Molybdate forms complexes with copper and binds to plasma proteins as a copper-molybdenum-sulfur (Cu-Mo-S) complex (Nederbragt 1980, 1982).

### 3.4.4 Elimination and Excretion

#### 3.4.4.1 Inhalation Exposure

Studies investigating the elimination and excretion of molybdenum following inhalation exposure were not identified.

#### 3.4.4.2 Oral Exposure

Absorbed molybdenum is excreted in urine and feces in humans. Urine is the dominant excretion route, accounting for approximately 75–90% of the absorbed dose (Giussani 2008; Novotny and Turnlund 2007). The fraction excreted in urine increases with increasing dietary intake (Novotny and Turnlund 2007). Urine also is the dominant excretory route for absorbed molybdenum in swine. Following an oral dose, approximately 90% of the dose was excreted in urine (Bell et al. 1964). To measure urinary and fecal excretion of molybdenum, Turnlund et al (1995a, 1995b) exposed four healthy adult males to various doses of a radioactive isotope of molybdenum (24–1,378 µg $^{100}$Mo/day) and administered intravenous doses of stable isotope of molybdenum (33 µg $^{97}$Mo). Six days after exposure to $^{100}$Mo in the diet, 17.8% of the $^{100}$Mo label was excreted in the urine at the lowest dose tested (total molybdenum dose of 24 µg/day). As the molybdenum dose increased, the amount excreted in the urine also increased; at the highest dose (1488 µg/day), 82.1% of the $^{100}$Mo was excreted in the urine. A similar pattern of urinary excretion was found when $^{97}$Mo was measured: 32.7% of the label at 24 µg/day and 86.7% at 1,488 µg/day. The percentage of the molybdenum dose excreted in the feces decreased with increasing doses. At the lowest dose tested, 9.4% of the $^{100}$Mo dose was excreted in the feces; at the highest dose, 7.5% of the $^{100}$Mo dose was excreted in the feces. In contrast, no consistent pattern of fecal $^{97}$Mo excretion was found. When total molybdenum excretion was measured, the study found that 41% was excreted in feces and 59% was excreted in urine at the lowest dose tested and 6% was excreted in feces and 94% was excreted in urine at the highest dose tested. Fecal excretion of absorbed molybdenum is

thought to result from biliary secretion. Studies conducted in rats have shown that, following an intravenous dose of $Mo^{[V]}$ or $Mo^{[VI]}$, approximately 1% of the molybdenum dose was secreted into bile in a period of 4 hours (Lener and Bibr 1979).

The rate of elimination of molybdenum from plasma has been studied in human clinical studies (Cantone et al. 1997; Rosoff and Spencer 1964; Thompson et al. 1996; Werner et al. 2000). Elimination is approximately biphasic, with mean half-times of 30 minutes and 6.6 hours (Giussani 2008).

The whole-body elimination rate in rats is dose-dependent (Bibr and Lener 1973). Following oral administration of $Mo^{[VI]}$ at doses <3 µg Mo/kg, elimination was mono-phasic with a half-time of approximately 47 hours. Following doses >3 µg Mo/kg, the rate of elimination increased, with an increasing proportion of elimination contributed by a fast phase having a half-time of 6 hours.

#### 3.4.4.3 Dermal Exposure

Studies evaluating the elimination and excretion of molybdenum following dermal exposure were not identified.

### 3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of

PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

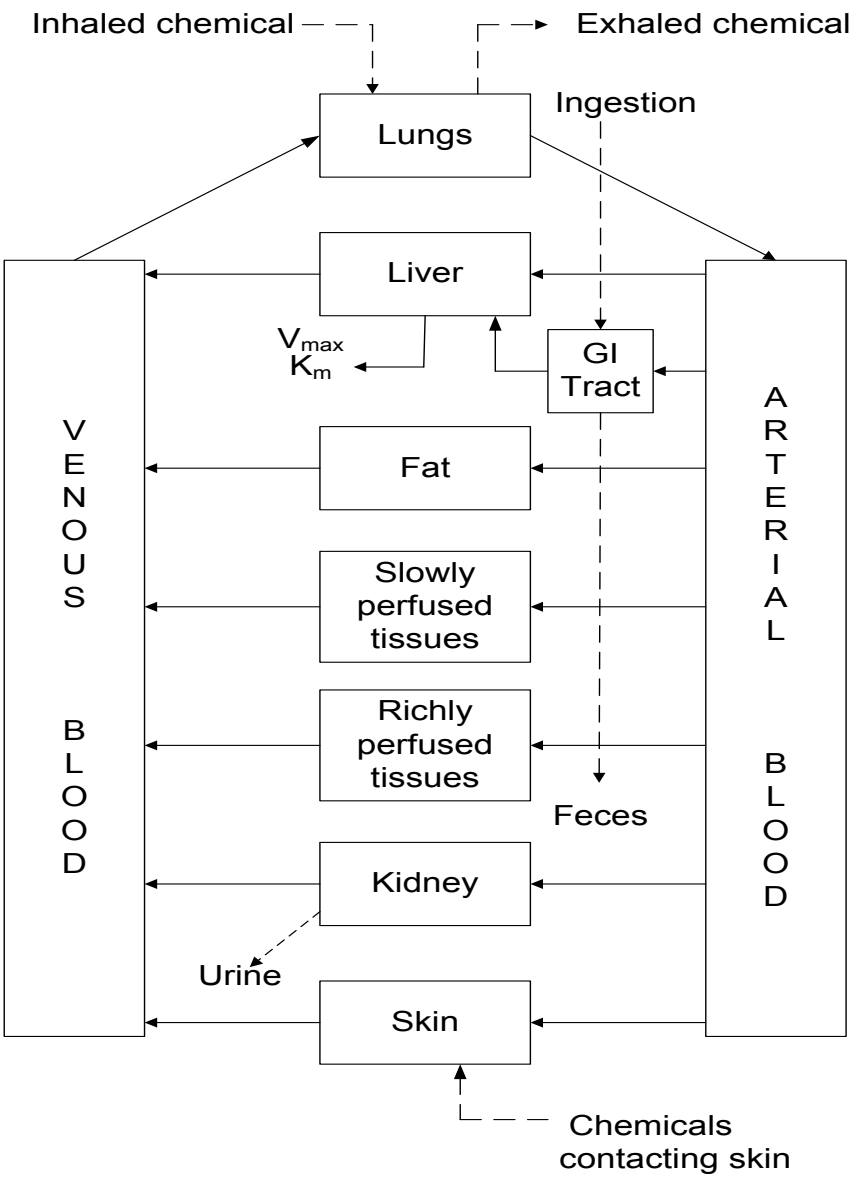
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for molybdenum exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Several multi-compartmental models of the kinetics of molybdenum in humans have been developed (Giussani 2008; Giussani et al. 1998, 2000; Novotny and Turnlund 2007; Thompson et al. 1996). The

**Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**




Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

latest of these are the Giussani (2008) and Novotny and Turnlund (2007) models. Both models yield similar predictions when applied to the same dosing scenarios (Giusanni 2008). The Giussani (2008) model has been adopted for use by the International Commission on Radiological Protection (ICRP) and is described in this section.

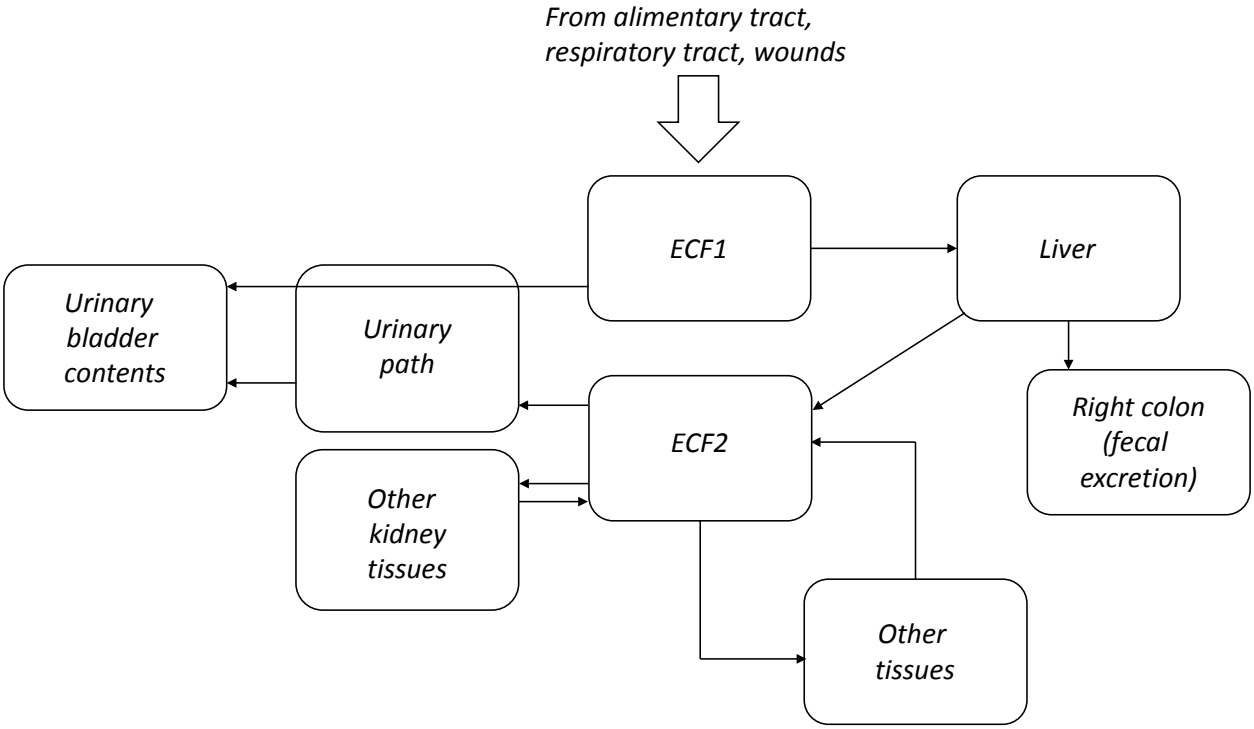
### Giussani (2008) Model.

Giussani (2008) developed a model of molybdenum kinetics in humans. The structure of the model is shown in Figure 3-4 and parameter values are presented in Table 3-5. Data used to derive and evaluate the model are described in Giusanni (2008) and included human clinical studies in which subjects were administered intravenous or oral doses of stable isotopes of molybdenum (Giusanni et al. 2006, 2007; Novotny and Turnlund 2006, 2007; Turnlund et al. 1995a; Werner et al. 1998, 2000). The Giussani (2008) model has been adopted for use by the ICRP and is described in this section.

The model consists of two central compartments representing extracellular fluids (ECF) and compartments representing liver, kidney (two subcompartments), and a lumped compartment representing all other tissues. All transfers of molybdenum between compartments are first order and governed by first-order rate coefficients ($day^{-1}$). The two ECF compartments represent fast and slow transfer pathways out of the ECF and were based on studies conducted in humans, which provide evidence for multi-phasic clearance of molybdenum from plasma (Giussani et al. 2007; Werner et al. 2000). The half-times for the two ECF compartments are approximately 30 minutes for ECF1 and 280 minutes for ECF2. Transfers from the fast compartment (ECF1) are to liver, kidney, and urine. Transfers from the slow compartment (ECF2) are to urine, kidney, and other tissues; the slow compartment also receives molybdenum from the liver. Retention half-times in tissues are 41 days for liver, 14.5 days for kidney, and 21.5 days for the other tissue compartment. Excretion of absorbed molybdenum occurs in urine (88%) and transfer from liver to the gastrointestinal tract (12%).

The model can simulate absorption from the gastrointestinal tract and respiratory tract. The absorption fraction for the gastrointestinal pathway uses an absorption fraction of 0.9 for molybdenum ingested in liquids and 0.6 for molybdenum ingested in the diet. The model predicts a steady state for constant dietary intake of molybdenum in adults, in which approximately 52% of the molybdenum body burden is in liver, 3% is in kidney, 45% is in other tissues, 53% of the daily dose is excreted in urine, and 47% of the daily dose is excreted in feces (Giussani 2008). The model is constructed to be able to interface with output from the ICRP Human Respiratory Tract Model (HRTM) (ICRP 1994; Baily et al. 2007). The

## Figure 3-4. The Proposed Systemic Model for Molybdenum Radionuclides




ECF = extracellular fluid

Source: Reprinted from Giussani (2008) with permission from Elsevier.

## Table 3-5. Transfer Rates ($Day^{-1}$) for the Molybdenum Model

| Transfer rate | Value ($day^{-1}$) |
|---|---|
| ECF1 to ECF2 | 12.5 |
| ECF1 to liver | 14.2 |
| ECF1 to urinary bladder contents | 6.5 |
| ECF2 to urinary path | 1.7 |
| ECF2 to other kidney tissues | 0.115 |
| ECF2 to other tissues | 1.73 |
| Liver to alimentary tract | 0.0048 |
| Liver to ECF2 | 0.0122 |
| Other kidney tissues to ECF2 | 0.0474 |
| Other tissues to ECF2 | 0.0323 |
| Urinary path to urinary bladder contents | 1.40 |
| Urinary bladder contents to urine | 12 |
| Modified parameters of the alimentary tract | |
| Stomach to small intestine (liquid form) | 100 |
| Stomach to small intestine (diet) | 40 |
| Small intestine to right colon (liquid form) | 10 |
| Small intestine to right colon (diet) | 16 |
| $f_A$ (liquid form)[a] | 0.9 |
| $f_A$ (diet)[a] | 0.6 |

[a]Dimensionless number.

ECF = extracellular fluid

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inputs to the Giussani (2008) model from the HRTM would be simulated transfers of molybdenum to the gastrointestinal tract (mucociliary transfer) and to blood (absorption from the respiratory tract), depending on the particle size and solubility of the inhaled molybdenum, and other physiological factors (e.g., age, activity).

### Novotny and Turnlund (2007) Model.

The major difference between the structures of the Giussani (2008) and Novotny and Turnlund (2007) models is that the Novotny and Turnlund (2007) model has a single lumped compartment representing all tissues outside of the vasculature. The Novotny and Turnlund (2007) model has two configurations: an intravenous configuration, which has two plasma compartments, representing fast and slower clearance, and an oral configuration, which has a single plasma compartment. Molybdenum exchanges between plasma and a lumped tissue compartment. Urinary excretion is represented as a direct transfer from plasma. Absorbed molybdenum is also transferred to the gastrointestinal tract.

Novotny and Turnlund (2006, 2007) conducted mass balance studies with subjects who ingested stable isotopes of molybdenum in the context of varying dietary intakes of molybdenum (22–1,490 μg Mo/day) and found that certain model parameters were dependent on dietary intake. These included, in association with increasing dietary intake, an increase in the first-order rate coefficients for gastrointestinal absorption, and urinary excretion, and a decrease in the rate coefficients for transfer from plasma to tissues. The largest adjustments were needed to simulate molybdenum kinetics in subjects who consumed >121 μg Mo/day and included a 70% decrease in the coefficient for transfer of molybdenum from plasma to tissues and a 660% increase in the rate coefficient for transfer from plasma to urine. These results suggest that high molybdenum intakes (>121 μg Mo/day) result in physiological adaptations that increase excretion of absorbed molybdenum (Novotny and Turnlund 2007).

## 3.5 MECHANISMS OF ACTION

### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** Mechanisms that participate in absorptive transport of molybdenum in the gastrointestinal tract have not been characterized. Molybdate ($MoO_4^{2-}$) and sulfate ($SO_4^{2-}$) show mutually competitive inhibition for absorptive transport in rat small intestine, suggesting involvement of a common transporter for both anions (Cardin and Mason 1975, 1976). This transporter may be the $Na^+/SO_4^{2-}$ symporter (NaS1 or SLC13A1) expressed in rodent small intestine and renal proximal tubule (Markovich

and Aronson 2007; Murer et al. 1994). In humans, NaS1 is expressed in kidney but not small intestine, suggesting that mechanisms of absorptive transport in humans may be different from that of rodents (Lee at al. 2000).

**Distribution.** Bacteria and eukaryotes express cell membrane molybdate transporters, one of which ($MoT_2$) also appears to be expressed in humans (Tejada-Jimenez et al. 2007, 2011). In eukaryotes, this transporter participates in the delivery of molybdate into cells for incorporation into molybdopterin-cofactor (Moco), the biologically active prosthetic group in molybdenum-dependent enzymes (Schwarz et al. 2009). $MoT_2$ transport of molybdate is inhibited by sulfate, suggesting a common carrier for molybdate and sulfate. A sulfate-insensitive oxalate-sensitive molybdate transporter has been described in mammalian MEK-293T cells grown in culture (Nakanishi et al. 2013). Uptake of molybdate into human red blood cells involves participation of the $Cl^{-1}/HCO_3^{-1}$ anion exchanger (Gimenez et al. 1993).

**Metabolism.** Molybdenum-dependent enzymes contain a molybdopterin cofactor (Moco), which is formed in a series of enzymatically catalyzed steps (Mendel and Bittner 2006). The final step, insertion of molybdate into Moco, may involve displacement of copper from of the molybdate binding site, which may provide a mechanism for copper-molybdenum interactions in regulating Moco synthesis and copper-induced deficiency in molybdenum-dependent enzymes (Mendel and Bittner 2006). Binding of molybdenum to plasma proteins involves formation of a Cu-Mo-S complex (Nederbragt 1980, 1982).

**Excretion.** Mechanisms that participate in the renal excretion of molybdenum have not been characterized. In sheep, reabsorption of filtered molybdate ($MoO_4^{2-}$) is saturable, which results in an increase in the fraction of filtered molybdate excreted as the plasma molybdate concentration increases and approaches or exceeds the tubular maximum (Ryan et al. 1987). In sheep and rat kidney, sodium-dependent reabsorptive transport of molybdate ($MoO_4^{2-}$) and sulfate ($SO_4^{-2}$) exhibit mutual inhibition (Ryan et al. 1987). This is consistent with participation of the $Na^+/SO_4^{2-}$ symporter (NaS1 or SLC13A1) in the reabsorption of molybdate. This symporter is also expressed in the human renal proximal tubule (Markovich and Aronson 2007; Murer et al. 1994).

### 3.5.2 Mechanisms of Toxicity

The mechanism of molybdenum toxicity has not been well-established. There are some indications that the mode of action may involve altered copper utilization; however, it is likely that other mechanisms, including direct molybdenum alterations, are involved. Support of the mode of action involving impaired

copper utilization comes from toxicology studies demonstrating more severe effects when animals are maintained on a copper-deficient diet; molybdenum induced alterations in copper levels in the plasma, liver, and kidneys; and apparent reversal of adverse effects following administration of high doses of copper. A number of the effects observed in animals orally exposed to molybdenum, particularly decreases in body weight and anemia (Arrington and Davis 1953; Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Johnson et al. 1969), are similar to those observed in copper-deficient animals. Administration of high levels of copper results in a fairly rapid improvement or prevents the effect from occurring (Arrington and Davis 1953; Lyubimov et al. 2004). In rats fed a copper-adequate diet, exposure to high levels of molybdenum in the diet resulted in significant increases in plasma copper levels (Nederbragt 1980, 1982), most of which were in a "tightly bound form" that did not appear to be associated with ceruloplasmin (major copper-carrying protein in the blood), as evidenced by the lack of an increase in ceruloplasmin levels (Nederbragt 1980). Significant increases in liver and kidney copper levels were also observed in rats exposed to molybdenum in the diet and maintained on a copper-adequate diet.

In ruminants, which appear to be very sensitive to molybdenum toxicity, it is believed that molybdenum reacts with sulfate generated in the rumen to form thiomolybdates; copper can bind to these thiomolybdates, which impairs its absorption. There is also some indication that cupric thiomolybdates can form in the blood if dietary copper levels are inadequate (Telfer et al. 2004). The copper in these cupric thiomolybdates is unavailable to ceruloplasmin and other copper-containing proteins, resulting in a functional copper deficiency (Vyskocil and Viau 1999). In monogastric animals exposed to sodium molybdate, administration of sulfate decreases the toxicity of molybdenum (Miller et al. 1956; Van Reen 1959). However, when rats were fed diets containing molybdate and sulfide, there was a substantial increase in plasma molybdenum and copper levels and liver molybdenum levels and a decrease in ceruloplasmin activity. In the plasma, there was a shift in the fraction of copper associated with albumin and ceruloplasmin (Mills et al. 1981a). Similar findings were observed in rats administered tetrathiomolybdates, but not in rats exposed to molybdates in the absence of sulfide (Mills et al. 1981a). In rats, exposure to tetrathiomolybdates resulted in effects similar to those observed in ruminants including signs of copper deficiency, including loss of pigmentation in hair and a similar distribution of copper between the plasma proteins (Mills et al. 1981b). However, these interactions between tetrathiomolybdate and copper only occurred when both were present in the gastrointestinal tract (Mills et al. 1981b). It is not known if the interactions between copper and molybdenum only occur at higher molybdenum doses. As discussed by Brewer et al. (2000), tetrathiomolybdate can form a tripartite complex with copper and protein, which can prevent copper absorption through the gastrointestinal tract.

When tetrathiomolybdate is not administered with food, it can complex with copper and serum albumin, which prevents cellular uptake of copper. Due to these mechanisms, tetrathiomolybdate is used to treat individuals with Wilson's disease, which is a metabolic defect that limits the excretion of copper. Other molybdenum compounds may also interfere with copper balance in humans. Significant increases in serum and urine copper levels were observed in men exposed 0.022 mg molybdenum/kg/day (the source of molybdenum was high molybdenum sorghum supplemented with ammonium molybdate) for 10 days, as compared to exposure to 0.00771 mg molybdenum/kg/day for 10 days (Deosthale and Gopalan 1974). However, there was no difference in fecal excretion of copper, suggesting that copper absorption was not affected. In contrast, another study (Turnlund and Keys 2000) did not find any significant alterations in serum copper levels in humans exposed to molybdenum levels of 22–1,490 μg/day (0.0003–0.02 mg/kg/day) for 24 days (subjects were fed diets containing naturally high or low levels of molybdenum).

Other investigators have suggested that the molybdenum-induced effects are due to oxidative damage (Zhai et al. 2013; Zhang et al. 2013). Zhai et al. (2013) showed that the levels of two enzymatic antioxidants (superoxide dismutase and glutathione peroxidase) paralleled the molybdenum-induced sperm effects. Increases in antioxidant levels and improvements in sperm parameters were observed at lower molybdenum doses. However, at higher molybdenum doses, there were significant decreases in antioxidant levels and significant decreases in sperm motility and concentration and an increase in the rate of sperm abnormalities. Zhang et al. (2013) reported a similar finding for superoxide dismutase and glutathione peroxidase levels and the rate of MII oocyte abnormalities.

### 3.5.3 Animal-to-Human Extrapolations

There are limited data to evaluate potential differences in the toxicity of molybdenum between laboratory animals and humans. Most of the available oral exposure studies were conducted in rats, and human data are mostly limited to a small number of cross-sectional studies. Within laboratory animal species, some differences have been observed between rats and rabbits, with rabbits appearing to be more sensitive than rats. However, the studies are not directly comparable due to differences in the copper content and other dietary constituents. In the absence of data to the contrary, it is assumed that the toxicity of molybdenum will be similar across species (excluding ruminants, see Section 3.5.2).

## 3.6 HAZARD IDENTIFICATION AND MINIMAL RISK LEVELS

### 3.6.1 Hazard Identification

Systematic review of the available human and animal studies that assessed potential health effects associated with inhalation and oral exposure to molybdenum identified a number of potential targets of toxicity. Hazard identification conclusions for molybdenum, resulting from this systematic review, are presented in Appendix B and are summarized as follows:

- Molybdenum is presumed to cause respiratory effects following inhalation exposure, based on an inadequate level of evidence from human studies and a high level of evidence from animal studies.
- Molybdenum is suspected to cause hepatic effects, based on an inadequate level of evidence from human studies and a moderate level of evidence from animal studies.
- Molybdenum is presumed to cause renal effects, based on a high level of evidence from animal studies; human data are lacking.
- Molybdenum is suspected to cause reproductive effects, based on a low level of evidence from human studies and a moderate level of evidence from animal studies.
- The data are not classifiable as to determine whether molybdenum results in developmental toxicity because some human and animal studies have reported developmental effects and other studies have not found effects.
- The data are not classifiable as to determine whether molybdenum results in alterations in uric acid levels based on a high level of evidence of no effect in animal studies and an inadequate level of evidence from human studies.

### 3.6.2 Minimal Risk Levels (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for molybdenum. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

#### 3.6.2.1 Inhalation MRLs

**Acute-Duration.** The database on the acute inhalation toxicity of molybdenum is limited to a study conducted by NTP (1997) that evaluated the effect of molybdenum trioxide on the nasal cavity and on body weight. No adverse effects were observed in the nasal cavity. However, weight loss was observed at the highest concentration tested (200 mg molybdenum/$m^3$); decreases in body weight gain were observed in male rats exposed to 67 mg molybdenum/$m^3$ and in female rats and mice exposed to 200 mg/$m^3$. Given the limited number of end points examined, the decrease in body weight gain was not considered a suitable basis for an acute-duration inhalation MRL because the database is inadequate for identifying the critical target of molybdenum toxicity following acute-duration inhalation exposure.

**Intermediate-Duration.** As with the acute-duration database, data on the intermediate-duration toxicity of molybdenum is limited to 90-day studies in rats and mice conducted by NTP (1997) that examined a wide range of potential targets, including reproductive end points. No toxicologically significant alterations were observed at concentrations of molybdenum trioxide as high as 67 mg/$m^3$. Consistent with ATSDR's practice of not using free-standing NOAELs as a point of departure (POD), an intermediate-duration inhalation MRL was not derived.

**Chronic-Duration.** There are limited data on the toxicity of inhaled molybdenum in humans. A study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides found no alterations in lung function, but did find increases in serum uric acid levels (Walravens et al. 1979); the TWA molybdenum concentration was 9.46 mg molybdenum/$m^3$. Another study of workers exposed to ultrafine molybdenum trioxide dust reported respiratory symptoms (dyspnea and cough), radiographic abnormalities, and impaired lung function (Ott et al. 2004); the study did not provide monitoring data. Confidence in these cohort studies was considered very low (see Appendix B for additional information).

NTP (1997) conducted a 2-year study in rats and mice that examined a wide range of potential targets of toxicity. Adverse effects were limited to the respiratory tract, specifically the nasal respiratory and olfactory epithelium, epiglottis, and lungs. The specific types of lesions and the incidence data are presented in Table 3-6.

Benchmark dose (BMD) modeling was used to fit the data for effects with statistically significant increases in incidences at the lowest concentration (squamous metaplasia of the epiglottis in male and female rats and mice, hyaline degeneration of the nasal respiratory and olfactory epithelium in female rats, histiocyte infiltration in the lungs in male mice, and alveolar epithelial metaplasia in male and female mice); the results of the modeling are presented in Appendix A. Benchmark models provided adequate fit for most of the datasets, predicting benchmark concentrations (BMCs) ranging from 0.46 to 5.73 mg molybdenum/$m^3$ and 95% lower confidence limits on the BMC (BMCL) ranging from 0.19 to 4.26 mg molybdenum/$m^3$. Human equivalent concentrations (HECs) were calculated by adjusting the BMCLs for intermittent exposure (6 hours/day, 5 days/week) and multiplying by the regional deposited dose ratio (RDDR) for the appropriate region of the respiratory tract. The lowest HEC was 0.012 mg molybdenum/$m^3$ for squamous metaplasia of the epiglottis in female mice. This HEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.0004 mg molybdenum/$m^3$.

#### 3.6.2.2 Oral MRLs

**Acute-Duration.** A small number of studies have evaluated the acute toxicity of molybdenum. One human study (Deosthale and Gopalan 1974) that looked at a limited number of potential end points did not find alterations in urinary uric acid levels in subjects exposed to doses as high as 0.022 mg molybdenum/kg/day for 10 days. In rabbits, exposure to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days resulted in a 60% increase in serum triglyceride levels (Bersenyi et al. 2008); no histological alterations were observed in the liver or kidneys. The toxicological significance of this finding is not known and has not been reported in a study of male rabbits exposed to 0.58 mg molybdenum/kg/day as ammonium heptamolybdate (Bersenyi et al. 2008) or rats exposed to 60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2013).

Reproductive effects have been observed in male and female mice and rabbits. In females, an increased rate of abnormal MII oocytes was observed at 11 mg molybdenum/kg/day in mice (Zhang et al. 2013); a second study did not find histological alterations in the ovaries of rabbits (Bersenyi et al. 2008). In males,

## Table 3-6. Incidence of Non-Neoplastic Respiratory Tract Lesions in Rats and Mice Exposed to Molybdenum Trioxide for 2 Years

| | Concentration (mg molybdenum/$m^3$) | | | |
|---|---|---|---|---|
| | 0 | 6.7 | 20 | 67 |
| Male rats | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 2/50 | 7/49 | 48/49[a] | 49/50[a] |
| Squamous metaplasia of epiglottis | 0/49 | 11/48[a] | 16/49[a] | 39/49[a] |
| Chronic lung inflammation in alveolus | 2/50 | 3/50 | 25/50[a] | 47/50[a] |
| Female rats | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 1/48 | 13/49[a] | 50/50[a] | 50/50[a] |
| Hyaline degeneration of nasal olfactory epithelium | 39/48 | 47/49[b] | 50/50[a] | 50/50[a] |
| Squamous metaplasia of epiglottis | 0/49 | 18/49[a] | 29/49[a] | 49/50[a] |
| Chronic lung inflammation | 14/50 | 13/50 | 43/50[a] | 49/50[a] |
| Male mice | | | | |
| Nasal suppurative inflammation | 2/50 | 6/50 | 10/49[b] | 8/50[b] |
| Nasal olfactory epithelium atrophy | 3/50 | 5/50 | 3/49 | 10/50[b] |
| Hyaline degeneration of nasal respiratory epithelium | 11/50 | 13/50 | 11/49 | 41/50[a] |
| Squamous metaplasia of epiglottis | 0/50 | 26/49[a] | 37/48[a] | 49/50[a] |
| Laryngeal hyperplasia | 1/50 | 3/49 | 6/48 | 41/50 |
| Histiocyte infiltration in the lungs | 2/50 | 16/50[a] | 9/49[b] | 9/50[b] |
| Alveolar epithelial metaplasia | 0/50 | 32/50[a] | 36/49[a] | 49/50[a] |
| Female mice | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 26/49 | 23/50 | 28/49 | 48/49[a] |
| Hyaline degeneration of nasal olfactory epithelium | 22/49 | 14/50 | 14/49 | 36/49[a] |
| Squamous metaplasia of epiglottis | 1/49 | 36/50[a] | 43/49[a] | 49/50[a] |
| Laryngeal hyperplasia | 1/49 | 1/50 | 7/49 | 35/50 |
| Alveolar epithelial metaplasia | 2/50 | 26/50[a] | 39/49[a] | 46/49[b] |

[a]Significantly different from controls; p≤0.01.
[b]Significantly different from controls; p≤0.05.

Source: NTP 1997

a significant decrease in sperm concentration and motility and an increase in sperm abnormalities were observed at 25 mg molybdenum/kg/day in mice (Zhai et al. 2013); a rabbit study reported a reduction in mature spermatocytes in rabbits exposed to 0.58 mg molybdenum/kg/day, but did not report the incidence or statistical significance (Bersenyi et al. 2008). Although the Bersenyi et al. (2008) study in male rabbits identified the lowest LOAEL for reproductive effects, it was not selected as the basis of the acute MRL because the incidence of the reduction in mature spermatocytes was not reported. Rather, the Zhang et al. (2013) was selected as the key study for the acute-duration oral MRL.

The data were not considered suitable for BMD modeling (see Appendix A); thus, a NOAEL/LOAEL approach was used to identify the POD for the MRL. The MRL of 0.05 mg molybdenum/kg/day was calculated by dividing the NOAEL of 5.3 mg molybdenum/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). It should be noted that the MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

**Intermediate-Duration.** Studies in laboratory animals have evaluated the intermediate-duration toxicity of molybdenum. A number of adverse effects have been reported including kidney damage (Bompart et al. 1990; Murray et al. 2013), decreases in body weight gain (Bompart et al. 1990; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956), hematological effects (Arrington and Davis 1953; Lyubimov et al. 2004), neurological effects (Arrington and Davis 1953), reproductive effects (Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2013; Pandey and Singh 2002), and developmental effects (Pandey and Singh 2002). The lowest LOAEL values identified are 1.5 mg molybdenum/kg/day for prolonged estrus phase without an effect on fertility in rats exposed to sodium molybdate in drinking water for 8 weeks (Fungwe et al. 1990) and 4.4 mg molybdenum/kg/day for anemia, decreases in body weight gain, and decreases in sperm motility and count in rats administered via gavage ammonium tetrathiomolybdate for 22–35 days (females) or 59–61 days (males) (Lyubimov et al. 2004). The observed renal effects included slight diffuse hyperplasia in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet (Murray et al. 2013) and increases in diuresis and creatinuria and decreases in creatinine clearance in rats administered 80 mg molybdenum/kg/day as ammonium heptamolybdate (Bompart et al. 1990); the NOAELs identified in these studies are 17 and 40 mg molybdenum/kg/day, respectively. Two studies have reported hematological effects—decreases in erythrocyte count, hemoglobin concentrations, and hematocrit levels in rats exposed to 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate (Lyubimov et al. 2004) and in rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate (Arrington and Davis 1953);

however, other studies have not found hematological effects in rats exposed to 60 or 70 mg molybdenum/kg/day as sodium molybdate (Gray and Daniel 1954; Murray et al. 2013). Neurological effects consisting of weakness of the front legs progressing to an "inability to maintain weight and legs spread outward" was observed in young rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate (Arrington and Davis 1953); no neurological effects were observed at 25 mg molybdenum/kg/day or in mature rabbits exposed to doses as high as 120 mg molybdenum/kg/day (Arrington and Davis 1953). Although several studies have reported reproductive effects, particularly alterations in sperm parameters, there is considerable overlap between the identified NOAELs and LOAELs that are summarized in Table 3-2. Some of the overlap may be explained by the copper content of the diet. In the Jeter and Davis (1954) and Murray et al. (2013) studies, the copper content of the diet exceeded the recommended intake for rats (5 ppm) (NAS 1995) by a factor of 4 or 2.8, respectively. Four studies examined the developmental toxicity of molybdenum following intermediate-duration exposure. No alterations in resorptions, post-implantation losses, or fetal body weights were observed in three studies with doses as high as 37.5 mg molybdenum/kg/day (Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014). A fourth study reported increases in post-implantation losses, increased resorption, and decreases in fetal growth in a study in which males only were administered 14 mg molybdenum/kg (5 days/week) for 60 days (Pandey and Singh 2002).

Reproductive toxicity in males and females consistently has the lowest LOAEL values. Reproductive effects have also been observed following acute-duration exposure, and the systematic review of the available human and animal data (Appendix B) showed that reproductive toxicity is "suspected to be a health effect following oral exposure." The Fungwe et al. (1990) study identified the lowest LOAEL of 1.5 mg molybdenum/kg/day; the NOAEL was 0.76 mg molybdenum/kg/day.

BMD modeling of the estrous cycle length data from the Fungwe et al. (1990) study was conducted to identify the POD for the MRL using a benchmark response (BMR) of 1 SD change from the control. The continuous variable models did not adequately fit the data and a NOAEL/LOAEL approach was used to identify the POD for the MRL. An MRL of 0.008 mg/kg/day was derived by dividing the NOAEL of 0.76 mg molybdenum/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet. The MRL is approximately 10-fold higher than the recommended dietary allowance of 0.0006 mg/kg/day (estimated using a reference body weight of 70 kg) (NAS 2001).

**Chronic-Duration.** Data on the chronic toxicity of molybdenum come from several population-based studies; most of these studies looked for associations between background exposure to molybdenum and adverse health outcomes. No laboratory animal studies were identified. Koval'skiy et al. (1961) found increases in blood uric acid and symptoms of gout in residents living in Armenia with high levels of molybdenum in the soil and food; the investigators estimated that the residents were exposed to 10–15 mg/day (0.14–0.21 mg/kg/day). A series of small studies of residents living in areas of Colorado with high levels of molybdenum in the drinking water did not find significant increases in uric acid levels; one study estimated that molybdenum intake was 500 µg/day (0.007 mg/kg/day) (EPA 1979). Other studies have found significant associations between serum or urinary molybdenum levels and the severity of complications from diabetes (Rodriguez Flores et al. 2011), high blood pressure (Yorita Christensen 2013), semen quality (Meeker et al. 2008), testosterone levels (Meeker et al. 2010), and psychomotor index in infants (molybdenum levels were measured in the mothers) (Vazques-Salas et al. 2014). However, none of these studies established causality, and the molybdenum levels accounted for only a small percentage of the variance. No chronic-duration animal toxicity studies were identified.

Although the Koval'sky et al. (1961) study provided an estimated dose, the study was not considered suitable for derivation of a chronic-duration oral MRL for molybdenum. The study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels.

## 3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in

1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to molybdenum. No *in vitro* studies were located regarding endocrine disruption of molybdenum.

## 3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to

toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are limited data on the toxicity of molybdenum in children. In studies in rat pups maintained on a caries-promoting diet, administration of 50 mg molybdenum/kg/day as sodium molybdate resulted in an increase in buccal enamel lesions (Hunt and Navia 1975), but exposure to 8 mg molybdenum/kg/day did not result in increases in dental caries (Van Reen et al. 1962). Arrington and Davis (1953) exposed young (6 weeks of age at the start of the study) and mature rabbits to sodium molybdate in the diet for 30–84 days. Marked muscular/skeletal effects were observed in the young rabbits, but were not observed in the mature rabbits. Since the investigators did not provide information on dietary intake, it is difficult to make direct comparisons across the studies.

An observational study did not find an association between maternal urinary molybdenum levels and newborn body weight or infant mental development (Shirai et al. 2010). But another study did find an association between third-trimester maternal urinary molybdenum levels and infant psychomotor

development indices (Vazquez-Salas et al. 2014). Two rat studies in which the copper content of the diet was adequate did not find significant alterations in fetal growth, survival, or malformations at maternal doses of 4.4 or 38 mg molybdenum/kg/day (Lyubimov et al. 2004; Murray et al. 2014). However, a third study reported decreases in growth and number of live fetuses in the offspring of male rats administered 14 mg molybdenum/kg as sodium molybdate 5 days/week for 60 days prior to mating with unexposed females (Pandey and Singh 2002).

## 3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of a generalizable sample of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for molybdenum from this report is discussed in Section 6.5. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to molybdenum are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial

cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by molybdenum are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11, Populations That Are Unusually Susceptible.

### 3.9.1 Biomarkers Used to Identify or Quantify Exposure to Molybdenum

Molybdenum levels can readily be measured in tissues, body fluids, and excreta. Dose-related increases in serum molybdenum levels were observed in rats and mice exposed via inhalation to molybdenum trioxide for 2 years (NTP 1997). In a study examining the relationship between plasma molybdenum levels and dietary intake, Turnland and Keyes (2004) reported a baseline plasma molybdenum level of 8.2±.5 nmol/L; 25 days after the subjects were maintained on a low molybdenum diet (22 μg/day), the plasma molybdenum level was 5.1±0.5 nmol/L. Although a significant correlation between plasma molybdenum and dietary molybdenum was observed, comparison between plasma molybdenum levels at different dietary intakes showed that a significant increase in plasma molybdenum was not observed until the dietary intake exceeded 460 μg/day (6.6 mg/kg/day) and that tripling the intake resulted in a doubling of the plasma molybdenum levels. Urinary molybdenum levels were also significantly correlated to dietary intakes (Turnland and Keyes 2004) and appeared to be more responsive to changes in dietary intake. At all dietary concentrations, the urinary molybdenum levels were slightly lower than the dietary intakes (Turnland and Keyes 2004). The investigators concluded that plasma molybdenum levels were an indicator of dietary intake, but urinary levels were more directly related to molybdenum intake.

Molybdenum levels were measured in urine samples collected during National Health and Nutrition Surveys. The geometric mean urinary molybdenum levels in the United States in 2011–2012 was 37.1 μg/L and the creatinine-corrected value was 42.0 μg/g creatinine (CDC 2015); see Section 6.5 for additional information.

Although several studies have reported molybdenum levels in hair samples (DiPietro et al. 1989; Nagra et al. 1992; Paschal et al. 1989), no relationship between molybdenum exposure and hair levels has been established. Furthermore, Miekeley et al. (1998) demonstrated large interlaboratory differences in the molybdenum levels measured in hair.

### 3.9.2 Biomarkers Used to Characterize Effects Caused by Molybdenum

No biomarkers to characterize effects caused by molybdenum have been identified.

## 3.10 INTERACTIONS WITH OTHER CHEMICALS

The interaction between copper and molybdenum has been well-established in animals. The levels of copper in the diet have been shown to influence the toxicity of molybdenum. Marked toxicity has been reported in studies in which the copper content of the diet was inadequate. Observed effects included mortality (Valli et al. 1969; Widjajakuma et al. 1973), marked decreases in body weight gain and weight loss (Brinkman and Miller 1961; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959), and anemia (Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Johnson et al. 1969; Valli et al. 1969). In general, these effects (or the severity of the effects) have not been observed when the diet contains an adequate level of copper (Mills et al. 1958; Murray et al. 2013; Pandey and Singh 2002; Peredo et al. 2013). Exposure to high levels of copper has been shown to reduce the toxicity of molybdenum. Administration of high doses of copper to moribund rabbits resulted in a return to normal body weight gain and increases in hemoglobin levels within 2–3 weeks (Arrington and Davis 1953). Lyubimov et al. (2004) showed that administration of a high dose of copper prevented the molybdenum-induced testicular toxicity observed in rats fed a copper-adequate diet. Similarly, in an environmental exposure study, Meeker et al. (2008) found a greater decline in sperm concentration in men with high molybdenum blood levels and copper blood levels below the median, as compared to when the men were not stratified by blood copper levels.

Kinetic studies have demonstrated differences in plasma, liver, and kidney copper and molybdenum concentrations in rats fed copper-deficient, copper-adequate, and copper-excessive diets (Nederbragt 1980). Excess copper in the diet resulted in a smaller increase in copper concentrations in plasma, liver, and kidneys and molybdenum concentrations in the liver and kidney, as compared to levels in rats fed a copper-adequate diet. Similarly, lower rises in liver copper and molybdenum and kidney molybdenum levels were observed in rats fed a copper-deficient and high-molybdenum diet, as compared to the copper-adequate diet. At the lowest molybdenum dose, kidney molybdenum levels were higher in the copper-

deficient groups. In another study (Nederbragt 1982), kidney levels of copper and molybdenum were 5 and 3 times higher, respectively, in the copper-adequate groups as compared to the copper-deficient group. Two human studies have also evaluated the effect of molybdenum on copper levels. In one study, increases in serum and urine copper levels were found following a 10-day exposure to 0.022 mg molybdenum/kg/day (Deosthale and Gopalan 1974). Another study found no significant alterations in serum copper levels in humans exposed to 0.0003–0.02 mg molybdenum/kg/day for 24 days (Turnlund and Keys 2000).

## 3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to molybdenum than will most persons exposed to the same level of molybdenum in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of molybdenum, or compromised function of organs affected by molybdenum. Populations who are at greater risk due to their unusually high exposure to molybdenum are discussed in Section 6.7, Populations with Potentially High Exposures.

The available data demonstrate the interaction between copper and molybdenum; more severe effects are observed in animals maintained on a copper-deficient diet (Brinkman and Miller 1961; Franke and Moxon 1961; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959; Widjajakuma et al. 1973). Administration of additional copper results in a reversal of the adverse effect (Arrington and Davis 1953). The findings in the animal studies are supported by a report by Koval'skiy et al. (1961) that gout-like symptoms and increased uric acid levels were observed in a population with high molybdenum levels in the soil and low copper intakes, but were not observed in an area with high molybdenum levels and adequate copper intakes. Thus, individuals with low copper intakes may be unusually susceptible to the toxicity of molybdenum.

Studies in rats suggest that the toxicity of molybdenum may be increased in animals maintained on a low protein diet. The magnitudes of the decrease in body weight gain (Bandyopadhyay et al. 1981; Cox et al. 1960) and decreases in femur breaking strength (Fejery et al. 1983) were greater in rats exposed to a low protein diet, as compared to those maintained on a diet with sufficient protein.

Since molybdenum is primarily excreted in the urine, individuals with kidney disease may also be more susceptible to molybdenum toxicity; however, this has not been investigated in humans or animals.

## 3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to molybdenum. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to molybdenum. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to molybdenum can be consulted for medical advice.

No texts were located that provided specific information about treatment following exposures to molybdenum.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

### 3.12.1 Reducing Peak Absorption Following Exposure

There are no established methods for managing initial exposure to molybdenum or for reducing peak absorption.

### 3.12.2 Reducing Body Burden

Molybdenum is readily eliminated from the body, and there is evidence that ingestion of high molybdenum doses results in physiological adaptations that increase urinary excretion (Novotny and Turnlund 2007).

### 3.12.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of molybdenum toxicity has not been well established. Studies in laboratory animals suggest that co-administration of a high copper diet can reduce the toxicity of molybdenum, but this has not been tested in humans, and exposure to high levels of copper may be toxic.

## 3.13 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of molybdenum is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of molybdenum.

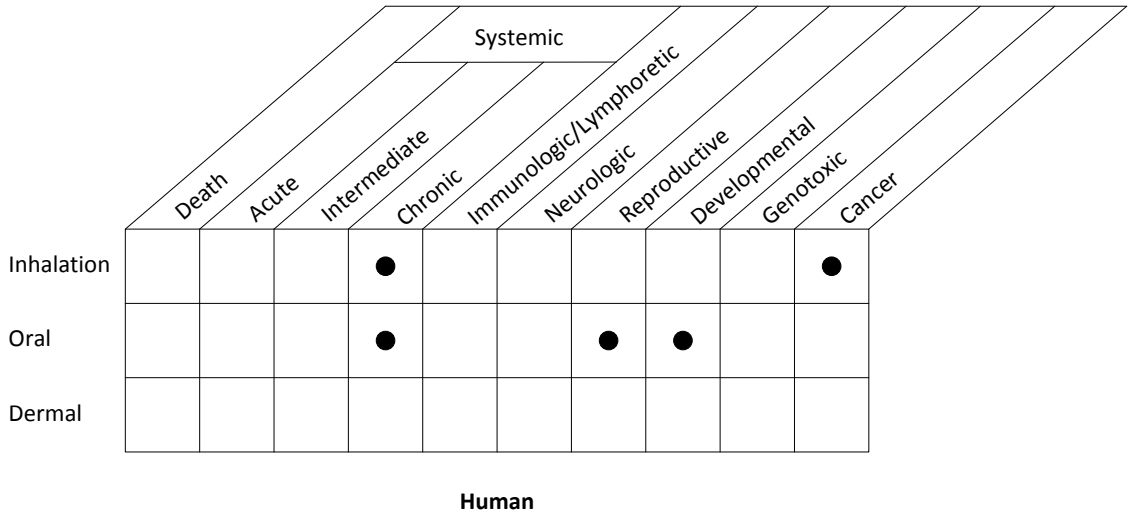
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 3.13.1 Existing Information on Health Effects of Molybdenum

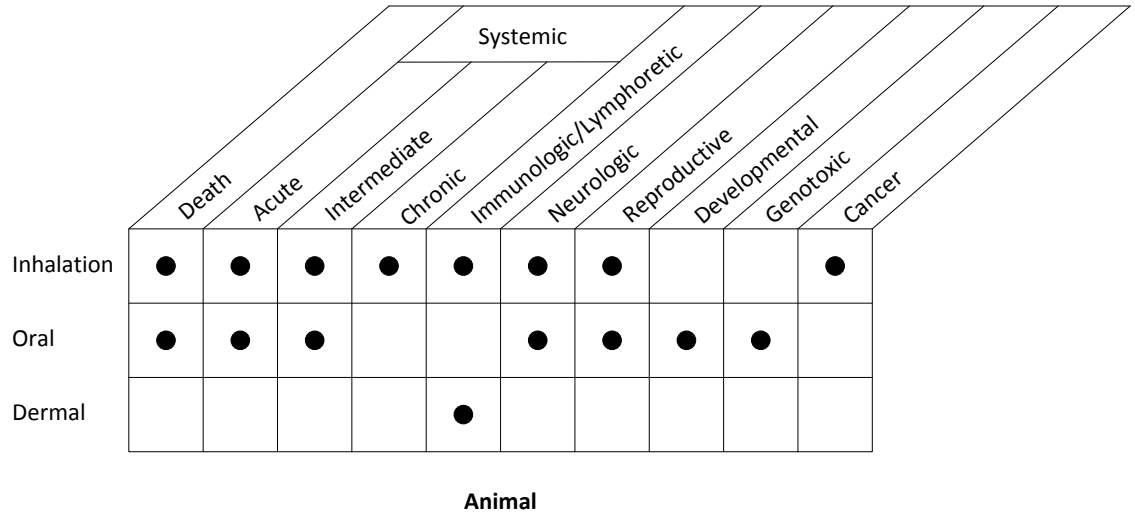
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to molybdenum are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of molybdenum. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature. A more detailed summary of the number of studies examining specific end points is presented in Tables B-3 and B-4 in Appendix B.

Data on the toxicity of inhaled molybdenum are limited to two occupational exposure studies in which the exposure is poorly characterized. A number of cross-sectional studies have examined the associations between a biomarker of molybdenum exposure (blood or urine levels) and a specific health effect. These studies are not sufficient to establish causality. Additionally, one study examined a community living in an area with high levels of molybdenum in the soil and locally grown foodstuffs. Human data on the

## Figure 3-5. Existing Information on Health Effects of Molybdenum




**Human**




**Animal**

● Existing Studies

dermal toxicity of molybdenum are limited to two patch testing studies of individuals undergoing knee or hip replacement.

Acute-duration studies examining a limited number of end points and comprehensive intermediate- and chronic-duration studies in rats and mice have investigated the inhalation toxicity of molybdenum. The chronic studies provided evidence that the respiratory tract is a primary target of toxicity and suggestive evidence of carcinogenicity; the intermediate-duration study did not identify adverse health effects. A number of studies in laboratory animals have examined the oral toxicity of molybdenum following acute- or intermediate-duration exposures. Studies in which the basal diet contained adequate levels of copper identified several targets of toxicity including the kidney, liver, and reproductive system; there was some indication that molybdenum exposure may also result in alterations in uric acid levels and developmental toxicity, but the data were not considered adequate for conclusive hazard identification. Data on the dermal toxicity of molybdenum are limited to a guinea pig sensitization assay.

### 3.13.2 Identification of Data Needs

**Acute-Duration Exposure.** No data were located regarding health effects after acute inhalation exposure to molybdenum in humans. In laboratory animals, the inhalation exposure data are limited to studies conducted in rats and mice (NTP 1997); however, the studies only examined the nasal cavity and body weight. Although increased mortality and decreases in body weight gain were observed, the studies are not adequate for identifying the primary target of toxicity. Thus, they were not considered adequate for derivation of an acute-duration inhalation MRL. Additional studies examining a wide-range of end points would be useful for characterizing the hazard of molybdenum following acute inhalation exposure.

In an acute experiment, no alterations in uric acid levels were observed in volunteers (Deosthale and Gopalan 1974); the study did not examine other potential end points. A small number of studies have examined the acute oral toxicity in laboratory animals, and none of them examined a wide-range of end points. One study found an increase in serum triglyceride levels in rabbits, but did not find any histological alterations in the liver or kidneys (Bersenyi et al. 2008). Three studies examining reproductive end points suggest that this is a sensitive target of acute molybdenum toxicity (Bersenyi et al. 2008; Zhai et al. 2013; Zhang et al. 2013). These studies identified LOAELs for effects on oocytes and sperm and were used to derive an acute-duration oral MRL for molybdenum.

Data on the dermal toxicity of molybdenum are limited to a contact sensitization study in guinea pigs, which found positive effects (Boman et al. 1979). The acute dermal toxicity database is considered inadequate for identifying sensitive targets of toxicity; additional studies examining a wide range of potential end points are needed.

**Intermediate-Duration Exposure.** The available data on the toxicity of molybdenum following intermediate-duration inhalation exposure are limited to 90-day studies examining a wide range of potential targets of toxicity in rats and mice (NTP 1997). No adverse effects were observed in these studies, and the studies were not considered suitable for derivation of an intermediate-duration inhalation MRL for molybdenum. Additional studies testing higher concentrations may identify sensitive targets.

A number of studies have examined the intermediate-duration toxicity of ingested molybdenum. Among studies in which the laboratory animals were provided a diet with adequate levels of copper, a number of targets of toxicity were identified including the liver, kidney, reproductive system, and possibly the developing organism (Bompart et al. 1990; Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2013; Pandey and Singh 2002). Based on a comparison of LOAEL values, the reproductive system appeared to be the most sensitive target of toxicity. An intermediate-duration oral MRL was derived based on alterations in oocyte morphology (Fungwe et al. 1990).

No studies have examined the dermal toxicity of molybdenum following intermediate-duration exposure; studies are needed to identify potential targets of toxicity for humans.

**Chronic-Duration Exposure and Cancer.** Two occupational exposure studies have reported mixed results on the effect of molybdenum on the respiratory tract (Ott et al. 2004; Walravens et al. 1979). There is insufficient information on the specific molybdenum compounds involved and limited data on exposure levels. Chronic exposure studies in rats and mice have identified the respiratory tract as a sensitive target of molybdenum toxicity (NTP 1997), and an inhalation MRL was derived based on the findings in the animal studies.

A number of studies have evaluated the chronic toxicity of ingested molybdenum in humans. A study of residents living in an area of Armenia with high molybdenum and low copper levels in the soil found increases in uric acid levels and gout-like symptoms (Koval'skiy et al. 1961); other studies in which residents were exposed to high levels of molybdenum in the water did not find alterations in uric acid (EPA 1979). Other studies that examined the potential of molybdenum to induce adverse health effects

presumably involved background environmental exposure (Meeker et al. 2008, 2010; Mendy et al. 2012; Schroeder and Kraemer 1974; Shiue and Hristova 2014; Vazquez-Salas et al. 2014; Yorita Christensen 2013). Although some of these studies reported statistically significant associations between biomarkers of molybdenum exposure (plasma or urine levels) and adverse effects, the studies do not establish causality and there may have been factors other than molybdenum exposure. No laboratory animal studies evaluated the chronic oral toxicity of molybdenum. Additional studies examining a wide range of potential end points are needed to identify the hazards associated with chronic ingestion of high levels of molybdenum and establish dose-response relationships.

One study evaluated the carcinogenicity of molybdenum in humans (Droste et al. 1999) and found a higher risk of lung cancer among workers in jobs related to molybdenum exposure; however, there was potential exposure to a number of other carcinogens. In the NTP (1997) rat and mouse studies, equivocal evidence for lung cancer was observed in male rats and some evidence of carcinogenicity was observed in male and female mice. No studies have examined the carcinogenicity of molybdenum following oral or dermal exposure. Chronic studies by these routes of exposure are needed to evaluate carcinogenicity.

**Genotoxicity.** There are limited data on the *in vivo* genotoxicity of molybdenum; a mouse study found weakly positive effects for micronuclei formation and dominant lethality (Titenko-Holland et al. 1998). Additional *in vivo* studies, as well as monitoring workers for genotoxicity, would be useful for assessing the genotoxic potential in humans. *In vitro* studies were negative for micronuclei formation (Gibson et al. 1997; Titenko-Holland et al. 1998) and positive for chromosomal aberrations and sister chromatid exchange (NTP 1997), but both were only tested in one study. Mixed results were found in tests of DNA repair, which may be reflective of the molybdenum compound tested (Kanematsu et al. 1980; Nishioka 1975); additional studies are needed to clarify these conflicting results.

**Reproductive Toxicity.** A study of men at an infertility clinic found associations between blood molybdenum levels and altered sperm parameters and reproductive hormone levels (Meeker et al. 2008, 2010). These studies do not establish causality; however, oral exposure studies in laboratory animals support the reproductive system as a target of molybdenum toxicity (Bersenyi et al. 2008; Fungwe et al. 1990; Lyubimov et al. 2004; Pandey and Singh 2002; Zhai et al. 2013; Zhang et al. 2013). Although reproductive effects are the basis of the acute- and intermediate-duration oral MRLs for molybdenum, there is considerable inconsistency across studies, and some studies testing higher doses have not found effects (Jeter and Davis 1954; Murray et al. 2013). Additional studies designed to assess potential

differences in routes of oral exposure and with different molybdenum compounds could help explain the conflicting results.

**Developmental Toxicity.** Two studies examined whether there was a relationship between molybdenum exposure and developmental effects in humans (Shirai et al. 2010; Vazquez-Salas et al. 2014) and found mixed results. Two studies in rats failed to find a relationship between oral exposure to molybdenum and birth outcomes (Lyubimov et al. 2004; Murray et al. 2014). A third study found decreases in fetal growth in a male-only exposure study (Pandey and Singh 2002).

**Immunotoxicity.** The immunotoxicity of molybdenum has not been adequately addressed. No inhalation or oral exposure studies addressed immune function; intermediate- and chronic-duration inhalation studies did not find histological alterations in the thymus or spleen (NTP 1997). Very low levels of positive results of patch tests were observed in patients undergoing hip or knee replacements (Koster et al. 2000; Menezes et al. 2004; Zeng et al. 2014). In animals, contact sensitization was observed in guinea pigs in a sensitization assay with molybdenum pentachloride (Boman et al. 1979). Studies examining immune function would be useful in evaluating whether this is a target of molybdenum toxicity.

**Neurotoxicity.** There are limited data on the neurotoxicity of molybdenum. No histological alterations in the brain or overt signs of toxicity were observed in laboratory animals after intermediate-duration inhalation (NTP 1997) or oral (Murray et al. 2013) exposure or chronic-duration inhalation exposure (NTP 1997). Additional studies, particularly in young animals, should be conducted to assess whether molybdenum affects the neuromuscular system, in the absence of copper deficiency.

**Epidemiological and Human Dosimetry Studies.** A small number of epidemiology studies were identified for molybdenum; however, most of these studies presumably involve background environmental exposure to molybdenum. Two occupational exposure studies found conflicting results regarding the respiratory toxicity of molybdenum (Walravens et al. 197; Ott et al. 2004). Additional studies of worker populations examining a wide range of potential end points, including the respiratory tract, would provide valuable information on the toxicity of inhaled molybdenum. General population studies have identified a number of potential targets of toxicity of ingested molybdenum including blood pressure (Shiue and Hrisova 2014), liver (Mendy et al. 2012), the reproductive system (Meeker et al. 2008, 2010), and the developing organism (Shirai et al. 2010); however, none of the studies established causality. Studies of populations exposed to high levels of molybdenum in drinking water or from foods

grown in molybdenum-rich soil would provide support for establishing sensitive targets of molybdenum toxicity. One study of a community living in an area with high molybdenum in the soil reported gout-like symptoms and increased uric acid levels (Koval'skiy et al. 1961); however, low intakes of copper may have contributed to these effects. Additional studies to confirm the results of this study would be valuable.

### Biomarkers of Exposure and Effect.

***Exposure.*** Molybdenum levels can be measured in blood, tissues, and excreta, and background urinary levels of molybdenum have been established in healthy individuals (CDC 2015). Blood and urinary levels have been shown to increase in response to increased molybdenum ingestion (Turnland and Keyes 2004), although plasma molybdenum levels are likely to be reflective of recent dietary intake. Studies that quantified the relationship between blood and/or urinary levels and intake would provide valuable information on screening and comparison with adverse effect levels.

***Effect.*** No biomarkers of effect were identified. The available data have identified the following sensitive targets: respiratory tract (inhalation only), kidney, and reproductive system. Studies examining the possible relationship between blood or urinary levels of molybdenum with these adverse health effects could facilitate medical surveillance leading to early detection and possible treatment.

**Absorption, Distribution, Metabolism, and Excretion.** For humans, detailed quantitative information is available regarding the absorption, distribution, and excretion of ingested molybdate ($Mo^{[VI]}O_4^{2-}$) and molybdenum incorporated into food. Although molybdate is most likely the dominant chemical species of molybdenum in the body, there are no data for humans on toxicokinetics following exposures to other forms of molybdenum that could occur in the environment, such as tetrathiomolybdate ($Mo^{VI}S_4^{2-}$) or $Mo^{IV}$ compounds. Studies conducted in rats have shown that molybdenum is absorbed following exposure to tetrathiomolybdate (Mills et al. 1981a). No quantitative information is available on the toxicokinetics of molybdenum in humans following chronic oral exposure, and there is no information on inhalation or dermal exposures. A study conducted in mice showed that molybdenum is absorbed following inhalation exposure to molybdenum trioxide (NTP 1997).

Studies conducted in humans have provided data for development of PBPK models of molybdenum kinetics in humans (Giussani 2008; Novotny and Turnlund 2007). Models have not been developed for rodents or other animal species that could be used in dosimetry extrapolation of animal bioassay results.

**Comparative Toxicokinetics.** The available data on the toxicity of molybdenum in humans and laboratory animals suggest that they have similar targets of toxicity; however, there are limited epidemiology data. The available data suggest similarities in the absorption, distribution, and elimination of ingested molybdenum in humans and rats. Additional studies are needed to compare the toxicokinetics of inhaled molybdenum and to assess whether there are species differences.

**Methods for Reducing Toxic Effects.** No information was identified on methods for reducing toxic effects of molybdenum. Although animal studies provide evidence that a high copper diet may decrease molybdenum toxicity, it is unclear whether this would be effective in humans.

**Children's Susceptibility.** Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the toxicity of molybdenum in children; studies are needed to evaluate whether the susceptibility of children differs from adults.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

### 3.13.3 Ongoing Studies

No ongoing studies on the toxicity of molybdenum or its toxicokinetic properties were identified in the National Institute of Health (NIH) RePORTER (2015) database. The International Molybdenum Association is currently sponsoring a 2-generation reproductive toxicity study in rats orally exposed to sodium molybdate.

# 4. CHEMICAL AND PHYSICAL INFORMATION

## 4.1 CHEMICAL IDENTITY

Molybdenum is a naturally occurring trace element that can be found extensively in natural minerals, but not as the free metal. Biologically, it plays an important role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (EPA 1979).

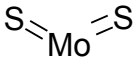
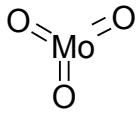
Molybdenum (Mo) metal exists as a dark-gray or black powder with a metallic luster or as a silvery-white mass (HSDB 2010). It is a member of the group VIb series of the periodic table and can exist in five different oxidation states (2–6), with the most common and stable species being Mo(IV) and Mo(VI) (Barceloux 1999). It does not occur naturally in the pure metallic form, but principally as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Important naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite. Molybdenum anions include molybdate, a tetrahedral poly atomic anion, or other isopolyanions, which can form salts used in industrial applications (EPA 1979). While molybdenum may occur as naturally as molybdenum sulfide, this compound can also be produced synthetically.

Under physiological conditions (pH>6.5), molybdate anion, $[MoO_4]^{2-}$ is the sole molybdenum species in aqueous media (Cruywagen 2000; Cruywagen et al. 2002). Molybdenum compounds (e.g., molybdenum trioxide and polymolybdates) transform rapidly to the $[MoO_4]^{2-}$ ion under environmental relevant test conditions (Deltombe et al. 1974; Greenwood and Earnshaw 1997).

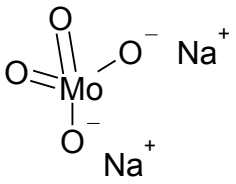
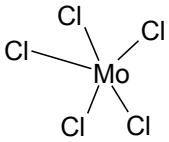
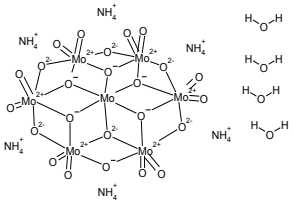
Molybdenum in nature consists of seven stable isotopes (masses 92, 94–98, and 100). Radioisotopes of masses 83–91, 93, 99, and 101–115 have been reported. The only one of major worldwide importance is Mo-99 ($^{99}Mo$), a 100% beta-emitting isotope with a 65.976-hour radioactive half-life that is used to produce technetium-99m (Tc-$99^m$ or $^{99m}Tc$) for medical scans (Doll et al. 2014; Parma 2009; Richards 1989).

Information regarding the chemical identity of molybdenum and molybdenum compounds is provided in Table 4-1.

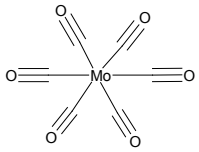
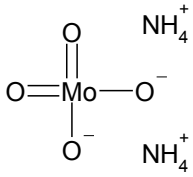
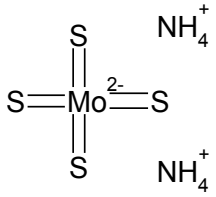
## Table 4-1. Chemical Identity of Molybdenum and Compounds[a]

| Characteristic | Information | | |
|---|---|---|---|
| Chemical name | Molybdenum | Molybdenum disulfide | Molybdenum trioxide |
| Synonym(s) | Molybdenum metallicum; MChVL; TsM1 | Molybdenite (natural mineral); molybdenum(IV) sulfide | Molybdenum(VI) oxide; molybdic acid anhydride; molybdic anhydride; molybdic oxide; molybdena |
| Registered trade name(s) | Amperit 105.054; Amperit 106.2; Metco 63 | DAG 325; Molykote | No data |
| Chemical formula | Mo | $MoS_2$ | $MoO_3$ |
| Chemical structure | Mo |  |  |
| Identification numbers: | | | |
| CAS Registry | 7439-98-7 | 1309-56-4 / 1317-33-5 (natural mineral form); 12612-50-9 (synthetic form) | 1313-27-5 |
| NIOSH RTECS | QA4680000[b] | QA4697000[b] | No data |
| EPA Hazardous Waste | No data | No data | No data |
| OHM/TADS | No data | No data | No data |
| DOT/UN/NA/IMDG | UN 3089; UN 4.1[c] | No data | UN 3288[c] |
| HSDB | 5032 | 1660 | 1661 |
| NCI | No data | No data | No data |

## Table 4-1. Chemical Identity of Molybdenum and Compounds[a]

| Characteristic | Information | | |
|---|---|---|---|
| Chemical name | Sodium molybdate | Molybdenum pentachloride | Ammonium heptamolybdate tetrahydrate |
| Synonym(s) | Disodium molybdate; molybdic acid, disodium salt | Molybdenum(V) chloride; pentachloromolybdenum | Ammonium paramolybdate tetrahydrate |
| Registered trade name(s) | No data | No data | No data |
| Chemical formula | $Na_2MoO_4$ | $MoCl_5$ | $(NH_4)_6Mo7O_{24}{\cdot}4H_2O$ |
| Chemical structure |  |  |  |
| Identification numbers: | | | |
| CAS registry | 7631-95-0 | 10241-05-1 | 12027-67-7/12054-85-2 |
| NIOSH RTECS | QA5075000[d] | QA4690000[e] | QA5076000[f] |
| EPA hazardous waste | No data | No data | No data |
| OHM/TADS | No data | No data | No data |
| DOT/UN/NA/IMDG shipping | No data | UN 2508[g] | No data |
| HSDB | 7540 | No data | 7540/1802 |
| NCI | No data | No data | No data |

## Table 4-1. Chemical Identity of Molybdenum and Compounds[a]

| Characteristic | Information | | |
|---|---|---|---|
| Chemical name | Molybdenum hexacarbonyl | Diammonium molybdate | Ammonium tetrathiomolybdate |
| Synonym(s) | Hexacarbonyl-molybdenum; molybdenum(0) hexacarbonyl | Ammonium molybdate; molybdic acid, diammonium salt[g] | Tiomolibdate diammonium; ammonium molybdenum sulfide; thiomolybdic acid, diammonium salt[g] |
| Registered trade name(s) | No data | No data | Coprexa; TM; ATTM[g] |
| Chemical formula | $Mo(CO)_6$ | $(NH_4)_2MoO_4$ | $(NH_4)_2MoS_4$ |
| Chemical structure |  |  |  |
| Identification numbers: | | | |
| CAS registry | 13939-06-5 | 13106-76-8 | 15060-55-6 |
| NIOSH RTECS | No data | QA4900000[h] | QA4668250[i] |
| EPA hazardous waste | No data | No data | No data |
| OHM/TADS | No data | No data | No data |
| DOT/UN/NA/IMDG shipping | No data | No data | No data |
| HSDB | 7540 | 7540 | 7540 |
| NCI | No data | No data | No data |

[a]All information obtained from HSDB (2009a, 2009b, 2009c, 2010) unless otherwise noted.
[b]Sigma-Aldrich 2015e
[c]NOAA 2015
[d]NIOSH 2015c
[e]Sigma-Aldrich 2015a
[f]Sigma-Aldrich 2015b
[g]ChemIDplus 2015
[h]Sigma-Aldrich 2015d
[i]RTECS 2013

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

## 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Metallic molybdenum, in the form of dust or powder, is a combustible/flammable solid and is potentially explosive (HSDB 2010).

Information regarding the physical and chemical properties of molybdenum and molybdenum compounds is provided in Table 4-2.

## Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

| Property | Information | | |
|---|---|---|---|
| Chemical name | Molybdenum | Molybdenite (natural mineral)/molybdenum disulfide | Molybdenum trioxide |
| Molecular weight | 95.94 | 160.07 | 143.95 |
| Color | Dark-gray or black | Black | White or slightly yellow or slightly blue |
| Physical state | Cubic powder | Crystalline solid | Crystalline solid |
| Melting point | 2,622°C | Not applicable | 795°C |
| Boiling point | 4,639°C | 450°C (sublimes) | 1,155°C (sublimes) |
| Density | 10.2 g/cm$^3$ | 5.06 (15°C/15°C) | 4.69 (26°C/4°C) |
| Odor | No data | Odorless | Odorless |
| Odor threshold: | | | |
| Water | No data | No data | No data |
| Air | No data | No data | No data |
| Solubility: | | | |
| Water at 25°C | Insoluble | Insoluble | 490 mg/L (28°C)[b] |
| Organic solvents | Soluble in nitric acid, concentrated sulfuric acid; slightly soluble in hydrochloric acid; insoluble in hydrofluoric acid, dilute sulfuric acid | No data | Insoluble[b] |
| Inorganic solvents | No data | Soluble in hot sulfuric acid, aqua regia, nitric acid | Soluble in aqueous alkali and ammonia; 140 mg/L in nitric acid (4 mol/L, 20°C)[b] |
| Partition coefficients: | | | |
| Log $K_{ow}$ | No data | No data | No data |
| Log $K_{oc}$ | No data | No data | No data |
| Vapor pressure: | | | |
| at 20°C | No data | No data | No data |
| at 2,469°C | 7.5x10$^{-3}$ mm Hg | No data | No data |
| at 2,721°C | 7.5x10$^{-2}$ mm Hg | No data | No data |
| at 3,039°C | 0.75 mm Hg | No data | No data |
| at 3,434°C | 7.5 mm Hg | No data | No data |
| at 3,939°C | 75 mm Hg | No data | No data |
| at 4,606°C | 750 mm Hg | No data | No data |
| Henry's law constant at 25°C | No data | No data | No data |
| Autoignition temperature | No data | No data | No data |
| Flashpoint | No data | No data | No data |
| Flammability limits | Flammable (dust or powder) | No data | Not flammable[c] |
| Explosive limits | No data | No data | No data |
| Conversion factors | No data | No data | No data |

## Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

| Property | Information | | |
|---|---|---|---|
| Chemical name | Sodium molybdate | Molybdenum pentachloride | Ammonium heptamolybdate tetrahydrate |
| Molecular weight | 205.92 | 273.21 | 1,235.8 |
| Color | White[b] | Dark green-black | Colorless or slightly greenish or yellowish[d] |
| Physical state | Crystalline solid[e] | Crystalline solid | Crystalline solid[d] |
| Melting point | 687°C[e] | 194°C | 90°C (loses $H_2O$) |
| Boiling point | Not applicable | No data | 190°C (decomposes) |
| Density | 3.78 g/cm$^3$[f] | 2.928 g/cm$^3$[g] | 2.86 (20°C)[d] |
| Odor | Odorless[e] | Odorless[c] | Odorless[e] |
| Odor threshold: | | | |
| Water | No data | No data | No data |
| Air | No data | No data | No data |
| Solubility: | | | |
| Water | 40 wt% (anhydrous salt in 100 g saturated solution, 25°C)[b] | Hydrolyzes | 206.5 g/L (20°C, tetrahydrate)[d] |
| Organic solvents | Soluble in ethanol; very soluble in carbon disulfide[b] | Soluble in carbon tetrachloride, benzene | Soluble in organic solvents[b] |
| Inorganic solvents | No data | No data | Soluble in aqueous alkali and ammonia; 140 mg/L in $HNO_3$ (4 mol/L, 20°C)[b] |
| Partition coefficients: | | | |
| Log $K_{ow}$ | No data | No data | No data |
| Log $K_{oc}$ | No data | No data | 0–2.614 |
| Vapor pressure at 20°C | No data | 1.75 mm Hg[g] | No data |
| Henry's law constant at 25°C | No data | No data | No data |
| Autoignition temperature | No data | No data | No data |
| Flashpoint | No data | No data | No data |
| Flammability limits | No data | No data | No data |
| Explosive limits | No data | No data | No data |
| Conversion factors | No data | No data | No data |

## Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

| Property | Information | | |
|---|---|---|---|
| Chemical name | Molybdenum hexacarbonyl | Diammonium molybdate | Ammonium tetrathiomolybdate |
| Molecular weight | 264.002 | 196.01[b] | 260.28[b] |
| Color | White[b] | Colorless, white, or slightly greenish-yellowish[h] | Deep red[b] |
| Physical state | Crystalline solid | Crystalline solid[b] | Crystalline solid[b] |
| Melting point | 150°C | No data | >300°C[i] |
| Boiling point | 156.4°C (sublimes)[b] | No data | No data |
| Density | 4.692 g/cm$^3$ (21°C)[b] | 1.4[h] | No data |
| Odor | No data | Odorless[h] | No data |
| Odor threshold: | | | |
| Water | No data | No data | No data |
| Air | No data | No data | No data |
| Solubility: | | | |
| Water | Insoluble[j] | 39 wt% (in 100 g saturated solution, 25°C)[b] | Insoluble (hygroscopic)[k] |
| Organic solvents | Soluble in most organic solvents[j] | No data | No data |
| Inorganic solvents | No data | No data | No data |
| Partition coefficients: | | | |
| Log $K_{ow}$ | No data | No data | No data |
| Log $K_{oc}$ | No data | No data | No data |
| Vapor pressure at 25°C | 9.8 mm Hg (20°C) | No data | No data |
| Henry's law constant at 25°C | No data | No data | No data |
| Autoignition temperature | No data | No data | No data |
| Flashpoint | No data | Not flammable[h] | No data |
| Flammability limits | No data | Not flammable[h] | No data |
| Explosive limits | No data | No data | No data |
| Conversion factors | No data | No data | No data |

[a]All information obtained from HSDB (2009a, 2009b, 2009c, 2010) unless otherwise noted.
[b]Sebenik et al. 2012
[c]NOAA 2015
[d]BIAC 2013
[e]ECHA 2015
[f]NIOSH 2015c
[g]Sigma-Aldrich 2015a
[h]NJDOH 2009
[i]Sigma-Aldrich 2015c
[j]Patnaik 1999
[k]Alfa Aesar 2015

# 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

## 5.1 PRODUCTION

Molybdenum is a naturally occurring trace element that can be found extensively in nature. Biologically, it plays an important role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (USGS 2015a).

Molybdenum does not occur naturally in the pure metallic form, but is in minerals principally as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Important naturally occurring molybdenum compounds are the minerals molybdenite ($MoS_2$, the predominant source), powellite, wulfenite, ferrimolybdate, and ilsemannite. Molybdenum may also form molybdate, a tetrahedral poly atomic anion, or other isopolyanions, which can form salts used in industrial applications. The earth's crust contains an average of 0.0001% (1 ppm) of molybdenum. Deposits that are economically feasible for mining contain ≥200 ppm of molybdenum, with lower concentrations obtained as a byproduct of copper mining (EPA 1979).

Molybdenite ($MoS_2$) is the principal mineral from which molybdenum is obtained. Mining and milling of crude ore produces molybdenite concentrate containing ≥90% of $MoS_2$, almost all of which is converted to technical-grade molybdenum trioxide. Molybdenum trioxide is the base material for the production of a variety of chemical compounds, ferromolybdenum, and purified molybdenum (EPA 1979).

Roasting molybdenite concentrate in a multiple hearth furnace at temperatures up to 600°C produces technical-grade molybdenum trioxide. This can be further purified by sublimation or selective recrystallization at about 1,000–1,100°C (EPA 1979).

Worldwide mine production of molybdenum was estimated to be 258,000 mt in 2013, with approximately 92% produced, in descending order, by China, the United States, Chile, Peru, Mexico, and Canada. The United States accounted for 24% of world production with 60,700 mt in 2013, down slightly from 61,500 mt in 2012. Primary molybdenum operations accounted for 53% of total U.S. molybdenum production, while byproduct production made up 47% of the total in 2013. All U.S. molybdenum concentrates and products are from the mining of ore (USGS 2015a). U.S. production of molybdenum increased roughly 8% in 2014 to 65,500 mt (USGS 2015b).

Molybdenum is a chemical that manufacturing and processing facilities would be required to report under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986 [SARA]) (EPA 1998a). Table 5-1 contains a list the number of facilities per state that produced, processed, or used molybdenum trioxide in 2013, as well as information on the amount of molybdenum on site and related activities and uses (TRI13 2015). Manufacturers are required to report Toxics Release Inventory (TRI) data to satisfy EPA requirements. The TRI data should be used with caution since only certain types of facilities are required to report (EPA 2005b). This is not an exhaustive list.

Molybdenum-99 ($^{99}$Mo) is a radioactive form of molybdenum and the only molybdenum radioisotope of commercial importance. It is produced in nuclear reactors; then processed, packaged, and shipped to medical facilities throughout the world, where the $^{99}$Tc progeny into which it transforms is eluted and injected into patients for imaging purposes (e.g., cardiac stress tests).

$^{99}$Mo has been being produced in one of eight nuclear reactors (mainly at the Chalk River complex in Canada) using highly enriched uranium, then commercialized at five processing facilities and six generator manufacturing facilities. The availability of those reactors was reduced by the closure of the Chalk River facility, and this has impacted the supply stream. The United States has established a high national priority on assuring an adequate supply of $^{99}$Mo and urged manufacturers to switch from using highly enriched uranium (HEU) to low enriched uranium (LEU) to reduce the use of HEU for civilian applications (Ballinger 2010; The White House 2012; USNRC 2015; Van Noorden 2013).

Currently, $^{99}$Mo can be produced by placing HEU or LEU targets in an operating nuclear reactor and allowing the neutron flux to produce $^{99}$Mo and its radioactive precursors. The quantity of $^{99}$Mo peaks after approximately 6 days, at which time, the target is removed, processed, and prepared for shipment. New facilities for producing $^{99}$Mo from LEU in the United States are being planned (Welsh et al. 2015).

## 5.2 IMPORT/EXPORT

Molybdenum-containing exports rose from 49,900 mt in 2010 to 55,300 mt in 2014, while imports for consumption rose from 19,700 mt in 2010 to 23,600 mt in 2014 (USGS 2015b). These data along with U.S. production volumes from 2010 to 2014 are summarized in Table 5-2.

## Table 5-1. Facilities that Produced, Processed, or Used Molybdenum Trioxide in 2013

| State[a] | Number of facilities | Minimum amount on site in pounds[b] | Maximum amount on site in pounds[b] | Activities and uses[c] |
|---|---|---|---|---|
| AL | 3 | 100 | 99,999 | 1, 4, 7, 10 |
| AR | 1 | 100,000 | 999,999 | 7 |
| AZ | 4 | 100,000 | 9,999,999 | 1, 4, 7, 9 |
| CA | 14 | 100 | 999,999 | 1, 2, 3, 4, 7, 10, 11, 12 |
| CO | 1 | 10,000 | 99,999 | 1, 6, 12, 13 |
| CT | 1 | 100,000 | 999,999 | 6 |
| DE | 1 | 100,000 | 999,999 | 12 |
| FL | 1 | 1,000 | 9,999 | 1, 5, 13 |
| HI | 1 | 100,000 | 999,999 | 2, 3, 6, 10 |
| IA | 2 | 1,000,000 | 9,999,999 | 1, 3, 4, 7 |
| IL | 9 | 10,000 | 999,999 | 1, 5, 6, 7, 10, 11, 12 |
| IN | 3 | 10,000 | 999,999 | 1, 5, 7, 10 |
| KS | 4 | 0 | 999,999 | 2, 3, 8, 10 |
| KY | 4 | 1,000 | 999,999 | 1, 2, 3, 4, 6, 7, 10 |
| LA | 19 | 10,000 | 9,999,999 | 1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12 |
| MD | 1 | 10,000 | 99,999 | 1, 4, 6, 7 |
| ME | 1 | 10,000 | 99,999 | 1, 2, 5, 6 |
| MI | 3 | 0 | 999,999 | 1, 5, 6, 7, 8, 10, 13 |
| MN | 3 | 10,000 | 9,999,999 | 1, 3, 6, 7, 9, 10, 11, 13 |
| MS | 3 | 10,000 | 999,999 | 1, 5, 7, 10 |
| MT | 2 | 1,000 | 99,999 | 1, 2, 3, 5, 6, 10, 12, 13 |
| ND | 3 | 1,000 | 99,999 | 1, 9, 10, 12, 13, 14 |
| NJ | 2 | 100,000 | 999,999 | 10 |
| NM | 2 | 10,000 | 99,999 | 10 |
| NV | 1 | 10,000 | 99,999 | 2, 3, 12 |
| OH | 11 | 1,000 | 999,999 | 1, 5, 6, 7, 8, 9, 11, 13 |
| OK | 5 | 10,000 | 999,999 | 1, 4, 5, 10, 11, 14 |
| OR | 3 | 1,000 | 99,999 | 7, 8 |
| PA | 16 | 100 | 49,999,999 | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 13 |
| TN | 2 | 10,000 | 999,999 | 6, 7, 9, 10 |
| TX | 42 | 0 | 99,999,999 | 1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14 |
| UT | 4 | 100 | 999,999 | 10, 11, 12 |
| WA | 3 | 1,000 | 999,999 | 7, 11, 12 |
| WI | 2 | 1,000 | 99,999 | 1, 5, 7, 11, 14 |

## Table 5-1. Facilities that Produced, Processed, or Used Molybdenum Trioxide in 2013

| State[a] | Number of facilities | Minimum amount on site in pounds[b] | Maximum amount on site in pounds[b] | Activities and uses[c] |
|---|---|---|---|---|
| WV | 1 | 1,000,000 | 9,999,999 | 2, 3, 7 |
| WY | 2 | 100 | 999,999 | 1, 10, 13 |

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI13 2015 (Data are from 2013)

## Table 5-2. Molybdenum U.S. Production, Import, and Export Data from 2010 to 2014 in Metric Tons

| | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|
| Total U.S. production | 59,400 | 63,700 | 61,500 | 60,700 | 65,500 |
| U.S. imports for consumption | 19,700 | 21,100 | 19,800 | 20,200 | 23,600 |
| U.S. exports for consumption | 49,900 | 56,700 | 48,900 | 53,100 | 55,300 |

Source: USGS 2015b

## 5.3 USE

Molybdenum is used primarily in metallurgical applications, including as an alloying agent in cast iron, steel, and superalloys to enhance properties such as hardenability, strength, toughness, and wear- and corrosion-resistance. Principally in the form of molybdenum trioxide or ferromolybdenum, molybdenum is commonly used in combination with other alloy metals like chromium, manganese, nickel, niobium, and tungsten. The leading form of molybdenum used by industry, particularly in stainless steel production, is molybdenum trioxide (USGS 2015a).

Molybdenum is used significantly as a refractory metal and in a variety of non-metallurgical chemical applications, such as catalysts, lubricants, and pigments. Most molybdenum catalysts are nitrogen deficient due to thermodynamically unfavorable conditions at atmospheric pressure; however, molybdenum nitride was recently produced in a high temperature and pressure environment by solid state ion exchange. Testing found its catalytic activity to be 3 times that of $MoS_2$ and its selectivity to hydrogenation to be 3 times that of $MoS_2$ for hydrosulfurizing dibenzothiophene (Wang et al. 2015). As green technology is becoming more popular, molybdenum has become increasingly important in areas like biofuels, catalysts, ethanol, solar panels, and wind power (USGS 2015a).

A radioactive isotope of molybdenum, $^{99}Mo$, is used as a source to produce the metastable radioisotope technetium-99m ($^{99m}Tc$), which is used in the vast majority of medical imaging tests performed today (Doll et al. 2014; Parma 2009; Richards 1989). It was estimated that 85% of all medical radioisotope procedures use $^{99m}Tc$ and that about 50,000 $^{99m}Tc$-based diagnostic procedures are performed in the United States each day, resulting in about 13 million procedures annually (Parma 2009).

Molybdenum concentrate produced by domestic mines is roasted, exported for conversion, or purified to lubricant-grade molybdenum disulfide. Purified $MoS_2$ is used directly as a solid or in coatings that are bonded onto the metal surface by burnishing, vapor deposition, or bonding processes that use binders, solvents, and mechanochemical procedures (Stiefel 2011).

Metallurgical applications accounted for about 87% of total molybdenum use in 2013. The principle non-metallurgical use was in catalysts, primarily catalysts used in petroleum refining. Molybdenum compounds are also used to produce pigments (USGS 2015a).

## 5.4 DISPOSAL

Recycling is the most environmentally acceptable means of disposal for stable molybdenum (USGS 2015b). Recovery processes have been developed for the recycling of molybdenum scrap, flue dusts, spent catalysts, and other industrial wastes (HSDB 2010).

Conventional waste water and water treatment methods are unsuccessful in the removal of molybdenum (EPA 1979). Removal of molybdenum in conventional waste water treatment plants averages only 15%. Carbon adsorption raised removal efficiency to about 50%.

Another method for removal of molybdenum from industrial waste streams involves the addition of ferric iron followed by dissolved-air flotation. This technique was shown to have a removal efficiency of 99% (EPA 1979). Milling and mining operations may also use ion exchange technology to treat effluent, which has reported removal efficiencies of about 98% (EPA 1979).

A $^{99m}$Tc generator containing a depleted uranium shield or sufficient residual $^{99}$Mo radioactivity to be considered radioactive can be disposed of by shipping to an authorized licensee following Nuclear Regulatory Commission agreement state requirements along with those of the Department of Transportation (USNRC 2015). If the $^{99}$Mo is allowed to decay sufficiently (typically ≥10 half-lives) and the internal shield is lead or tungsten, then disposal should follow state and local requirements.

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# 6. POTENTIAL FOR HUMAN EXPOSURE

## 6.1 OVERVIEW

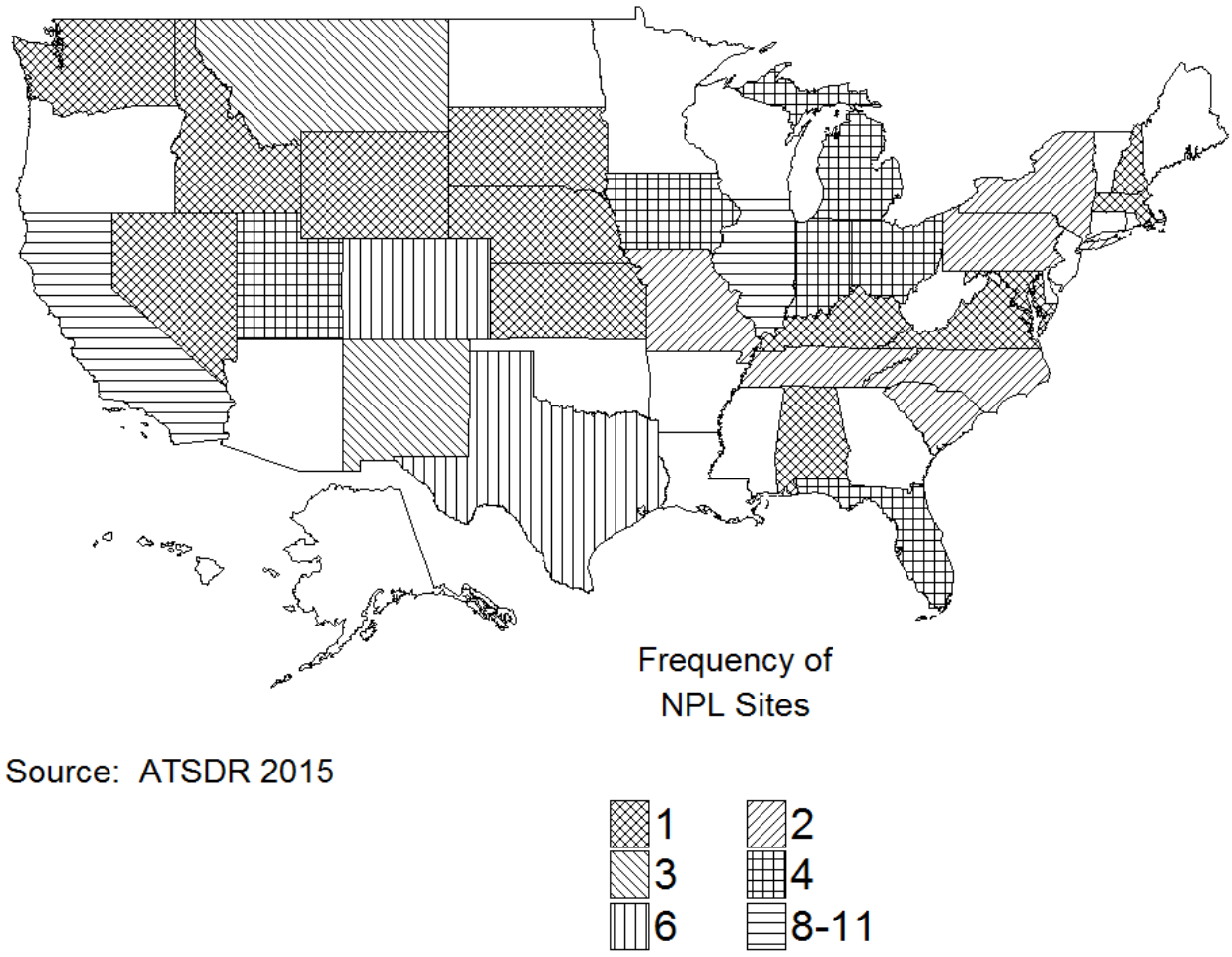
Molybdenum has been identified in at least 86 of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites in which molybdenum has been evaluated is not known. The frequency of these sites can be seen in Figure 6-1.

Molybdenum is a naturally occurring trace element that can be found extensively in nature. Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (EPA 1979). A radioactive isotope of molybdenum ($^{99}$Mo) is used as a source for producing metastable technetium-99 ($^{99m}$Tc), which is an important radiopharmaceutical that is used in the vast majority of high resolution medical imaging tests conducted today (Parma 2009). Important, naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite. Molybdenum may also form molybdate, a tetrahedral polyatomic anion, or other isopolyanions, which can form salts used in industrial applications. The molybdate ion is the most common form of molybdenum found in the aqueous environment (EPA 1979).

If released to the atmosphere, molybdenum will be returned to earth by wet and dry deposition. In water, pH levels and oxidation/reduction conditions of the sediment govern the speciation of molybdenum and adsorption potential in natural aquifers. In the pH range of 3–5, molybdenum tends to exist as hydrogen molybdate and is adsorbed to sediment composed of clay and other oxic minerals (Fitzgerald et al. 2008). The adsorption and mobility of molybdenum in soils is also inversely correlated with pH. Adsorption of molybdenum to 36 surface and subsurface soils was maximized under acidic conditions (pH 2–5) and decreased rapidly at pH 5–8 (Goldberg et al. 2002). The availability of molybdenum to plants and vegetation is also affected by pH and soil properties. Since adsorption to soil decreases with increasing pH, it becomes more bioavailable for uptake to vegetation under nonacidic conditions.

Molybdenum is infrequently detected in ambient air, but is a natural constituent of water and soils. The earth's crust contains an average of 0.0001% (1 ppm) of molybdenum, and surface waters usually have molybdenum concentrations of <5 µg/L (EPA 1979). A decade-long study conducted by the U.S. Geological Survey (USGS) of over 5,000 monitoring and drinking water wells from over 40 major aquifers in the United States reported a median molybdenum concentration of 1 µg/L (USGS 2011).

**Figure 6-1. Frequency of NPL Sites with Molybdenum**




Source: ATSDR 2015

Anthropogenic activities such as mining operations may result in localized areas where molybdenum levels greatly exceed background levels.

The primary route of exposure for the general population to molybdenum is through the ingestion of food. The National Academy of Sciences (NAS) has estimated that the average dietary intakes (AVDIs) of molybdenum by adult men and women are 109 and 76 µg/day, respectively (NAS 2001). Other routes of exposure, such as inhalation of ambient air, ingestion of drinking water, and dermal exposure, are negligible for the general population; however, they may be important routes of exposure in certain occupational settings such as mining activities and metallurgical applications where molybdenum is used. For example, molybdenum levels in air samples of two plants that produce molybdenum salts were 0.5–200 and 0.2–30 mg/m$^3$, depending upon the location of the sample and operation being performed (EPA 1979). Respirable dust samples contained molybdenum at levels of 0.471, 1.318, 0.142, and 0.318 mg/m$^3$ during mining, crushing, milling, and open pit operations, respectively, at a Colorado mine (EPA 1979).

The extensive nationwide use of radioactive $^{99}$Mo in generators that produce $^{99m}$Tc for nuclear medicine imaging scans can expose medical staff and the public in medical facilities to low levels of ionizing radiation. The extent of those exposures are limited by Nuclear Regulatory Commission and agreement state regulations (USNRC 2016a, 2016b).

## 6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Molybdenum mining, milling, and smelting, along with its association with uranium mining and milling, copper mining and milling, shale oil production, oil refining, and coal-fired power plants, have resulted in major releases to the environment (EPA 1979).

### 6.2.1 Air

Estimated releases of 109,063 pounds (~49.5 metric tons) of molybdenum to the atmosphere from 178 domestic manufacturing and processing facilities in 2013 accounted for about 12% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2015). These releases are summarized in Table 6-1.

The primary source of molybdenum emissions to the atmosphere is coal combustion. In 1970, it was estimated that 550 mt of molybdenum were released via coal combustion in the United States, in comparison to 900 mt estimated from all air pollution sources. A total of 909 mt of molybdenum can be emitted from a single 1,000 megawatt power plant per year (EPA 1979). The concentration of molybdenum in fly ash from coal combustion ranges from 7 to 160 mg/kg (Barceloux 1999).

### 6.2.2 Water

Estimated releases of 23,474 pounds (~10.6 metric tons) of molybdenum to surface water from 178 domestic manufacturing and processing facilities in 2013 accounted for about 2.6% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2015). These releases are summarized in Table 6-1.

As a result of secondary treatment processes in publicly owned treatment works (POTWs), up to 85% of molybdenum that enters POTWs can be subsequently released to surface water. This information is available for some chemicals in the open literature.

Per year, it has been estimated that natural processes result in the release of $3.6x10^{10}$ g of molybdenum into surface waters (EPA 1979).

Aqueous effluents from industries with a high presence of molybdenum, including molybdenum mining, milling, and smelting, uranium mining and milling, copper mining and milling, shale oil production, oil

## Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Molybdenum Trioxide[a]

| | | Reported amounts released in pounds per year[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Total release | | |
| State[c] | RF[d] | Air[e] | Water[f] | UI[g] | Land[h] | Other[i] | On-site[j] | Off-site[k] | On- and off-site |
| AL | 3 | 2 | 0 | 0 | 43 | 0 | 2 | 43 | 45 |
| AR | 1 | 7 | 0 | 0 | 188 | 2,288 | 7 | 2,476 | 2,483 |
| AZ | 4 | 18,002 | 0 | 0 | 149 | 0 | 18,002 | 149 | 18,151 |
| CA | 14 | 443 | 42 | 0 | 92,870 | 278 | 91,967 | 1,666 | 93,632 |
| CO | 1 | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 3 |
| CT | 1 | 688 | 0 | 0 | 0 | 9,677 | 688 | 9,677 | 10,364 |
| DE | 1 | 14 | 0 | 0 | 0 | 0 | 14 | 0 | 14 |
| FL | 1 | 255 | 2,451 | 0 | 8,002 | 0 | 10,708 | 0 | 10,708 |
| HI | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IA | 2 | 22,800 | 3,700 | 0 | 250 | 0 | 26,750 | 0 | 26,750 |
| IL | 9 | 11,400 | 2,437 | 0 | 38,444 | 3,522 | 13,837 | 41,966 | 55,803 |
| IN | 3 | 280 | 4,000 | 0 | 50,090 | 2,278 | 54,282 | 2,366 | 56,648 |
| KS | 4 | 250 | 0 | 0 | 10,638 | 0 | 255 | 10,633 | 10,888 |
| KY | 4 | 1,303 | 1 | 0 | 1,014 | 174 | 1,314 | 1,178 | 2,492 |
| LA | 19 | 4,797 | 103 | 67,073 | 73,687 | 374 | 71,876 | 74,158 | 146,033 |
| MD | 1 | 500 | 1,192 | 0 | 250 | 8,800 | 1,942 | 8,800 | 10,742 |
| ME | 1 | 163 | 21 | 0 | 0 | 0 | 184 | 0 | 184 |
| MI | 3 | 592 | 75 | 0 | 0 | 0 | 667 | 0 | 667 |
| MN | 3 | 343 | 1 | 0 | 375 | 0 | 344 | 375 | 719 |
| MS | 3 | 51 | 970 | 0 | 6,800 | 0 | 1,022 | 6,799 | 7,821 |
| MT | 2 | 60 | 240 | 0 | 0 | 93 | 300 | 93 | 393 |
| ND | 2 | 1 | 0 | 0 | 38,053 | 0 | 1 | 38,053 | 38,054 |
| NJ | 2 | 9 | 0 | 0 | 6,641 | 0 | 9 | 6,641 | 6,650 |
| NM | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NV | 1 | 4 | 0 | 0 | 68,622 | 0 | 68,626 | 0 | 68,626 |
| OH | 11 | 2,630 | 280 | 31,751 | 5,019 | 3,975 | 34,386 | 9,269 | 43,655 |
| OK | 5 | 2,386 | 255 | 0 | 52 | 12,474 | 2,641 | 12,526 | 15,167 |
| OR | 3 | 47 | 0 | 0 | 1,885 | 0 | 1,500 | 432 | 1,932 |
| PA | 16 | 30,360 | 648 | 0 | 43,710 | 10,711 | 32,914 | 52,515 | 85,429 |
| TN | 2 | 10 | 250 | 0 | 0 | 0 | 260 | 0 | 260 |
| TX | 41 | 11,386 | 6,658 | 76,400 | 89,559 | 76 | 118,274 | 65,805 | 184,079 |
| UT | 4 | 11 | 0 | 0 | 0 | 0 | 11 | 0 | 11 |
| WA | 3 | 260 | 0 | 0 | 0 | 0 | 260 | 0 | 260 |
| WI | 2 | 2 | 150 | 0 | 836 | 0 | 152 | 836 | 988 |
| WV | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

## Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Molybdenum Trioxide[a]

| | | Reported amounts released in pounds per year[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Total release | | |
| State[c] | RF[d] | Air[e] | Water[f] | UI[g] | Land[h] | Other[i] | On-site[j] | Off-site[k] | On- and off-site |
| WY | 2 | 5 | 0 | 0 | 16,000 | 0 | 16,005 | 0 | 16,005 |
| Total | 178 | 109,063 | 23,474 | 175,224 | 553,177 | 54,719 | 569,202 | 346,454 | 915,657 |

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI13 2015 (Data are from 2013)

refining, and coal-fired power plants, contain molybdenum at concentrations ranging from 100 to 800,000 µg/L (EPA 1979). Molybdenum levels in leachate samples obtained from a landfill located in Caledonia, Wisconsin ranged from 1.28 to 16 µg/L (WDNR 2013).

Effluent concentrations of molybdenum from three molybdenum mining and milling operations (two in Colorado, one in New Mexico) ranged on the order of 1,000–10,000 µg/L. In 1972, a mine in Colorado released approximately 100,000 kg of molybdenum into a receiving stream. Releases of molybdenum from coal power plants to surface waters in the United States average about 1,800 mt/year. A uranium mill in Colorado reported leaking of the tailings ponds containing 860,000 µg/L molybdenum in 1965. Some uranium operations in New Mexico reported as much as 1,000 µg/L molybdenum in aqueous effluents. Copper milling operations have reported molybdenum effluent concentrations as high as 30,000 µg/L (EPA 1979).

### 6.2.3 Soil

Estimated releases of 553,177 pounds (~251 metric tons) of molybdenum to soils from 178 domestic manufacturing and processing facilities in 2013 accounted for about 58% of the estimated total environmental releases from facilities required to report to the TRI (TRI13 2015). An additional 175,224 pounds (~79 metric tons), constituting about 19% of the total environmental emissions, were released via underground injection (TRI13 2015). These releases are summarized in Table 6-1.

Metals, such as molybdenum, may leach into soil via municipal solid waste incineration bottom ash (IMOA 2015).

## 6.3 ENVIRONMENTAL FATE

### 6.3.1 Transport and Partitioning

Molybdenum released to the air by industrial processes will be subject to atmospheric deposition (IMOA 2015). Deposition from the atmosphere is only a minor source to terrestrial and aquatic environments (Fitzgerald et al. 2008).

Molybdenum can be leached into the aquatic environment near industrial use areas via direct release or atmospheric wet deposition by rain (IMOA 2015). The pH of water, along with the composition and redox conditions of the sediment, greatly affect the speciation and adsorption behavior of molybdenum in

natural waterbodies. Molybdenum accumulation in the sediment phase is favored under conditions of low pH and in sediments with low redox potential and high iron and organic matter content (Fitzgerald et al. 2008). In more favorable reducing geochemical conditions, solid-phase iron and manganese oxyhydroxides tend to undergo dissolution, and sorbed molybdenum may be released back into the water phase.

In a seasonally anoxic basin, the distribution of molybdenum in the pore water of sediments was relatively uniform. In a perennially oxic basin, however, there was a redistribution of molybdenum in the sediment-water interface subsequent to deposition. This was determined to be a consequence of adsorption of molybdenum to iron oxyhydroxides at a rate of 36 $cm^3$/molecule-second in the first 1–2 cm depth (IMOA 2015).

Geological uplift and atmospheric deposition result in the molybdenum enrichment of surface soils (IMOA 2015). Molybdenum concentrations are found to be the highest in the top soil layer, due to strong binding to natural organic matter. Goldberg et al. (2002) studied the adsorption potential of molybdenum as a function of pH on 36 surface and subsurface soil samples from 27 soil series belonging to six different soil orders, which provided a wide range of soil physical-chemical characteristics such as organic carbon content, cation exchange capacity, and iron content. In general, maximum adsorption occurred under acidic pH conditions (pH 2–5) and sorption decreased rapidly from pH 5 to 8 and was minimal in all soils at pH >9.

As reviewed by Regolia et al. (2012), the bioaccumulation factor (BAF) ranged from 30.1 to 71.6 (average of 49) in fish exposed to molybdenum levels <65 ug/L. At higher molybdenum levels (up to 766 µg/L), the BAF ranged from 0.4 to 9.9 (average 1.4). A laboratory study in rainbow trout found a similar inverse relationship between molybdenum concentration in the water and bioconcentration factor (BCF) (Regolia et al. 2012). A 60-day exposure to 880 µg/L resulted in tissue levels below the limit of detection. Exposure to 11,100 µg/L for 28 days resulted in whole-body molybdenum levels of 0.53 mg/kg fish; the calculated average BCF was 0.05. In another study, fish in a creek near a molybdenum tailings pile had measured BCFs of <100 after a 2-week exposure (CCME 1999). The molybdenum levels in the liver and kidney were higher than in controls; the molybdenum concentration of the water was not reported. Molybdenum is not expected to bioaccumulate in fish or vegetation.

### 6.3.2 Transformation and Degradation

As a naturally occurring trace element, molybdenum can be found extensively in nature. The predominant form of molybdenum in natural waters is as the molybdate anion, $MoO_4^{-2}$ (Barceloux 1999), while naturally occurring molybdenum salts are the dominant form in dry environments (EPA 1979).

#### 6.3.2.1 Air

No information regarding the chemical forms of molybdenum in the atmosphere and their transformations could be located. It is generally assumed that metals, especially those from combustion sources, exist in the atmosphere as oxides since metallic species are readily attacked by atmospheric oxidants.

#### 6.3.2.2 Water

Molybdenum in aquatic systems readily forms organometallic complexes. The predominant form of molybdenum in natural waters is as the molybdate anion, $MoO_4^{-2}$ (Barceloux 1999). It can also exist as molybdenum sulfide and bimolybdate (CCME 1999). The molybdate species is most abundant in aquatic environments with pH >7, whereas at pH <7, polymeric species, such as a tetrahedral polyatomic anion or other isopolyanions, may form. At pH <5, molybdenum may also form complexes with excess iron and aluminum (CCME 1999; Cruywagen 2000; Cruywagen et al. 2002).

In low redox environments, the molybdate anion can be reduced to molybdenum disulfide or molybdenite (Fitzgerald et al. 2008).

#### 6.3.2.3 Sediment and Soil

Molybdenum is found naturally in soil as the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite (EPA 1979; Fitzgerald et al. 2008).

The predominant form of molybdenum in wet soil is as the molybdate anion, $MoO_4^{-2}$ (Barceloux 1999).

#### 6.3.2.4 Other Media

No data for the degradation of molybdenum in other media were located.

## 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to molybdenum depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of molybdenum in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on molybdenum levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring molybdenum in a variety of environmental media are detailed in Chapter 7.

### 6.4.1 Air

Molybdenum concentrations in ambient air have been reported to range from below detection limits to 0.03 mg/m$^3$ (EPA 1979). Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 µg/m$^3$, are higher than those found in rural areas, 0.001–0.0032 µg/m$^3$ (Barceloux 1999).

### 6.4.2 Water

It has been reported that concentrations of molybdenum are generally <1.0 µg/L in surface waters (USGS 2006) and 1.0 µg/L in drinking water (USGS 2011). Groundwaters contain about 1.0 µg/L (USGS 2011). It was noted that concentrations >20 µg/L can be attributed to anthropogenic sources, such as mining, upgrading, or other industrial processes (EPA 1979). Near industrial sources, surface water molybdenum concentrations can reach 0.2–0.4 mg/L and groundwater concentrations can reach 25 mg/L (Barceloux 1999). Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations, far exceeding the USGS health-based screening level of 40 µg/L (USGS 2011).

A USGS study of surface water from 51 of the nation's major river basins was conducted from 1991 to 2002 (USGS 2006). The median concentration of molybdenum in 2,773 surface water samples was <1.0 µg/L, with a maximum concentration of 157 µg/L. There were eight samples (approximately 0.29% of the total) that exceeded the USGS health-based screening level of 40 µg/L for molybdenum.

In a study of surface waters collected from 197 sampling stations in Colorado, molybdenum was found at concentrations <10 µg/L in 87% of the 299 samples. Samples that contained concentrations >5 µg/L were concluded to be the result of proximity to mineralization or mining and milling operations (EPA

1979). However, another study comparing surface waters draining highly mineralized areas to those with baseline molybdenum areas found that molybdenum mineralization did not contribute significantly to concentrations in surface waters. The waters from streams draining the highly mineralized areas rarely had molybdenum concentrations above 1–2 µg/L (EPA 1979).

DOI (1967) collected river and lake water samples from 100 sampling stations around the United States from 1962 to 1967. The samples were taken from areas susceptible to contamination, including highly populated areas, industrial areas, recreational use areas, and state and national boundaries. Molybdenum was detected in the water samples at maximum concentrations >100 µg/L at 38 of the sample sites, while 26 sites had mean molybdenum concentrations >50 µg/L.

In sea water, the mean molybdenum concentration has been reported as 4–12 µg/L (EPA 1979). Kulathilake and Chatt (1980) reported the molybdenum concentration in the Atlantic Ocean as 7.2–7.9 µg Mo/L. Another study reported that the molybdenum concentration in the North Atlantic ranged from 0.5 to 1.0 µg Mo/L (Chan and Riley 1966). In the Pacific Ocean, measured molybdenum concentrations included 8.8 µg Mo/L in the Eastern Pacific (Kiriyama and Kuroda 1984) and 1.5 µg Mo/L in the Western Pacific (Nakata et al. 1983). Kawabuchi and Kuroda (1969) reported a mean molybdenum concentration of 7.7 µg Mo/L in Tokyo Bay. Molybdenum concentrations measured in the English Channel ranged from 12 to 16 µg Mo/L (Chan and Riley 1966), while the Irish Sea was reported to have a mean molybdenum concentration of 8.4 µg Mo/L (Riley and Taylor 1968).

A comprehensive groundwater monitoring study conducted from 1992 to 2003 by the USGS of 5,183 monitoring and drinking-water wells representative of over 40 principal aquifers in humid and dry regions and in various land-use settings reported that the median concentration of molybdenum in 3,063 samples was 1.0 µg/L, with a maximum value of 4,700 µg/L (USGS 2011). Approximately 1.5% of the groundwater samples had molybdenum levels exceeding the USGS health-based screening level of 40 µg/L (USGS 2011). Levels of molybdenum tended to be greatest in glacial unconsolidated sand and gravel aquifers as compared to other major aquifer groups in the study.

A report issued by the Wisconsin Department of Natural Resources found elevated levels of molybdenum in private supply wells and groundwater monitoring wells near the We Energies Oak Creek power plant located in Caledonia, Wisconsin (WDNR 2013). Molybdenum levels in 21 private well samples exceeded the state of Wisconsin groundwater enforcement standard of 40 µg/L. It was not determined

whether the elevated levels of molybdenum were naturally occurring or were a consequence of the activities of the power plant and the coal ash fill areas located nearby the plant.

In a study of finished drinking water supplies from the 100 largest cities in the United States in 1964, median and maximum molybdenum concentrations of 1.4 and 68 µg/L, respectively, were reported (USGS 1964). Another study reported a mean molybdenum concentration of 8 µg/L in samples collected from 161 drinking water sources from 44 states in the United States (Hadjimarkos 1967). Molybdenum levels measured onsite at 12 public water facilities across England and Wales ranged from below the detection limit (0.03 µg/L) to 1.51 µg/L over an 18-month collection period (Smedley et al. 2014). Corresponding molybdenum levels in tap water from 24 residences in three towns (North Wales, the English Midlands, and South East England) served by these public water facilities ranged from <0.03 to 1.00 µg/L. The study indicated that there was little variability in molybdenum concentrations when comparing levels in tap water versus respective water supply facilities, construction ages of the residences (i.e., new homes versus older homes), and pre-flush versus post-flush tap samples, suggesting that water distribution pipework has a negligible effect on supplied tap water levels of molybdenum.

Drinking water may also be affected by industrial contamination, as water treatment facilities are ineffective at removing molybdenum from source waters. In tap waters samples collected in 1971 from Golden, Colorado, a community that derives its water supply from a stream draining a molybdenum mine and mill, the mean molybdenum concentration was reported to be 440 µg/L. However, after the mine closed in 1974, the mean concentration in drinking water samples decreased to 150 µg/L by January 1975, 60 µg/L by June 1975, and 30 µg/L by 1977 (EPA 1979).

### 6.4.3 Sediment and Soil

Globally, most soils contain molybdenum at concentrations between 0.6 and 3.5 ppm, although total concentrations in soils can vary widely depending on geological composition or industrial contamination. The average concentration of soils is generally 1–2 ppm. In the United States, it has been reported that the median concentration of molybdenum in soils is 1.2–1.3 ppm, with a range of 0.1–40 ppm (EPA 1979). The Forum of European Geological Surveys (FOREGS), under the International Union of Geological Sciences/International Association of Geochemistry (IUGS/IAGC) Global Geochemical Baselines Programme, collected 840 top soil samples from 26 European countries and reported molybdenum concentrations ranging from <0.1 to 21.3 mg/kg (mean 0.943 mg/kg) (FOREGS 2005).

Above average molybdenum soil concentrations may occur in areas containing molybdenum-rich rock formations or in areas of industrial contamination. Natural sources sampled, including soils covering a mineralized area, soil derived from a marine black shale, alluvial soils on the eastern footslopes of Sierra Nevada, and soils formed from volcanic ash in Kauai, Hawaii, contained mean molybdenum concentrations of 76, 12, 17.4, and 14.9 ppm, respectively. Soils sampled near industrial contamination, such as soils downstream from a molybdenum mine and mill in Colorado, soil irrigated with water contaminated by a uranium mill, and soils 2 miles from a molybdenum smelter in Pennsylvania, had mean molybdenum concentrations of 59, 61, and 29 ppm, respectively (EPA 1979).

Typical molybdenum concentrations found in stream sediments were reported to range from 1 to 5 ppm (EPA 1979). Sediments in streams that drain water from natural deposits of molybdenum in the United States have been reported to have molybdenum concentrations ranging from 10 to 200 ppm. Another study reported molybdenum levels of up to 300 ppm in sediments derived from black marine shales in England. Stream sediment collected from water below a molybdenum mine and mill in Colorado had molybdenum concentrations ranging from 50 to 1,800 ppm (mean of 530 ppm). Molybdenum content in stream sediments have been shown to reflect mineralization, as the concentration increases with decreasing sediment grain size (EPA 1979). FOREGS collected 848 freshwater sediment samples from 26 European countries and reported molybdenum concentrations ranging from 0.12 to 117 mg/kg (mean 1.34 mg/kg) (FOREGS 2005).

### 6.4.4 Other Environmental Media

In a study detecting and comparing trace elements in the milk of guinea pigs (n=87), dairy cattle (n=48), horses (n=35), and humans (n=84), the average molybdenum concentrations measured were 0.026, 0.022, 0.016, and 0.017 ppm, respectively (Anderson 1992). Average concentrations of molybdenum detected in six kinds of milk, including cow's milk-based formula, breast milk, soya milk, bottled milk, dried milk, and evaporated milk, were 18, 4, 160, 34, 35, and 29 µg/L, respectively (Biego et al. 1998). Most of the molybdenum is in the cream fraction (Archibald 1951).

Food derived from aboveground plants, such as legumes, leafy vegetables, and cauliflower generally has a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet (Barceloux 1999).

Typical concentrations of molybdenum in plants are 1–2 ppm; however, a range of tenths to hundreds of ppm have been reported (EPA 1979).

Tobacco contains molybdenum concentrations of 0.3–1.76 µg/g (Barceloux 1999).

## 6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Molybdenum exposure to the general population via ambient air and drinking water is expected to be negligible compared with exposure through food (Barceloux 1999). Molybdenum does not occur naturally in the pure metallic form. It is principally found as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Therefore, almost all exposure is to a molybdenum compound rather than the metal alone. The average dietary intakes of molybdenum in the United States by adult men and women are 109 and 76 µg/day, respectively (NAS 2001). A study of the dietary intake of adult residents in Denver, Colorado reported a mean molybdenum ingestion rate of 180 µg/day (range 120–240 µg/day) (Barceloux 1999). Daily intake ranged from 74 to 126 µg molybdenum in a study of older children and adults in the Northeastern United States (Barceloux 1999).

The European Food Safety Authority (EFSA) used dietary intake studies to derive estimates of which foods were most responsible for molybdenum intake in European populations (EFSA 2013). Cereals and cereal-based products (including bread) are the largest contributors to molybdenum intake in a Western diet; these products contribute one-third to one-half of the total molybdenum intake. Other contributors to total molybdenum intake include dairy products and vegetables.

A summary of molybdenum concentrations positively identified in foods analyzed during the FDA Total Diet Study (TDS) of 2006–2011 is summarized in Table 6-2 (FDA 2014). The data for molybdenum arose from Market Basket Surveys conducted in 2010 and 2011, in which 382 store-bought foods purchased in four geographic regions of the United States (northeast, southeast, central, and west) were analyzed. Only those food items in which the molybdenum content of at least one sample was above the detection limit of the analytical method are reported. Another survey of levels of molybdenum in food found the highest molybdenum concentrations in legumes; grains and grain products; nuts; meat, fish, and poultry (including liver); eggs; and milk, yogurt, and cheese (76.7, 30.0, 29.5, 8.9, 6.3, and 4.6 µg/100 g, respectively) (Pennington and Jones 1987).

## Table 6-2. Molybdenum Levels Detected in Foods in the 2010 and 2011 Market Basket Surveys[a]

| Food | Number of samples | Positive detections | Mean (mg/kg) | Median (mg/kg) | Maximum (mg/kg) | LOD (mg/kg) | LOQ (mg/kg) |
|---|---|---|---|---|---|---|---|
| Liver (beef/calf), pan-cooked with oil | 8 | 8 | 1.450 | 1.425 | 1.660 | 0.700 | 3.000 |
| Pinto beans, dry, boiled | 8 | 8 | 1.320 | 1.270 | 1.640 | 0.700 | 3.000 |
| Pork and beans, canned | 8 | 1 | 0.088 | 0 | 0.700 | 0.700 | 3.000 |
| Peanut butter, smooth/creamy | 8 | 3 | 0.508 | 0 | 1.880 | 0.900 | 3.000 |
| Shredded wheat cereal | 8 | 5 | 0.554 | 0.883 | 0.984 | 0.700 | 3.000 |
| Raisin bran cereal | 8 | 1 | 0.088 | 0 | 0.701 | 0.700 | 3.000 |
| Crisped rice cereal | 8 | 8 | 0.898 | 0.837 | 1.280 | 0.700 | 3.000 |
| Granola w/ raisins | 8 | 6 | 0.589 | 0.772 | 0.815 | 0.700 | 3.000 |
| Oat ring cereal | 8 | 8 | 1.260 | 1.290 | 1.440 | 0.700 | 3.000 |
| Collards, fresh/frozen, boiled | 8 | 2 | 0.262 | 0 | 1.580 | 0.500 | 2.000 |
| Chili con carne w/ beans, canned | 8 | 2 | 0.179 | 0 | 0.730 | 0.700 | 3.000 |
| Refried beans, canned | 8 | 2 | 0.254 | 0 | 1.100 | 0.800 | 3.000 |
| White beans, dry, boiled | 8 | 8 | 1.137 | 1.116 | 1.780 | 0.700 | 3.000 |
| Granola bar, w/ raisins | 8 | 1 | 0.164 | 0 | 1.310 | 0.800 | 3.000 |
| Candy bar, chocolate, nougat, and nuts | 8 | 1 | 0.115 | 0 | 0.922 | 0.800 | 3.000 |

[a]Trace values were defined as results ≥LOD and <LOQ. Results ≥LOD and <LOQ (trace values) were used as reported when calculating the means.

LOD = limit of detection; LOQ = limit of quantification

Source: FDA 2014

Since molybdenum is biologically essential for good health, it is sometimes necessary for individuals to take vitamins containing molybdenum or dietary molybdenum supplements. Based on data from NHANES, the median molybdenum intake from dietary supplements was about 23 and 24 µg/day for men and women who reported supplement use, respectively. Dietary supplements generally contain molybdenum in the form of sodium molybdate or ammonium molybdate (Momcilovic 1999; NAS 2001).

It was reported in 1979 that in the United States, the average human intake of molybdenum via drinking water was <5 µg/day (EPA 1979). Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum (>50 µg/L) (EPA 1979).

Urinary levels of molybdenum were measured for the U.S. population from NHANES studies from 1999 to 2012 (CDC 2015). For survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012, the geometric mean urinary concentrations of molybdenum were 43.2, 42.5, 39.4, 44.3, 47.1, 45.5, and 42.0 µg/g of creatinine, respectively. The 95$^{th}$ percentile mean concentrations of molybdenum in urine were 144, 130, 120, 132, 137, 143, and 130 µg/g of creatinine in survey years 1999–2000 (sample size 2,257), 2001–2002 (sample size 2,689), 2003–2004 (sample size 2,558), 2005–2006 (sample size 2,576), 2007–2008 (sample size 2,627), 2009–2010 (sample size 2,848), and 2011–2012 (sample size 2,502), respectively (CDC 2015). When the population was divided by age, the geometric mean urinary concentrations (2011–2012 data) were 83.5, 44.4, and 38.6 µg/g creatinine for ages 6–11, 12–19, and ≥20 years, respectively (CDC 2015).

Paschal et al. (1998) analyzed the levels of molybdenum and 12 other metals in the urine of 496 residents of the United States obtained from the NHANES III survey conducted from 1988 to 1994. The specimens randomly selected were from a broad spectrum of the population (e.g., both urban and rural communities, both male and females and persons aged 6–88 years from all major ethnicities). The geometric mean molybdenum concentration of the samples was 46.8 µg/L and the 25$^{th}$, 50$^{th}$, 75$^{th}$, and 95$^{th}$ percentiles were 27.9, 56.5, 93.9, and 168.0, µg/L, respectively. The creatinine-adjusted 25$^{th}$, 50$^{th}$, 75$^{th}$, and 95$^{th}$ percentiles were 30.9, 45.7, 64.3, and 133.8 µg/g, respectively, with a geometric mean of 39.6 µg/g. Urinary molybdenum levels were about 1–2 orders of magnitude greater than any of the other 12 metals analyzed.

Molybdenum levels in whole blood are typically <5 ng/mL in the general population; however, blood samples from persons from areas with natural molybdenum deposits or from molybdenum mining areas may have concentrations of up to 150 µg/mL (Barceloux 1999).

Blood samples collected from 18 miners at a molybdenum mine in New Mexico had plasma molybdenum levels <5 µg/L in 12 of the 18 samples and 6–18 µg/L in the remaining 6 samples. The concentration of molybdenum in urine collected from 11 of the miners ranged from 20 to 74 µg/L. It was noted that molybdenum levels in urine and blood of miners mainly exposed to molybdenite may not be above average, since molybdenite is a relatively insoluble compound (EPA 1979).

In a survey of a molybdenite mining, crushing, and milling operation in Colorado, mean molybdenum levels in respirable dust samples were 0.471, 1.318, 0.142, and 0.318 mg/m$^3$ during mining, crushing, milling, and open pit operations, respectively (EPA 1979). In settled dust and air samples collected from a molybdenum smelting operation, concentrations of molybdenum, in the form of molybdenum trioxide, were 57–61% and 3–33 mg/m$^3$, respectively (EPA 1979). Forty air samples collected above a crucible in a molybdenum trioxide smelting plant contained a mean molybdenum concentration of 0.22 mg/m$^3$, while air samples collected in the breathing zone of workers had molybdenum concentrations ranging from 1.4 to 5.4 mg/m$^3$ (EPA 1979). The air concentrations of molybdenum in two plants that produce molybdenum salts were 0.5–200 and 0.2–30 mg/m$^3$ (EPA 1979). More recent monitoring data for mining and milling operations were not located; current levels may be lower due to possible changes in occupational standards, engineering and administrative controls, and personal protective equipment requirements.

Workers involved in metal refining and metal working may be exposed to airborne particulates containing molybdenum. In a study assessing the exposure of a group of 20 workers performing welding, polishing, and assembly of stainless steel constructions, molybdenum was detected in personal air samplers at concentrations of 0.27–9.7, 0.03–4.2, and 0.14–0.60 µg/m$^3$, respectively. Stationary air samplers in the facility detected course (equivalent aerodynamic diameter [EAD] 2–10 µm) and fine (EAD <2 µm) molybdenum particles at concentrations of 0.015–0.087 and 0.093–0.54 µg/m$^3$, respectively (Kucera et al. 2000).

The National Occupational Exposure Survey (NOES) conducted by NIOSH in 1983 estimated that 245,024 workers employed at 15,996 facilities were potentially exposed to molybdenum (pure, powder, and unknown forms) in the United States (RTECS 2009). The NOES database does not contain

information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

The extensive nationwide use of radioactive $^{99}$Mo in generators that produce $^{99m}$Tc for nuclear medicine imaging scans can expose medical staff and the public in medical facilities to low levels of ionizing radiation. The extent of those exposures are limited by the Nuclear Regulatory Commission and agreement state regulations (USNRC 2016a, 2016b).

## 6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.8, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

Breast milk and infant formula are the primary sources of molybdenum in infants aged 0–6 months (NAS 2001). The primary source of dietary molybdenum intake among children in the United States is milk (EPA 1979). Several studies have measured molybdenum levels in human breast milk; average molybdenum levels ranged from 1.5 to 17 µg/L (Anderson 1992; Aquilio et al. 1996; Biego et al. 1998; Bougle et al. 1988). As shown in Table 6-3, highest molybdenum concentrations occur within the first week after birth and tend to be higher in the mothers of term infants, as compared to preterm infants (Aquilio et al. 1988; Bougle et al. 1988).

## Table 6-3. Molybdenum Levels in Breast Milk in Mothers of Term and Preterm Infants

| | Molybdenum levels in breast milk (µg/L) | | |
|---|---|---|---|
| Lactation day | Term infants | Preterm infants | Reference |
| 2-6 | 6.8 | 3.9[a] | Aquilio et al. 1996 |
| 12-16[b] | 5.7 | 2.4[a] | |
| 21[c] | 3.6 | 1.9[a] | |
| 3-5 | 10.2 | 4.0[a] | Bougle et al. 1988 |
| 7-10[d] | 4.8 | 3.7 | |
| 14[d] | 1.5 | 1.4 | |
| 30[d] | 2.6 | 1.9 | |
| 60[e] | No data | 1.2 | |

[a]Significantly different from term infant levels ($p<0.05$).
[b]Significantly different from molybdenum concentration at 2-6 days ($p<0.01$).
[c]Significantly different from molybdenum concentration at 2-6 days ($p<0.05$).
[d]Significantly different from molybdenum concentration for whole group at 3-5 days ($p<0.01$).
[e]Significantly different from molybdenum concentration at for whole group at 3-5 days ($p<0.05$).

Urinary levels of molybdenum in children 6–11 years old were measured during the NHANES study assessing exposure from 1999 to 2012 (CDC 2015). For survey years 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, and 2011–2012, the mean urinary concentrations of molybdenum were 85.9, 77.2, 72.5, 81.0, 90.4, 88.6, and 83.5 µg/g of creatinine, respectively. The 95$^{th}$ percentile mean concentrations of molybdenum in urine were 214, 185, 160, 201, 274, 195, and 259 µg/g of creatinine in survey years 1999–2000 (sample size 310), 2001–2002 (sample size 368), 2003–2004 (sample size 290), 2005–2006 (sample size 355), 2007–2008 (sample size 394), 2009–2010 (sample size 378), and 2011–2012 (sample size 398), respectively (CDC 2015).

## 6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in an industrial setting such as mining, metal refining, and metal working can be exposed to significant levels of molybdenum (Kucera et al. 2000). Populations living close to areas with high molybdenum contamination from industrial effluents and high mineral deposits are at risk for higher exposures (EPA 1979).

$^{99}$Mo generators are the major source of ionizing radiation exposure to nuclear medicine staff in medical facilities that perform $^{99m}$Tc diagnostic imaging scans (Ahasan 2004).

## 6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of molybdenum is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of molybdenum.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 6.8.1 Identification of Data Needs

**Physical and Chemical Properties.** The physical-chemical properties of molybdenum are provided in Chapter 4. No data needs are identified.

**Production, Import/Export, Use, Release, and Disposal.** According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2013, became available in October of 2014. This database is updated yearly and should provide a list of industrial production facilities and emissions.

**Environmental Fate.** Molybdenum is a naturally occurring trace element that can be found extensively in nature (EPA 1979). Its transport and partitioning are well understood. No data needs are identified.

**Bioavailability from Environmental Media.** Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans (EPA 1979). Its bioavailability is well documented. No data needs are identified.

**Food Chain Bioaccumulation.** Measured BCFs of molybdenum in fish suggest that bioaccumulation in aquatic organisms is not high. No data needs are identified.

**Exposure Levels in Environmental Media.** Reliable monitoring data for the levels of molybdenum in contaminated media at hazardous waste sites are needed so that the information obtained on levels of molybdenum in the environment can be used in combination with the known body burden of molybdenum to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

**Exposure Levels in Humans.** Exposure to molybdenum to the general population is almost entirely through food. Food derived from aboveground plants, such as legumes, leafy vegetables, and cauliflower generally has a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet. Vitamins and nutritional supplements are also a source of dietary exposure. Drinking water coming from sources close to areas with high molybdenum

contamination from industrial effluents may contain a higher concentration of molybdenum. Exposure to molybdenum in an industrial setting such as mining can be significant (Barceloux 1999; EPA 1979; Momcilovic 1999; NAS 2001).

This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** There are limited data on estimates of molybdenum exposure in children. Milk is reported to be the primary source of dietary molybdenum intake among children in the United States (Biego et al. 1998; EPA 1979); however, this is based on older data. More recent monitoring data would be valuable in assessing whether molybdenum exposure sources vary between children and adults.

Child health data needs relating to susceptibility are discussed in Section 3.13.2, Identification of Data Needs: Children's Susceptibility.

**Exposure Registries.** The information amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance; however, no exposure registries for molybdenum were located. Molybdenum is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. Molybdenum will be considered in the future when chemical selection is made for sub-registries to be established.

### 6.8.2 Ongoing Studies

As part of the National Health and Nutrition Evaluation Survey (NHANES), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human urine samples for molybdenum. These data will give an indication of the frequency of occurrence and background levels of these compounds in a representative sample of the U.S. general population.

# 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring molybdenum, its metabolites, and other biomarkers of exposure and effect to molybdenum. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

## 7.1 BIOLOGICAL MATERIALS

Table 7-1 lists methods used for determining molybdenum in biological materials. Inductively coupled plasma-mass spectrometry (ICP-MS) is a precise, sensitive, multi-element technique capable of measuring biological fluids (typically urine, blood, or serum) with minimal sample preparation and still achieving sub-µg/L method detection limits. Currently, the most widely used ICP-MS instruments are quadrupole analyzers (Q-ICP-MS), with or without collision or reaction gas technology to remove polyatomic interferences (especially problematic for lower mass isotopes [i.e., below m/z 100, but not typically deemed necessary for molybdenum analysis]). Sector field instruments (SF-ICP-MS) have higher sensitivity compared to Q-ICP-MS and resolve isobaric and polyatomic interferences using physical resolution capabilities, but are typically higher cost than Q-ICP-MS. Inductively coupled plasma optical (atomic) emission spectrometry (ICP-OES/ICP-AES) is, like ICP-MS, a multi-element technique but with higher limits of detection (µg/L). Electrothermal atomic absorption spectrometry (ETAAS) is a widely accepted technique that is less expensive than ICP instruments and capable of detecting µg/L levels of elements in a wide variety of sample types with small (µL) sample sizes. However, ETAAS instruments are more limited in multi-element capabilities than ICP instruments.

ICP analysis coupled with AES is used in NIOSH method 8005 for the determination of molybdenum in blood or tissue (NIOSH 1994a). The detection limits for this method are 1 µg/100 g blood and 0.2 µg/g tissue, which is the average LOD for 20 elements, including molybdenum.

## Table 7-1. Analytical Methods for Determining Molybdenum in Biological Samples

| Sample matrix[a] | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Human plasma ($^{95}$Mo, $^{96}$Mo isotopes) | Addition of 10 µg vanadium-51. Dried at 35°C, powdered, and compressed. Irradiation of sample with 10 µA proton beam for 6 hours. | PAA/HPGe | 2 ng/mL | No data | Cantone et al. 1997 |
| Blood or tissue | Acid digestion with 3:1:1 (v/v/v) nitric, perchloric, and sulfuric acids. Heat. | ICP/AES (NIOSH method 8005) | 1 µg/100 g blood; 0.2 µg/g tissue | 126% (3.1% RSD at 4.0 µg/ 100 mL blood) | NIOSH 1994a |
| Blood | Direct injection of 20 µL sample in a ratio 1:2 with 0.1% (v/v) Triton X-100™ to the platform pretreated with Erbium (25 µg). | ETAAS | 0.6 µg/L | No data | Burguera et al. 2002 |
| Blood | 500 µL of blood diluted 1:10 with 100 µL of 0.1% (v/v) Triton-X-100™, 500 µL of 25 µg/L Tb in 2% (v/v) $HNO_3$, and 3,900 µL of 0.5% (v/v) $NH_4OH$. | Q-ICP-MS | 0.05 µg/L (LOQ) | 103% | Heitland et al. 2006 |
| Blood | 1 mL blood microwave digested (23 minutes) with 2 mL concentrated $HNO_3$ and 1 mL 30% $H_2O_2$. Digestate diluted 1+9 with 10 µg/L Ga and Y in water. | SF-ICP-MS | 0.008 µg/L | No data | Sarmiento-González et al. 2008 |
| Urine | Urine diluted 1+9 with 2% v/v $HNO_3$, 10 µg/L Ir. | Q-ICP-MS | 0.8 µg/L | No data | Caldwell et al. 2005 |
| Urine | Add nitric acid. Adjust pH to 2.0 with 5M NaOH. Extraction with 60 mg polydithiocarbamate resin. Agitate and filter. | ICP/AES (NIOSH method 8310) | 0.1 µg/ sample | 100% | NIOSH 1994b |
| Urine | Repeated acid digestion with nitric acid followed by drying. | TIMS | No data | No data | Giussani et al. 1995; 2007 |
| Fecal samples | Homogenize and dry samples followed by acid digestion using nitric acid. Separate from other metals by eluting with hydrochloric acid using an ion exchange column. | TIMS | No data | 50% | Turnlund et al. 1993 |

## Table 7-1. Analytical Methods for Determining Molybdenum in Biological Samples

| Sample matrix[a] | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Milk | 3 g liquid (0.5 mg dried) milk mixed with 3 mL water. Add 4 mL 25% TMAH, 4 mL 5 % w/v Triton X-100™, and 4 mL $H_2O_2$ (20 volume). Water bath (70°C) for 2 hours with periodic vortexing. Digest diluted to 20 mL with water and 1mL of 400 µg/L Sb. Centrifuged at 5,000 rpm for 5 minutes. | Q-ICP-MS | 0.01 µg/g powder | No data | Reid et al. 2008 |
| Milk (mammal) | 5 mL homogenized milk wet washed with nitric and perchloric acids (10:1 v/v). | ICP | 0.08 ppm | No data | Anderson 1992 |
| Milk (formula, human, soy, bottled, dried, evaporated) | Digestion in microwave oven with 6 mL 65% nitric acid and 1 mL 30% perhydrol. Dilution to a nitric acid concentration of 2%. | ICP/MS | 0.9 µg/L | 97.8% | Biego et al. 1998 |

[a]Molybdenum is the target analyte unless otherwise specified.

AES = atomic emission spectrometry; HPGe = high-purity geranium detector; ICP = inductively coupled argon plasma spectroscopy; LOQ = limit of quantification; MS = mass spectrometry; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; PAA = proton activation analysis; Q-ICP-MS = quadrapole inductively coupled plasma-mass spectrometry; rpm = rotations per minute; RSD = relative standard deviation; SF-ICP-MS = sector field inductively coupled plasma-mass spectrometry; TIMS = thermal ionization mass spectrometry

A method for detecting stable molybdenum isotopes in human blood uses proton activation analysis followed by the measurement of gamma-rays emitted from the activation using a high-purity geranium (HPGe) radiation detector (Cantone et al. 1997). The detection limit for this method was reported to be 2 ng/mL.

NIOSH method 8310 describes a technique for the determination of molybdenum in urine by extraction with a polydithiocarbamate resin. This method uses ICP-AES analysis and has a detection limit of 0.1 µg/sample (NIOSH 1994b).

A method using ICP analysis for the detection of trace elements in homogenized milk has been described (Anderson 1992). The limit of detection was reported as 0.08 ppm. Another method for the detection of molybdenum in various types of milk, including cow's milk-based formula, breast milk, soy milk, bottled milk, dried milk, and evaporated milk was described that uses digestion vessels for sample preparation followed by ICP-MS and has a detection limit of 0.9 µg/L (Biego et al. 1998).

## 7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for determining molybdenum in environmental samples. Analytical methods determine the total molybdenum content of the samples.

A variety of techniques have been effective in the analytical detection of molybdenum. Emission spectroscopy, x-ray fluorescence, and neutron activation have all been used successfully for aqueous samples; however, these methods are not cost effective. The most widely used analytical methods for the determination of molybdenum in water samples are colorimetric, atomic absorption spectrophotometry (AAS), either flame or graphite furnace (GF), and ICP with AES (EPA 1979; NIOSH 2003a, 2003b, 2003c). Spectral interferences are the primary problems encountered in ICP-AES analysis (NIOSH 2014b).

Molybdenum in air samples can be analyzed using NIOSH methods 7300 and 7301, both of which use acid ashing for sample preparation followed by ICP-AES detection. The limit of detection for these two methods is 0.8 ng/mL of digest or 0.020 µg per filter using either a 5- or 0.45-µm mixed cellulose ester filter with an air volume collection range of 5–67 L of air (NIOSH 2003a, 2003b). NIOSH method 7303 is also used for the analysis of molybdenum in air, but uses hot block digestion instead of acid ashing.

## Table 7-2. Analytical Methods for Determining Molybdenum in Environmental Samples

| Sample matrix[a] | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Air | Filter collection on 0.8 µm membrane filter. Acid ashing with nitric/perchloric (4:1) acid. | ICP-AES (NIOSH Method 7300) | 0.8 ng/mL[b] (800 µg/mL) | 105.3% (2.47% RSD at 2.4 ng/mL) | NIOSH 2003a |
| Air | Filter collection on 0.8 µm membrane filter. Acid ashing with 5% aqua regia (nitric/HCl (1:3)) acid. | ICP-AES (NIOSH Method 7301) | 0.8 ng/mL[b] (800 µg/mL) | 108.9% (2.7% RSD at 2.4 µg/filter) | NIOSH 2003b |
| Air | Filter collection on 0.8 µm membrane filter. Hot block digestion at 95°C with 5% HCl and 5% nitric acid. | ICP-AES (NIOSH Method 7303) | 0.0072 µg/mL[b] | 90–110% | NIOSH 2003c |
| Occupational dust | Filter collection on 0.8 µm MCE filter. Add 10 mL of 1:1 nitric acid and water. Microwave digestion. | ICP-AES (NIOSH Method 7302) | 0.2 µg/sample | 96.8% (5.41% RSD at 2.25 µg/sample) | NIOSH 2014a |
| Dust | Wipe surface, place wipe in beaker, and add 20 mL concentrated nitric acid and 1 mL concentrated perchloric acid and heat. | ICP-AES (NIOSH Method 9102) | 0.010 µg/sample | No data | NIOSH 2003d |
| Dust | Filter collection on 5.0 µm PVC filter. Add 12 mL of 5:1 nitric acid and water. Microwave digestion. | ICP-AES (NIOSH Method 7304) | 0.4 µg/sample | 87.79% (at 4.5 µg/sample) | NIOSH 2014b |
| Water | Filter sample through 0.45 µm membrane filter, acidify using nitric acid. | ICP-MS (EPA Method 200.8) | 0.01–0.3 µg/L | 101% | EPA 1994 |
| Water | Separation and preconcentration with $TiO_2$ nanoparticles on silica gel. Elution with 0.5 mol/L NaOH. | GF-AAS | 0.6 ng/L (600 µg/L) | 100% (3.4% RSD at 10 ng/mL) | IMOA 2015 |
| Water | Evaporation to dryness. Pyrolysis and atomization at high temperatures. | GF-AAS (USGS-NWQL I-1492-96) | 1 µg/L | No data | USGS 1997 |
| Water and soil | Addition of thiocyanate and MTOAC. Extraction with PBITU in 1-pentanol. | Spectro-photometry | 5 ng/mL ($5x10^3$ µg/mL) | No data | IMOA 2015 |
| Water and waste | Extraction by refluxing with nitric and HCl acids. | GF-AAS (EPA-NERL 246.2) | 3 µg/L | No data | EPA 1983 |

## Table 7-2. Analytical Methods for Determining Molybdenum in Environmental Samples

| Sample matrix[a] | Preparation method | Analytical method | Sample detection limit | Percent recovery | Reference |
|---|---|---|---|---|---|
| Hand wipes | Wipe added to 20 mL 4:1 nitric acid/perchloric acid. Heating and drying. Dissolution in 0.5 mL acid mixture. | ICP-AES (NIOSH Method 9102) | 0.010 µg/ sample | No data | NIOSH 2003d |

[a]Molybdenum is the target analyte unless otherwise specified.
[b]Dectection limit is based on a per mL of acid digest used in the sample preparation procedure.

AAS = atomic absorption spectrophotometry; AES = atomic emission spectroscopy; GF = graphite furnace; EPA = Environmental Protection Agency; HCl = hydrochloric acid; ICP = inductively coupled argon plasma spectroscopy; IMOA = International Molybdenum Association; MCE = mixed cellulose ester membrane; MS = mass spectrometry; MTOAC = methyltrioctyl ammonium chloride; NaOH = sodium hydroxide; NEMI = National Environmental Methods Index; NERL = National Exposure Research Laboratory; NIOSH = National Institute for Occupational Safety and Health; NWQL = National Water Quality Laboratory; PBITU = N-phenylbenzimidoyl thiourea; PVC = polyvinyl chloride; RSD = relative standard deviation; $TiO_2$ = titanium dioxide; USGS = U.S. Geological Survey

The detection method is also ICP-AES, with a detection limit of 0.0072 µg/mL of digest and a limit of quantification (LOQ) of 0.60 µg/sample with a collection volume range of 0.5–10,000 L of air (NIOSH 2003c).

Methods have also been reported for the detection of molybdenum in metal and nonmetal dust. NIOSH methods 7302 and 7304 use microwave digestion for sample preparation followed by ICP-AES detection (NIOSH 2014). The limits of detection were reported to be 0.2 µg/sample for method 7302 and 0.4 µg/sample for method 7304.

A method for determining trace amounts of molybdenum in water samples separated and preconcentrated with titanium dioxide nanoparticles on silica gel followed by GF-AAS detection has been reported (IMOA 2015). The detection limit is 0.6 ng/L. Two other methods using GF-AAS for the determination of molybdenum in water and waste samples that have detection limits of 1 and 3 µg/L have been described (NEMI 2015).

Molybdenum in environmental samples has been determined using surfactant-mediated liquid-liquid extraction followed by spectrophotometry. The detection limit is 5 ng/mL (IMOA 2015).

NIOSH method 9102 uses ICP-AES for determination of molybdenum on hand wipes and has a detection limit of 0.01 µg/wipe (NIOSH 2003d).

## 7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of molybdenum is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of molybdenum.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 7.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.**

***Exposure.*** Methods for determining background and elevated levels of molybdenum in biological materials are well developed, sensitive, specific, and reliable. Standardized methods are available from NIOSH and other sources.

***Effect.*** No biomarkers of effect were identified.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.** Methods for determining background and elevated levels of molybdenum in environmental media are well-developed, sensitive, and selective. Standardized methods of analysis for molybdenum in air, water, soil, and milk are available from EPA, NIOSH, and other sources. Analytical methods measure total molybdenum.

### 7.3.2 Ongoing Studies

No ongoing studies were identified in the NIH RePORTER database.

# 8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

The international and national regulations, advisories, and guidelines regarding molybdenum in air, water, and other media are summarized in Table 8-1.

A chronic-duration inhalation MRL of 0.0004 mg molybdenum/$m^3$ was derived for molybdenum. The MRL is based on a $BMCL_{HEC}$ of 0.013 mg molybdenum/$m^3$ calculated from the incidence data for squamous metaplasia in female mice (NTP 1997) and an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

An acute-duration oral MRL of 0.05 mg molybdenum/kg/day was derived based on a NOAEL of 5.3 mg molybdenum/kg/day for increased rate of abnormal MII oocytes in female mice (Zhang et al. 2013) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An intermediate-duration oral MRL of 0.008 mg molybdenum/kg/day was derived based on a NOAEL of 0.76 mg molybdenum/kg/day for increased estrous cycle length in female rats (Fungwe et al. 1990) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

## Table 8-1. Regulations, Advisories, and Guidelines Applicable to Molybdenum

| Agency | Description | Information | Reference |
|---|---|---|---|
| INTERNATIONAL | | | |
| Guidelines: | | | |
| IARC | Carcinogenicity classification | No data | IARC 2015 |
| WHO | Air quality guidelines | No data | WHO 2010 |
| | Drinking water quality guidelines | Not established[a] | WHO 2011 |
| NATIONAL | | | |
| Regulations and Guidelines: | | | |
| a. Air | | | |
| ACGIH | TLV (8-hour TWA) | | ACGIH 2015 |
| | Molybdenum (soluble compounds) | 0.5 mg/m$^3$ [b] | |
| | Molybdenum (Metal and insoluble compounds) | 10 mg/m$^3$ [c] | |
| | | 3 mg/m$^3$ [b] | |
| AIHA | ERPGs | No data | AIHA 2014 |
| DOE | PACs | | DOE 2012a |
| | PAC-1[d] | | |
| | Molybdenum | 10 mg/m$^3$ | |
| | Molybdenum(IV) sulfide | 50 mg/m$^3$ | |
| | Molybdenum dioxide | 1.1 mg/m$^3$ | |
| | Molybdenum trioxide | 0.75 mg/m$^3$ | |
| | Ammonium molibdate | 3.5 mg/m$^3$ | |
| | Diammonium dimolybdate | 2.6 mg/m$^3$ | |
| | Ammonium molybdate(VI) tetrahydrate | 2.8 mg/m$^3$ | |
| | Disodium molybdate | 1.1 mg/m$^3$ | |
| | Sodium molybdate dihydrate | 2.9 mg/m$^3$ | |
| | Molybdenum carbide | 11 mg/m$^3$ | |
| | Molybdenum pentachloride | 4.3 mg/m$^3$ | |
| | Molybdenum hexacarbonyl | 83 mg/m$^3$ | |

## Table 8-1. Regulations, Advisories, and Guidelines Applicable to Molybdenum

| Agency | Description | Information | Reference |
|---|---|---|---|
| NATIONAL (*cont.)* | | | |
| DOE (*cont.*) | PACs (*cont.*) | | |
| | PAC-2[d] | | |
| | Molybdenum | 10 mg/m$^3$ | |
| | Molybdenum(IV) sulfide | 66 mg/m$^3$ | |
| | Molybdenum dioxide | 1.1 mg/m$^3$ | |
| | Molybdenum trioxide | 0.75 mg/m$^3$ | |
| | Ammonium molibdate | 82 mg/m$^3$ | |
| | Diammonium dimolybdate | 29 mg/m$^3$ | |
| | Ammonium molybdate(VI) tetrahydrate | 11 mg/m$^3$ | |
| | Disodium molybdate | 1.1 mg/m$^3$ | |
| | Sodium molybdate dihydrate | 2.9 mg/m$^3$ | |
| | Molybdenum carbide | 11 mg/m$^3$ | |
| | Molybdenum pentachloride | 150 mg/m$^3$ | |
| | Molybdenum hexacarbonyl | 920 mg/m$^3$ | |
| | PAC-3[d] | | |
| | Molybdenum | 17 mg/m$^3$ | |
| | Molybdenum(IV) sulfide | 400 mg/m$^3$ | |
| | Molybdenum dioxide | 6.9 mg/m$^3$ | |
| | Molybdenum trioxide | 25 mg/m$^3$ | |
| | Ammonium molibdate | 2,700 mg/m$^3$ | |
| | Diammonium dimolybdate | 170 mg/m$^3$ | |
| | Ammonium molybdate(VI) tetrahydrate | 66 mg/m$^3$ | |
| | Disodium molybdate | 230 mg/m$^3$ | |
| | Sodium molybdate dihydrate | 210 mg/m$^3$ | |
| | Molybdenum carbide | 51 mg/m$^3$ | |
| | Molybdenum pentachloride | 880 mg/m$^3$ | |
| | Molybdenum hexacarbonyl | 5500 mg/m$^3$ | |
| EPA | AEGLs | No data | EPA 2015a |
| | Hazardous air pollutant | No data | EPA 2013a |
| NIOSH | REL (up to 10-hour TWA) | | NIOSH 2015a, 2015b |
| | Molybdenum (soluble compounds as Mo) | Not established[e] | |
| | IDLH | | |
| | Molybdenum (insoluble compounds) | 5,000 mg/m$^3$ | |
| | Molybdenum (soluble compounds) | 1,000 mg/m$^3$ | |

## Table 8-1. Regulations, Advisories, and Guidelines Applicable to Molybdenum

| Agency | Description | Information | Reference |
|---|---|---|---|
| NATIONAL (*cont.)* | | | |
| OSHA | PEL (8-hour TWA) for general industry, shipyards and construction | | OSHA 2013a, 2013b, 2014 |
| | Molybdenum (soluble compounds) | 5 mg/m$^3$ | |
| | Molybdenum (insoluble compounds as Mo; total dust) | 15 mg/m$^3$ | |
| USNRC | Annual limit on intake | | NAS 2014 |
| | $^{99}$Molybdenum compounds except oxides, hydroxides, and molybdenum disulfide | 3x10$^3$ µCi | |
| | Derived air concentration | | |
| | $^{99}$Molybdenum compounds except oxides, hydroxides, and molybdenum disulfide | 1x10$^{-6}$ µCi/mL | |
| b. Water | | | |
| EPA | Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act | No data | EPA 2013b 40 CFR 116.4 |
| | Drinking water standards and health advisories for molybdenum | | EPA 2012 |
| | 1-day health advisory for a 10-kg child | 0.08 mg/L | |
| | 10-day health advisory for a 10-kg child | 0.08 mg/L | |
| | DWEL | 0.2 mg/L | |
| | Life-time health advisory | 0.04 mg/L | |
| | National primary drinking water standards | No data | EPA 2009 |
| | National recommended water quality criteria: Human health for the consumption of | No data | EPA 2015b |
| | Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act | No data | EPA 2013c 40 CFR 117.3 |
| c. Food | | | |
| FDA | EAFUS | No data[f] | FDA 2013 |
| d. Other | | | |
| ACGIH | Carcinogenicity classification | | ACGIH 2015 |
| | Molybdenum (soluble compounds) | A3[g] | |

## Table 8-1. Regulations, Advisories, and Guidelines Applicable to Molybdenum

| Agency | Description | Information | Reference |
|---|---|---|---|
| NATIONAL (*cont.)* | | | |
| EPA | Carcinogenicity classification | No data | IRIS 2003 |
| | RfC | No data | |
| | RfD (Molybdenum) | $5x10^{-3}$ mg/kg-day | |
| | Superfund, emergency planning, and community right-to-know | No data | EPA 2014a<br>40 CFR 302.4 |
| | Effective date of toxic chemical release reporting | | EPA 2014b<br>40 CFR 372.65 |
| | Molybdenum trioxide | 01/01/1987 | |
| | TSCA chemical lists and reporting periods | No data | EPA 2014c<br>40 CFR 712.30 |
| DHHS | Carcinogenicity classification | No data | NTP 2014 |

[a]Reason for not establishing a guideline value: occurs in drinking-water at concentrations well below those of health concern.
[b]Respirable fraction; deposited in the gas-exchange region.
[c]Inhalable fraction; deposited anywhere in the respiratory tract.
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2012b).
[e]A proposed PEL TWA of 5 mg/m$^3$ for soluble compounds as molybdenum was reviewed by NIOSH in 1988. As a result, NIOSH questioned whether the proposed PEL was adequate to protect workers from recognized health hazards. Additionally, NIOSH also concluded that the documentation cited by OSHA was inadequate to support the proposed PEL (as an 8-hour TWA) of 10 mg/m$^3$ for insoluble compounds as molybdenum (NIOSH 2015b).
[f]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[g]A3: confirmed animal carcinogen with unknown relevance to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

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# 9. REFERENCES

*ACGIH. 2015. Molybdenum. In: TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 43.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect 103(7):103-112.

*Ahasan MM. 2004. Assessment of radiation dose in nuclear medicine hot lab. Iran J Radiat Res 2(2):75-78.

*AIHA. 2014. Current ERPG Values (2014). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2014%20ERPG%20Values.pdf. March 4, 2015.

*Alfa Aesar. 2015. Safety data sheet. Ammonium tetrathiomolybdate. Stock number: 43493. Printing date 10/17/2015. Alfa Aesar. https://www.alfa.com/en/content/msds/USA/43493.pdf. November 13, 2015.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies of Experimental Biology, 1987-2008, 2041.

*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, and replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

*Anderson RR. 1992. Comparison of trace elements in milk of four species. J Dairy Sci 75:3050-3055.

*Aquilio E, Spagnoli R, Seri S, et al. 1996. Trace element content in human milk during lactation of preterm newborns. Biol Trace Elem Res 51:63-70.

*Archibald JG. 1951. Molybdenum in cows' milk. J Dairy Sci 34(10):1026-1029.

*Arlauskas A, Baker RU, Bonin AM, et al. 1985. Mutagenicity of metal ions in bacteria. Environ Res 36:379-388.

+*Arrington LR, Davis GK. 1953. Molybdenum toxicity in the rabbit. J Nutr 51(2):295-304.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

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* Cited in text
+ Cited in supplemental document

*ATSDR. 2015. Molybdenum. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources. November 8, 2016.

*Bailey MR, Ansoborlo E, Guilmette RA, et al. 2007. Updating the ICRP human respiratory tract model. Radiat Prot Dosimetry 127(1-4):31-34.

+*Bandyopadhyay SK, Chatterjee K, Tiwari RK, et al. 1981. Biochemical studies on molybdenum toxicity in rats: Effects of high protein feeding. Int J Vit Nutr Res 51(4):401-409.
*Barceloux DG. 1999. Molybdenum. J Toxicol Clin Toxicol 37(2):231-237.

*Bayram E, Topcu Y, Karakaya P, et al. 2013. Molybdenum cofactor deficiency: Review of 12 cases (MoCD and review). Eur J Paediatr Neurol 17:1-6.

*Bell MCD, B. G., Lowrey RS, Wright PL. 1964. Comparison of $Mo^{99}$ metabolism in swine and cattle as affected by stable molybdenum. J Nutr 84:367-372.

*Berger GS, ed. 1994. Epidemiology of endometriosis. In: Endometriosis: Modern surgical management of endometriosis. New York, NY: Springer-Verlag, 3-7.

+*Bersenyi A, Berta E, Kadar I, et al. 2008. Effects of high dietary molybdenum in rabbits. Acta Vet Hung 56(1):41-55. 10.1556/AVet.56.2008.1.5.

*BIAC. 2013. SIDS initial assessment profile. Highly soluble molybdenum salts. Business and Industry Advisory Committee to the OECD. http://webnet.oecd.org/HPV/UI/handler.axd?id=7feeff59-de60-4000-8d08-f3c9c7770149. November 13, 2015.

*Bibr B, Lener J. 1973. Excretion of molybdenum by experimental animals. Physiol Bohemoslov 22(2):167-178.

*Bibr B, Deyl Z, Lener J, et al. 1977. Investigation of the reaction of molybdenum with collagen *in vivo*. Int J Pept Protein Res 10(3):190-196.

*Biego GH, Joyeux M, Hartemann P, et al. 1998. Determination of mineral contents in different kinds of milk and estimation of dietary intake in infants. Food Addit Contam 15(7):775-781.

*Boman A, Wahlberg JE, Hagelthorn G. 1979. Sensitizing potential of beryllium, copper and molybdenum compounds studied by the guinea pig maximization method. Contact Dermatitis 5(5):332-333. I 10.1111/j.1600-0536.1979.tb04891.x.

+*Bompart G, Pecher C, Prevot D, et al. 1990. Mild renal failure induced by subchronic exposure to molybdenum: Urinary kallikrein excretion as a marker of distal tubular effect. Toxicol Lett 52(3):293-300.

*Bougle D, Bureau F, Foucault P, et al. 1988. Molybdenum content of term and preterm human milk during the first 2 months of lactation. Am J Clin Nutr 48(3):652-654.

*Bougle D, Voirin J, Bureau F, et al. 1989. Molybdenum. Normal plasma values at delivery in mothers and newborns. Acta Paediatr Scand 78(2):319-320.

## 9. REFERENCES

*Brewer GJ, Dick RD, Grover DK, et al. 2000. Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study. Clin Cancer Res 6(1):1-10.

+*Brinkman GL, Miller RF. 1961. Influence of cage type and dietary zinc oxide upon molybdenum toxicity. Science 134(3489):1531-1532.

*Burguera JL, Burguera M, Rondon C. 2002. An on-line flow-injection microwave-assisted mineralization and a precipitation/dissolution system for the determination of molybdenum in blood serum and whole blood by electrothermal atomic absorption spectrometry. Talanta 58(6):1167-1175.

*Caldwell KL, Hartel J, Jarrett J, et al. 2005. Inductively coupled plasma mass spectrometry to measure multiple toxic elements in urine in NHANES 1999-2000. Atom Spectrosc 26(1):1-7.

*Cantone MC, De Bartolo D, Giussani A, et al. 1997. A methodology for biokinetic studies using stable isotopes: Results of repeated molybdenum investigations on a healthy volunteer. Appl Radiat Isot 48(3):333-338.

*Cantone MC, de Bartolo D, Molho N, et al. 1993. Response to a single oral test of molybdenum stable isotopes for absorption studies in humans. Physiol Meas 14(2):217-225.

*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 45:921-926.

*CCME. 1999. Canadian water quality for the protection of aquatic life: Molybdenum. Canadian environmental quality guidelines. Winnipeg, Canada: Canadian Council of Ministers of the Environment.

*CDC. 2015. Fourth national report on human exposures to environment chemicals. Updated tables, February 2015. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. National Center for Environmental Health, Division of Laboratory Science. http://ww.cdc.exposure report/. September 24, 2015.

*Chan KM, Riley JP. 1966. The determination of molybdenum in natural waters, silicates and biological materials. Anal Chim Acta 36:220-229.

*ChemIDplus. 2015. Molybdenum chloride (MoCl5). RN: 10241-05-1. ChemIDplus: A Toxnet database. Bethesda, MD: U.S. National Library of Medicine. http://chem.sis.nlm.nih.gov/chemidplus/. November 13, 2015.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

+Cook GA, Lesperance AL, Bohman VR, et al. 1966. Interrelationship of molybdenum and certain factors to the development of the molybdenum toxicity syndrome. J Anim Sci 25(1):96-101.

*Costa LG, Aschner M, Vitalone A, et al. 2004. Developmental neuropathology of environmental agents. Annu Rev Pharmacol Toxicol 44:87-110. 10.1146/annurev.pharmtox.44.101802.121424.

*Coughtrey PJ, Thorne MC. 1983. Molybdenum. In: Radionuclide distribution and terrestrial and aquatic ecosystems. A critical review of data. Rotterdam: A.A. Balkema, 351-375.

+Cox DH, Davis GK, Shirley RL, et al. 1960. Influence of excess dietary molybdenum on rat and calf liver and heart enzymes. J Nutr 70:63-68.

*Cruywagen JJ. 2000. Protonation, oligomerization, and condensation reactions of vanadate(V), molybdate(VI), and tungstate(VI). Adv Inorg Chem 49:127-182.

*Cruywagen JJ, Draaijer AG, Heyns JBB, et al. 2002. Molybdenum(VI) equilibria in different ionic media. Formation constants and thermodynamic quantities. Inorg Chim Acta 331(1):322-329. 10.1016/S0020-1693(02)00700-4.

*Dang HS, Jaiswal DD, Somasundaram S, et al. 1984. Concentrations of four essential trace elements in breast milk of mothers from two socio-economic groups: Preliminary observations. Sci Total Environ 35:85-89.

*Deltombe E, de Zoubov N, Pourbaix M. 1974. Molybdenum. In: Pourbaix M, Franklin JA, eds. Atlas of electrochemical equilibria in aqueous solutions. Houston, TX: National Association of Corrosion Engineers, 272-279.

+*Deosthale YG, Gopalan C. 1974. The effect of molybdenum levels in sorghum (*Sorghum vulgare* Pers.) on uric acid and copper excretion in man. Br J Nutr 31(3):351-355.

*DiPietro ES, Phillips DL, Paschal DC, et al. 1989. Determination of trace elements in human hair: Reference intervals for 28 elements in nonoccupationally exposed adults in the US and effects of hair treatments. Biol Trace Elem Res 22(1):83-100.

*DOE. 2012a. Table 3: PACs by CASRN (pdf). PAC Rev 27 tables - PAC data and chemical properties presented in pdf and excel tables. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 27 for Chemicals of Concern - March 2012. Oak Ridge, TN: U.S. Department of Energy. http://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-27-chemicals-concern-march-2012. March 4, 2015.

*DOE. 2012b. Protective action criteria (PAC): Chemicals with AEGLs, ERPGs, & TEELs. Definition of PACs (AEGLs, ERPGs or TEELs). Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 27 for Chemicals of Concern - March 2012. Oak Ridge, TN: U.S. Department of Energy. http://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-27-chemicals-concern-march-2012. March 24, 2015.

*DOI. 1967. Trace metals in water of the United States. A five year summary of trace metals in rivers and lakes of the United States (October 1, 1967 - September 30, 1967). Cincinnati, OH: United States Department of the Interior, Federal Water Pollution Control Administration, Division of Pollution Surveillance. PB215680.

*Doll CG, Sorensen CM, Bowyer TW, et al. 2014. Abatement of xenon and iodine emissions from medical isotope production facilities. J Environ Radioact 130:33-43.

+*Droste JH, Weyler JJ, Van Meerbeeck JP, et al. 1999. Occupational risk factors of lung cancer: A hospital based case-control study. Occup Environ Med 56(5):322-327.

*ECHA. 2015. Disodium molybdate. Physical and chemical properties. European Chemicals Agency. http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb7d44e-5b59-695c-e044-00144f67d031/DISS-9eb7d44e-5b59-695c-e044-00144f67d031_DISS-9eb7d44e-5b59-695c-e044-00144f67d031.html. November 10, 2015.

*EFSA. 2013. Scientific opinion on dietary reference values for molybdenum. EFSA panel on dietetic products, nutrition, and allergies (NDA). European Food Safety Authority. EFSA Journal 11(8):3333. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3333.pdf. November 11, 2015.

*Ek CJ, Dziegielewska KM, Habgood MD, et al. 2012. Barriers in the developing brain and neurotoxicology. Neurotoxicology 33(3):586-604. 10.1016/j.neuro.2011.12.009.

*Engel RW, Price NO, Miller RF. 1967. Copper, manganese, cobalt, and molybdenum balance in pre-adolescent girls. J Nutr 92(2):197-204.

*EPA. 1979. Human health effects of molybdenum in drinking water. U.S. Environmental Protection Agency. EPA600179006. PB292755. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000Z0FV.txt. October 2, 2015.

*EPA. 1983. Molybdenum. Method 246.2 (Atomic absorption, furnace technique). In: Methods for chemical analysis of water and wastes. U.S. Environmental Protection Agency. 246 242-241 to 246 242-242. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30000Q10.txt. October 6, 2015.

*EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600687008. PB88179874.

*EPA. 1990. Nonoccupational pesticide exposure study (NOPES). Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600390003.

*EPA. 1994. Method 200.8. Determination of trace elements in waters and wastes by inductively coupled plasma- mass spectrometry. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring Systems Laboratory, Office of Research and Development. EPA600R94111.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA630R96012.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F090004. http://water.epa.gov/drink/contaminants/upload/mcl-2.pdf. March 4, 2015.

*EPA. 2012. 2012 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf. March 4, 2015.

*EPA. 2013a. The Clean Air Act amendments of 1990 list of hazardous air pollutants. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/ttn/atw/orig189.html. March 4, 2015.

*EPA. 2013b. Subchapter D-water programs. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 116.4. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol22/pdf/CFR-2014-title40-vol22-sec116-4.pdf. March 4, 2015.

*EPA. 2013c. Subpart A - general provisions. Determination of reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 117.3. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol22/pdf/CFR-2014-title40-vol22-sec117-3.pdf. March 4, 2015.

*EPA. 2014a. Subchapter J-Superfund, emergency planning, and community right-to-know programs. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 302.4. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol28/pdf/CFR-2014-title40-vol28-sec302-4.pdf. March 4, 2015.

*EPA. 2014b. Subpart D - Specific toxic chemical listings. Chemicals and chemical categories to which this part applies. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 372.65. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol28/pdf/CFR-2014-title40-vol28-sec372-65.pdf. March 4, 2015.

*EPA. 2014c. Subpart B - Manufacturers reporting - preliminary assessment information. Chemical lists and reporting periods. U.S. Environmental Protection Agency. Code of Federal Regulations 40 CFR 712.30. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol31/pdf/CFR-2014-title40-vol31-sec712-30.pdf. April 9, 2015.

*EPA. 2015a. Final AEGLs (176). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/oppt/aegl/pubs/compiled_aegl_update09jun2015.pdf. July 23, 2015.

*EPA. 2015b. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Science and Technology. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm. July 23, 2015.

*Fairhall LT, Dunn RC, Sharpless NE, et al. 1945. The toxicity of molybdenum. Public Health Bulletin, No 293(36):52.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. January 8, 2014.

*FDA. 2014. Total diet study. Elements results summary statistics. Market baskets 2006 through 2011. College Park, MD: U.S. Food and Drug Administration. http://www.fda.gov/downloads/Food/FoodScienceResearch/TotalDietStudy/UCM184301.pdf. November 11, 2015.

+Feaster JP, Davis GK. 1959. Sulfate metabolism in rabbits on high molybdenum intake. J Nutr 67(2):319-323.

9. REFERENCES

+*Fejery P, Toth P, Kobor A. 1983. The effect of fluorine and molybdenum on some of the mechanical characteristics of the hard tissues in rats kept on a low and on a normal protein diet. J Int Assoc Dent Child 14:9-14.

+*Fell BF, Dinsdale D, El-Gallad TT. 1979. Gut pathology of rats dosed with tetrathiomolybdate. J Comp Pathol 89(4):495-514.

*Fitzgerald D, Nicholson R, Regoli L. 2008. Environmental management criteria for molybdenum and selenium: A review relevant to the mining industry. University of British Columbia. https://circle.ubc.ca/bitstream/handle/2429/9191/10Fitzgerald%20Nicholson%20Paper.pdf?sequence=1. September 24, 2015.

*Fomon SJ. 1966. Body composition of the infant: Part 1: The male reference infant. In: Faulkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35(Suppl 5):1169-1175.

*FOREGS. 2005. Statistical data of analytical results. In: Geochemical Atlas of Europe, Part 1: Background information, methodology and maps. Forum of European Geological Surveys. http://weppi.gtk.fi/publ/foregsatlas/article.php?id=15. May 24, 2016.

+*Franke KW, Moxon AL. 1937. The toxicity of orally ingested arsenic, selenium, tellurium, vanadium, and molybdenum. J Pharmacol Exp Ther 61:89-102.

*Friel JK, Andrews WL, Jackson SE, et al. 1999. Elemental composition of human milk from mothers of premature and full-term infants during the first 3 months of lactation. Biol Trace Elem Res 67:225-247.

+*Fungwe TV, Buddingh F, Demick DS, et al. 1990. The role of dietary molybdenum on estrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats. Nutr Res 10(5):515-524.

*Fungwe TV, Buddingh F, Yang MT, et al. 1989. Hepatic, placental, and fetal trace elements following molybdenum supplementation during gestation. Biol Trace Elem Res 22(2):189-199.

*Gibson DP, Brauninger R, Shaffi HS, et al. 1997. Induction of micronuclei in Syrian hamster embryo cells: Comparison to results in the SHE cell transformation assay for National Toxicology Program test chemicals. Mutat Res 1(2):61-70.

*Gimenez I, Garay R, Alda JO. 1993. Molybdenum uptake through the anion exchanger in human erythrocytes. Pflugers Archiv 424(3-4):245-249.

+*Gipp WF, Pond WG, Smith SE. 1967. Effects of level of dietary copper, molybdenum, sulfate and zinc on bodyweight gain, hemoglobin and liver copper storage of growing pigs. J Anim Sci 26(4):727-730.

*Giussani A. 2008. A recycling systemic model for the biokinetics of molybdenum radionuclides. Sci Total Environ 404(1):44-55. 10.1016/j.scitotenv.2008.06.019.

*Giussani A, Arogunjo AM, Claire Cantone M, et al. 2006. Rates of intestinal absorption of molybdenum in humans. Appl Radiat Isot 64(6):639-644. 10.1016/j.apradiso.2005.12.013.

*Giussani A, Cantone MC, Hollriegl V, et al. 2007. Modelling urinary excretion of molybdenum after oral and intravenous administration of stable tracers. Radiat Prot Dosimetry 127(1-4):136-139. 10.1093/rpd/ncm263.

*Giussani A, Hansen C, Nusslin F, et al. 1995. Application of thermal ionization mass spectrometry to investigations of molybdenum absorption in humans. Int J Mass Spectrom Ion Phys 148:171-178.

*Giussani A, Roth P, Werner E, et al. 1998. A biokinetic model for molybdenum radionuclides: New experimental results. Radiat Prot Dosimetry 79:367-370.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(2):65-71.

*Goldberg S, Johnston CT, Suarez DL, et al. 2008. Mechanism of molybdenum adsorption on soils and soil minerals evaluated using vibrational spectroscopy and surface complexation modeling. In: Barnett MO, Kent DB, eds. Developments in earth and environmental sciences. Elsevier B.V., 235-266. http://www.ars.usda.gov/sp2UserFiles/Place/20360500/pdf_pubs/P2162.pdf. November 11, 2015.

*Goldberg S, Lesch SM, Suarez DL. 2002. Predicting molybdenum absorption by soils using soil chemical parameters in the constant capacitance model. Soil Sci Soc Am J 66:1836-1842.

*Gould L, Kendall NR. 2011. Role of the rumen in copper and thiomolybdate absorption. Nutr Res Rev 24(2):176-182. 10.1017/s0954422411000059.

+*Gray LF, Daniel LJ. 1954. Some effects of excess molybdenum on the nutrition of the rat. J Nutr 53(1):43-51.

*Greenwood NN, A. E. 1997. Chapter 23. Chromium, molybdenum and tungsten. In: Chemistry of the elements. Burlington, MA: Elsevier Butterworth-Heinemann, 1002-1039.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.

*Hadjimarkos DM. 1967. Effect of trace elements in drinking water on dental caries. J Pediatr 70(6):967-969.

*Heitland P, Koster HD. 2006. Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS. J Trace Elem Med Biol 20(4):253-262. 10.1016/j.jtemb.2006.08.001.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

+*Howell JM, Shunxiang Y, Gawthorne JM. 1993. Effect of thiomolybdate and ammonium molybdate in pregnant guinea pigs and their offspring. Res Vet Sci 55(2):224-230.

*HSDB. 2009a. Molybdenum, compounds. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. November 12, 2015.

*HSDB. 2009b. Molybdenum disulfide. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. November 12, 2015.

*HSDB. 2009c. Molybdenum trioxide. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. November 12, 2015.

*HSDB. 2010. Molybdenum. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. September 24, 2015.

+*Hunt CE, Navia JM. 1973. Effects of Sr, Mo, Li and B on developing teeth and other tissues of neonatal rats. Trace Substances in Environmental Health VI, 159-168.

+*Hunt CE, Navia JM. 1975. Pre-eruptive effects of Mo, B, Sr and F on dental caries in the rat. Arch Oral Biol 20(8):497-501.

*IARC. 2015. Agents classified by the IARC monographs. Volumes 1–113. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications_Vol1-113.pdf. July 30, 2015.

*ICRP. 1994. Molybdenum. In: Age-dependent doses to members of the public from intake of radionuclides: Part 2 ingestion dose coefficients. ICRP publication 67. Tarrytown, NY: International Commission on Radiological Protection. Elsevier Science, Inc, 45-47.

*ICRP. 2012. Compendium of dose coefficients based on ICRP publication 60. ICRP Publication 119. Annals of the ICRP. International Commission on Radiological Protection. Vol. 41 (Supplement 1).

*IMOA. 2015. IMOA. 2015. Health, safety & environment. Background chemistry of molybdenum. Molybdenum analysis. International Molybdenum Association. http://www.imoa.info/HSE/environmental_data/chemistry/molybdenum_analysis.php. September 23, 2015.

*IRIS. 2003. Molybdenum (CASRN 7439-98-7). Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/0425.htm. July 23, 2015.

*Iyengar GV, Kollmer WE, Bowen HJM. 1978. The elemental composition of human tissues and body fluids. In: Iyengar GV, Kollmer WE, Bowen HJM, eds. The elemental composition of human tissues and body fluids. New York: Verlag Chemie.

+*Jeter MA, Davis GK. 1954. The effect of dietary molybdenum upon growth, hemoglobin, reproduction and lactation of rats. J Nutr 54(2):215-220.

+*Johnson HL, Miller RF. 1961. The interrelationships between dietary molybdenum, copper, sulfate, femur alkaline phosphatase activity and growth of the rat. J Nutr 75:459-464.

+*Johnson RH, Little JW, Bickley HC. 1969. Some effects of molybdenum on connective tissue. J Dent Res 48(6):1290-1295.

*Kanematsu N, Hara M, Kada T. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

*Kawabuchi K, Kuroda R. 1969. A combined ion-exchange spectrophotometric method for the determination of molybdenum and tungsten in sea water. Anal Chim Acta 46:23-30.

*Kearns GL, Abdel-Rahman SM, Alander SW, et al. 2003. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157-1167. 10.1056/NEJMra035092.

*Kiriyama T, Kuroda R. 1984. Application of anion-exchange techniques to the determination of traces of molybdenum in sea-water. Talanta 31(6):472-474.

+*Kline RD, Corzo MA, Hays VW, et al. 1973. Related effects of copper, molybdenum and sulfide on performance, hematology and copper stores of growing pigs. J Anim Sci 37(4):936-941.

*Komatsu Y, Sadakata I, Ogra Y, et al. 2000. Excretion of copper complexed with thiomolybdate into the bile and blood in LEC rats. Chem Biol Interact 124:217-231.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29(18):4430-4433.

*Koster R, Vieluf D, Kiehn M, et al. 2000. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet 356(9245):1895-1897. 10.1016/s0140-6736(00)03262-1.

+*Koval'skiy VV, Yarovaya GA, Shmavonyan DM. 1961. Changes of purine metabolism in man and animals under conditions of molybdenum biogeochemical provinces [Translation]. Zhurnal Obshchey Biologii 22(3):179-191.

*Krachler M, Li FS, Rossipal E, et al. 1998. Changes in the concentrations of trace elements in human milk during lactation. J Trace Elem Med Biol 12:159-176.

*Krachler M, Rossipal E, Micetic-Turk D. 1999. Concentrations of trace elements in arterial and venous umbilical cord sera. Trace Elem Electrolytes 16(1):46-52.

*Kucera J, Bencko V, Papoyova A, et al. 2000. 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 9:171-175.

*Lee A, Beck L, Markovich D. 2000. The human renal sodium sulfate cotransporter (SLC13A1;hNaSi-1) cDNA and gene: Organization, chromosomal localization, and functional characteristics. Genomics 70(3):354-363.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*Lener J, Bibr B. 1979. Biliary excretion and tissue distribution of pentavalent and hexavalent molybdenum in rats. Toxicol Appl Pharmacol 51(2):259-264.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*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):172-178. 10.1016/j.fertnstert.2014.09.020.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

*Lyubimov AV, Mercieca MD, Smith AC, et al. 2003. Oral developmental toxicity study of ammonium tetrathiomolybdate (NSC-714598) in rabbits. Birth Defects Res Part A Clin Mol Teratol 67(5):328.

*Lyubimov AV, Merceica MD, Tomaszewski JE, et al. 2002. The developmental toxicity of tetrathiomolybdate (TTM, NSC-714598) and protective effects of copper in rats. Teratology 65(6):309.

+*Lyubimov AV, Smith JA, Rousselle SD, et al. 2004. The effects of tetrathiomolybdate (TTM, NSC-714598) and copper supplementation on fertility and early embryonic development in rats. Reprod Toxicol 19(2):223-233. 10.1016/j.reprotox.2004.07.006.

*Markovich D, Aronson PS. 2007. Specificity and regulation of renal sulfate transporters. Annu Rev Physiol 69:361-375.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

+*Meeker JD, Rossano MG, Protas B, et al. 2008. Cadmium, lead, and other metals in relation to semen quality: Human evidence for molybdenum as a male reproductive toxicant. Environ Health Perspect 116(11):1473-1479. 10.1289/ehp.11490.

*Meeker JD, Rossano MG, Protas B, et al. 2009. Multiple metals predict prolactin and thyrotropin (TSH) levels in men. Environ Res 109:869-873.

+*Meeker JD, Rossano MG, Protas B, et al. 2010. Environmental exposure to metals and male reproductive hormones: Circulating testosterone is inversely associated with blood molybdenum. Fertil Steril 93(1):130-140. 10.1016/j.fertnstert.2008.09.044.

*Mendel RR, Bittner F. 2006. Cell biology of molybdenum. Biochim Biophys Acta 1763(7):621-635. 10.1016/j.bbamcr.2006.03.013.

*Mendel RR, Kruse T. 2012. Cell biology of molybdenum in plants and humans. Biochim Biophys Acta 1823(9):1568-1579. 10.1016/j.bbamcr.2012.02.007.

+*Mendy A, Gasana J, Vieira ER. 2012. Urinary heavy metals and associated medical conditions in the US adult population. Int J Environ Health Res 22(2):105-118. 10.1080/09603123.2011.605877.

*Menezes LM, Campos LC, Quintao CC, et al. 2004. Hypersensitivity to metals in orthodontics. Am J Orthod 126(1):58-64. 10.1016/s0889540604000836.

*Miekeley N, Carneiro MTW, Silveira CLP. 1998. How reliable are human hair reference intervals for trace elements? Sci Total Environ 218(1):9-17.

*Miller RF, Price NO, Engel RW. 1956. Added dietary inorganic sulfate and its effect upon rats fed molybdenum. J Nutr 60(4):539-547.

*Mills CF, El-Gallad TT, Bremner I. 1981a. Effects of molybdate, sulfide, and tetrathiomolybdate on copper metabolism in rats. J Inorg Biochem 14(3):189-207.

*Mills CF, El-Gallad TT, Bremner I, et al. 1981b. Copper and molybdenum absorption by rats given ammonium tetrathiomolybdate. J Inorg Biochem 14(2):163-175.

+*Mills CF, Monty KJ, Ichihara A, et al. 1958. Metabolic effects of molybdenum toxicity in the rat. J Nutr 65(1):129-142.

*Momcilovic B. 1999. A case report of acute human molybdenum toxicity from a dietary molybdenum supplement - a new member of the "*Lucor metallicum*" family. Arh Hig Rada Toksikol 50(3):289-297.

+Montenegro MA, Sanchez Negrette M, Gimeno EJ, et al. 2002. Effects of high molybdenum intake on 1,2-dimethylhydrazine-induced intestinal tumors in rats. Biocell 26(3):339-345.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5(6):485-527.

*Murer HI, Markovich D, Biber J. 1994. Renal and small intestinal sodium-dependent symporters of phosphate and sulphate. J Exp Biol 196:167-181.

+*Murray FJ, Sullivan FM, Tiwary AK, et al. 2013. 90-Day subchronic toxicity study of sodium molybdate dihydrate in rats. Regul Toxicol Pharmacol 70(3):579-588. 10.1016/j.yrtph.2013.09.003.

+*Murray JF, Tyl RW, Sullivan FM, et al. 2014. Developmental toxicity study of sodium molybdate dihydrate administered in the diet to Sprague Dawley rats. Reprod Toxicol 49:202-208. 10.1016/j.reprotox.2014.09.001.

*Nagra MS, Pallah BS, Sahota GPS, et al. 1992. A study of trace elements in scalp hair and fingernails of industrial workers of Ontario, Canada. J Radioanal Nucl Chem 162(2):283-288.

+Nakadaira H, Endoh K, Yamamoto M, et al. 1995. Distribution of selenium and molybdenum and cancer mortality in Niigata, Japan. Arch Environ Health 50(5):374-380. 10.1080/00039896.1995.9935970.

*Nakanishi Y, Iida S, Ueoka-Nakanishi H, et al. 2013. Exploring dynamics of molybdate in living animal cells by a genetically encoded FRET nanosensor. PLoS ONE 8(3):e58175. 10.1371/journal.pone.0058175.

*Nakata R, Okazaki S, Hori T, et al. 1983. Collection of trace metals from sea water by column electrolysis for neutron activation - γ-spectrometry. Anal Chim Acta 149:67-75.

*NAS. 1977. Nutrient requirements of rabbits fed ad libitum (percentage or amount per kg of diet). In: Nutrient requirements of rabbits, second revised edition, 1977. National Academy of Sciences. National Research Council, 14. http://www.nap.edu/catalog/35/nutrient-requirements-of-rabbits-second-revised-edition-1977. September 24, 2015.

*NAS. 1995. Nutrient requirements of laboratory animals, fourth revised edition, 1995. National Academy of Sciences. National Research Council, 11-102. http://www.nap.edu/catalog/4758/nutrient-requirements-of-laboratory-animals-fourth-revised-edition-1995. September 24, 2015.

*NAS. 2001. Molybdenum and copper. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academy of Sciences, National Academies Press. http://www.nap.edu/catalog/10026.html. September 24, 2015.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC, 15-35.

*Nederbragt H. 1980. The influence of molybdenum on the copper metabolism of the rat at different Cu levels of the diet. Br J Nutr 43(2):329-338.

*Nederbragt H. 1982. Changes in the distribution of copper and molybdenum after Mo administration and subsequent additional oral or intraperitoneal Cu administration to rats. Br J Nutr 48(2):353-364.

*NIOSH. 1994a. Elements in blood or tissue: Method 8005, Issue 2. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/8005.pdf. October 2, 2015.

*NIOSH. 1994b. Metals in urine: Methods 8310, Issue 2. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Health and Safety. http://www.cdc.gov/niosh/docs/2003-154/pdfs/8310.pdf. October 2, 2015.

*NIOSH. 2003a. Elements by ICP (nitric/perchloric acid ashing): Method 7300, Issue 3. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7300.pdf. October 2, 2015.

*NIOSH. 2003b. Elements by ICP (Aqua Regia Ashing): Method 7301, Issue 1. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7301.pdf. October 2, 2015.

*NIOSH. 2003c. Elements by ICP (Hot Block/HCl/HNO3 Ashing): Method 7303, Issue 1. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7303.pdf. October 2, 2015.

*NIOSH. 2003d. Elements on wipes: Methods 9102, Issue 1. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/9102.pdf. October 2, 2015.

*NIOSH. 2006. International Chemical Safety Cards (ICSC): Molybdenum. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/ipcsneng/neng1003.html. September 24, 2015.

*NIOSH. 2014a. Elements by ICP (microwave digestion): Method 7302, Issue 1. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7302.pdf. October 2, 2015.

*NIOSH. 2014b. Elements by ICP (microwave digestion): Methods 7304, Issue 1. NIOSH Manual of Analytical Methods (NMAM), fourth edition. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/docs/2003-154/pdfs/7304.pdf. October 2, 2015.

*NIOSH. 2015a. Molybdenum. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/npgd0433.html. July 31, 2015.

*NIOSH. 2015b. Appendix D - Substances with no established RELs. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/nengapdxd.html. July 31, 2015.

*NIOSH. 2015c. International Chemical Safety Cards (ICSC). Sodium molybdate. CAS #: 7631-95-0. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/ipcsneng/neng1010.html. November 13, 2015.

*Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat Res 31(3):185-190.

*NJDOH. 2009. Hazardous substance fact sheet. Ammonium molybdate. New Jersey Department of Health. http://nj.gov/health/eoh/rtkweb/documents/fs/0105.pdf. November 13, 2015.

*NOAA. 2015. CAMEO Chemicals version 2.4.2. Molybdenum trioxide. CAS Number: 1313-27-5. National Oceanic and Atmospheric Administration. http://cameochemicals.noaa.gov/chemical/8862. November 12, 2015.

*Novotny JA, Turnlund JR. 2006. Molybdenum kinetics in men differ during molybdenum depletion and repletion. J Nutr 136(4):953-957.

*Novotny JA, Turnlund JR. 2007. Molybdenum intake influences molybdenum kinetics in men. J Nutr 137(1):37-42.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council. National Academy Press. PB93216091.

+*NTP. 1997. NTP technical report on the toxicology and carcinogenesis studies of molybdenum trioxide (CAS No. 1313-27-5) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park: National Toxicology Program. NTP TR 462. NIH Publication No. 97-3378. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr462.pdf. September 24, 2015.

*NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation.

*NTP. 2014. Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/. April 9, 2015.

*NTP. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf. October 2, 2015.

*Nusbaum RE, Butt EM, Gilmour TC, et al. 1965. Relation of air pollutants to trace metals in bone. Arch Environ Health 10:227-232.

*Ogawa HI, Shibahara T, Iwata H, et al. 1994. Genotoxic activities *in vivo* of cobaltous chloride and other metal chlorides as assayed in the *Drosophila* wing spot test. Mutat Res 320(1-2):133-140.

*Olivier P, Marzin D. 1987. Study of the genotoxic potential of 48 inorganic derivatives with the SOS chromotest. Mutat Res 189(3):263-270.

*OSHA. 2013a. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1910.1000. http://www.gpo.gov/fdsys/pkg/CFR-2014-title29-vol6/pdf/CFR-2014-title29-vol6-sec1910-1000.pdf. March 4, 2015.

*OSHA. 2013b. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z - Shipyards. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1915.1000. http://www.gpo.gov/fdsys/pkg/CFR-2013-title29-vol7/pdf/CFR-2013-title29-vol7-sec1915-1000.pdf. March 4, 2015.

*OSHA. 2014. Appendix A to Part 1926.55. 1970 American Conference of Governmental Industrial Hygienists' threshold limit values of airborne contaminants. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1926.55. http://www.gpo.gov/fdsys/pkg/CFR-2014-title29-vol8/pdf/CFR-2014-title29-vol8-sec1926-55.pdf. March 4, 2015.

+*Ostrom CA, Van Reen R, Miller CW. 1961. Changes in the connective tissue of rats fed toxic diets containing molybdenum. J Dent Res 40:520-528. I 10.1177/00220345610400032001.

+*Ott HC, Prior C, Herold M, et al. 2004. Respiratory symptoms and bronchoalveolar lavage abnormalities in molybdenum exposed workers. Wien Klin Wochenschr 116(Suppl 1):25-30.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Pande R, Kumar R, Singh SP, et al. 2002. Molybdenum in rat tissue. Hum Exp Toxicol 21(1):33-35.

+*Pandey R, Singh SP. 2002. Effects of molybdenum on fertility of male rats. Biometals 15(1):65-72.

*Parma E. 2009. The supply of the medical radioisotope Tc-99m/Mo-99. Recent shortages call for action in developing a domestic production capability. Albuquerque, NM: Sandia National Laboratories. SAND2009-6898P. http://local.ans.org/trinity/files/parma091106.pdf. November 13, 2015.

+*Parry NM, Phillippo M, Reid MD, et al. 1993. Molybdenum-induced changes in the epiphyseal growth plate. Calcif Tissue Int 53(3):180-186.

*Paschal DC, Dipietro ES, Phillips DL, et al. 1989. Age dependence of metals in hair in a selected USA population. Environ Res 48(1):17-28.

*Paschal DC, Ting BG, Morrow JC, et al. 1998. Trace metals in urine of United States residents: Reference range concentrations. Environ Res 76(1):53-59.

*Patnaik P. 1999. Molybdenum hexacarbonyl. In: A comprehensive guide to the hazardous properties of chemical substances. New York, NY: John Wiley & Sons, Inc., 591.

*Pennington JA, Jones JW. 1987. Molybdenum, nickel, cobalt, vanadium, and strontium in total diets. J Am Diet Assoc 87(12):1644-1650.

+*Peredo HA, Andrade V, Donoso AS, et al. 2013. Sodium molybdate prevents hypertension and vascular prostanoid imbalance in fructose-overloaded rats. Auton Autacoid Pharmacol 33(3-4):43-48. 10.1111/aap.12010.

*Prakash R. 1989. Glycogen in the muscles of rats poisoned by metal ions. Arhiv Hig Rada Toksikol 40(4):363-366.

+*Rana SV, Chauhan A. 2000. Influence of methionine and zinc on liver collagen in molybdenotic rats. Biol Trace Elem Res 73:85-91.

+Rana SV, Kumar A. 1979. Enzyme modification in rat kidney after individual and combined treatments with molybdenum and copper. Ind Health 17(1):11-19.

+Rana SV, Kumar A. 1980a. Enzymological studies on the liver of rats fed with molybdenum and copper. Toxicol Lett 6(3):163-166.

+*Rana SV, Kumar A. 1980b. On the lipid accumulation in molybdenotic rats. Indian J Exp Biol 18(7):726-728.

+*Rana SV, Kumar A. 1980c. Proteins, lipids and carbohydrates in the liver and kidney of rats after molybdenum and copper treatment. Bull Environ Contam Toxicol 25(1):146-152.

+Rana SV, Kumar A. 1981. Effect of molybdenum and copper on key enzymes of rat kidney with special reference to physiological antagonism. Toxicol Lett 7(6):393-397.

+*Rana SV, Kumar A. 1983. Liver and kidney function in molybdenum and copper poisoning. Arhiv Hig Rada Toksikol 34(1):9-13.

+*Rana SV, Prakash R. 1986. Collagen in the liver of metal fed rats. Exp Pathol 29(3):193-195.

+*Rana SV, Kumar A, Bhardwaj NG. 1980. Lipids in the liver and kidney of rats, fed various heavy metals. Acta Anat 108(3):402-412.

+*Rana SVS, Prakash R, Kumar A, et al. 1985. A study of glycogen in the liver of metal-fed rats. Toxicol Lett 29(1):1-4.

*Regoli L, Van Tilborg W, Heijerick D, et al. 2012. The bioconcentration and bioaccumulation factors for molybdenum in the aquatic environment from natural environmental concentrations up to the toxicity boundary. Sci Total Environ 435-436:96-106.

*Reid HJ, Bashammakh AA, Goodall PS, et al. 2008. Determination of iodine and molybdenum in milk by quadrupole ICP-MS. Talanta 75:189-197.

*Richards P. 1989. Technetium-99m: The early days. In: DOE's International symposium on technetium in chemistry and nuclear medicine, Padova, Italy, 5-8 Sep 1989. Upton, NY: Brookhaven National Laboratory, Medical Department. BNL-43197. CONF-8909193-1. ON: DE89017817. http://www.osti.gov/scitech/servlets/purl/5612212. November 15, 2015.

*Riley JP, Taylor D. 1968. The use of chelating ion exchange in the determination of molybdenum and vanadium in sea water. Anal Chim Acta 41:173-175.

+*Robinson GA, Valli VE, McSherry BJ, et al. 1969. The survival of DF32 P-labelled erythrocytes in molybdate-fed rabbits. Can J Physiol Pharmacol 47(4):343-347.

*Robinson MF, McKenzie JM, Tomson CD, et al. 1973. Metabolic balance of zinc, copper, cadmium, iron, molybdenum and selenium in young New Zealand women. Br J Nutr 30(2):195-205.

+*Rodriguez Flores CR, Puga MP, Wrobel K, et al. 2011. Trace elements status in diabetes mellitus type 2: Possible role of the interaction between molybdenum and copper in the progress of typical complications. Diabetes Res Clin Pract 91(3):333-341. 10.1016/j.diabres.2010.12.014.

*Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718.

*Rosoff B, Spencer H. 1964. Fate of molybdenum-99 in man. Nature 202:410-411.

*Rossman TG, Molina M, Meyer LW. 1984. The genetic toxicology of metal compounds: I. Induction of λ prophage in E Coli $WP2_S(\lambda)$. Environ Mutagen 6(1):59-69.

*Rossman TG, Molina M, Meyer L, et al. 1991. Performance of 133 compounds in the λ prophage induction endpoint of the microscreen assay and a comparison with S. *typhimurium* mutagenicity and rodent carcinogenicity assays. Mutat Res 260:349-367.

*RTECS. 2009. Molybdenum, RTECS# QA4680000, CAS# 7439-98-7. Registry of Toxic Effects of Chemical Substances, National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh-rtecs/qa476940.html. September 17, 2015.

*RTECS. 2013. Molybdate(2-), tetrathioxo-, diammonium, (T-4)-. RTECS number: QA4668250. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc. November 13, 2015.

*Ryan J, McKillen M, Mason J. 1987. Sulphate/molybdate interactions: *in vivo* and *in vitro* studies on the group VI oxyanion transport system in ovine renal tubule epithelial cells. Ann Vet Res 18(1):47-55.

*Sarmiento-Gonzalez A, Marchante-Gayon JM, Tejerina-Lobo JM, et al. 2008. High-resolution ICP-MS determination of Ti, V, Cr, Co, Ni, and Mo in human blood and urine of patients implanted with a hip or knee prosthesis. Anal Bioanal Chem 391(7):2583-2589. 10.1007/s00216-008-2188-4.

+*Sasmal N, Kar NC, Mukherjee D, et al. 1968. The effect of molybdenum on ascorbic acid metabolism in rats. Biochem J 106(3):633-637.

*Saunders NR, Ek CJ, Habgood MD, et al. 2008. Barriers in the brain: A renaissance? Trends Neurosci 31(6):279-286. 10.1016/j.tins.2008.03.003.

*Saunders NR, Liddelow SA, Dziegielewska KM. 2012. Barrier mechanisms in the developing brain. Front Pharmacol 3(10.3389/fphar.2012.00046):Article 46. 10.3389/fphar.2012.00046.

*Scheuplein R, Charnley G, Dourson M. 2002. Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35(3):429-447.

+*Schroeder HA, Kraemer LA. 1974. Cardiovascular mortality, municipal water, and corrosion. Arch Environ Health 28:303-311.

+Schroeder HA, Mitchener M. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch Environ Health 23(2):102-106.

*Schroeder HA, Balassa JJ, Tipton IH. 1970. Essential trace metals in man: Molybdenum. J Chronic Dis 23:481-499.

*Schwarz G, Mendel RR, Ribbe MW. 2009. Molybdenum cofactors, enzymes and pathways. Nature 460:839-847.

*Sebenik RF, Burkin AR, Dorfler RR, et al. 2012. Molybdenum and molybdenum compounds. In: Ullmann's encyclopedia of industrial chemistry. John Wiley and Sons, Inc. http://onlinelibrary.wiley.com/doi/10.1002/14356007.a16_655/abstract. November 13, 2015.

+*Shirai S, Suzuki Y, Yoshinaga J, et al. 2010. Maternal exposure to low-level heavy metals during pregnancy and birth size. J Environ Sci Health A 45(11):1468-1474. 10.1080/10934529.2010.500942.

+*Shiue I, Hristova K. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. Hypertens Res 37(12):1075-1081. 10.1038/hr.2014.121.

*Sievers E, Dorner K, Garbe-Schonberg D, et al. 2001a. Molybdenum metabolism: Stable isotope studies in infancy. J Trace Elem Med Biol 15(2-3):185-191. 10.1016/s0946-672x(01)80065-1.

*Sievers E, Oldigs HD, Dorner K, et al. 2001b. Molybdenum balance studies in premature male infants. Eur J Pediatr 160(2):109-113.

*Sigma-Aldrich. 2015e. Safety data sheet. Version 4.6. Product number: 234842. Molybdenum(IV) sulfide. Sigma-Aldrich. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=234842&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F234842%3Flang%3Den. November 12, 2015.

*Sigma-Aldrich. 2015a. Safety data sheet. Version 5.5. Product number: 241938. Molybdenum(V) chloride. Sigma-Aldrich. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=241938&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F241938%3Flang%3Den. November 12, 2015.

*Sigma-Aldrich. 2015b. Safety data sheet. Version 4.5. Product number: 431346. Zammonium molybdate tetrahydrate. Sigma-Aldrich. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=431346&brand=SIAL&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Fsial%2F431346%3Flang%3Den. November 12, 2015.

*Sigma-Aldrich. 2015c. Safety data sheet. Version 4.8. Product number: 323446. Ammonium tetrathiomolybdate. Sigma-Aldrich. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=323446&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F323446%3Flang%3Den. November 13, 2015.

*Sigma-Aldrich. 2015d. Safety data sheet. Version 4.5. Product number: 277908. Ammonium molybdate. Sigma-Aldrich. http://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=277908&brand=ALDRICH&PageToGoToURL=http%3A%2F%2Fwww.sigmaaldrich.com%2Fcatalog%2Fproduct%2Faldrich%2F277908%3Flang%3Den. November 12, 2015.

*Singh I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in *Saccharomyces cerevisiae*. Mutat Res 117:149-152.

*Smedley PL, Cooper DM, Lapworth DJ. 2014. Molybdenum distributions and variability in drinking water from England and Wales. Environ Monit Assess 186:6403-6416. 10.107/s10661-014-3863-x.

*Sorensen LB, Archambault M. 1963. Visualization of the liver by scanning with $Mo^{99}$ (molybdate) as tracer. J Lab Clin Med 62:330-340.

+*Spence JA, Suttle NF, Wenham G, et al. 1980. A sequential study of the skeletal abnormalities which develop in rats given a small dietary supplement of ammonium tetrathiomolybdate. J Comp Pathol 90(1):139-153.

*Stiefel EI. 2011. Molybdenum compounds. In: Kirk-Othmer encyclopedia of chemical techology. John Wiley & Sons. 10.1002/0471238961.1315122519200905.a01.pub3

*Sumino K, Hayakawa K, Shibata T, et al. 1975. Heavy metals in normal Japanese tissues: Amounts of 15 heavy metals in 30 subjects. Arch Environ Health 30(10):487-494.

*Tejada-Jimenez M, Galvan A, Fernandez E. 2011. Algae and humans share a molybdate transporter. Proc Natl Acad Sci USA 108(16):6420-6425. 10.1073/pnas.1100700108.

*Tejada-Jimenez M, Llamas A, Sanz-Luque E, et al. 2007. A high-affinity molybdate transporter in eukaryotes. Proc Natl Acad Sci USA 104(50):20126-20130. 10.1073/pnas.0704646104.

*Telfer SB, Kendall NR, Illingworth DV, et al. 2004. Molybdenum toxicity in cattle: An underestimated problem. Cattle Pract 12:259-263.

*The White House. 2012. Fact sheet: Encouraging reliable supplies of molybdenum99 produced without highly enriched uranium. Washington, DC: The White House. https://www.whitehouse.gov/the-press-office/2012/06/07/fact-sheet. May 24, 2016.

*Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

*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):963-972.

*Tipton IH, Cook MJ. 1963. Trace elements in human tissue Part II. Adult subjects from the United States. Health Phys 9:103-145.

*Tipton IH, Schroeder HA, Perry HM, et al. 1965. Trace elements in human tissue. Part III. Subjects from Africa, the Near and Far East and Europe. Health Phys 11:403-451.

*Tipton IH, Stewart PL, Martin PG. 1966. Trace elements in diets and excreta. Health Phys 12(12):1683-1689.

*Titenko-Holland N, Shao J, Zhang L, et al. 1998. Studies on the genotoxicity of molybdenum salts in human cells *in vitro* and mice *in vivo*. Environ Mol Mutagen 32(3):251-259.

*TRI 13 2015. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. May 15, 2015.

*Turnlund JR, Keyes WR. 2000. Dietary molybdenum. Effect on copper absorption, excretion, and status in young men. In: Trace elements in man and animals. New York, NY: Plenum Publishers, 951-953.

*Turnlund JR, Keyes WR. 2004. Plasma molybdenum reflects dietary molybdenum intake. J Nutr Biochem 15(2):90-95. 10.1016/j.jnutbio.2003.10.003.

*Turnlund JR, Keyes WR, Peiffer GL. 1993. Isotope ratios of molybdenum determined by thermal ionization mass spectrometry for stable isotope studies of molybdenum metabolism in humans. Anal Chem 65(13):1717-1722.

*Turnlund JR, Keyes WR, Peiffer GL. 1995a. Molybdenum absorption, excretion, and retention studied with stable isotopes in young men at five intakes of dietary molybdenum. Am J Clin Nutr 62(4):790-796.

*Turnlund JR, Keyes WR, Peiffer GL, et al. 1995b. Molybdenum absorption, excretion, and retention studied with stable isotopes in young men during depletion and repletion. Am J Clin Nutr 61(5):1102-1109.

*Ulitzur S, Barak M. 1988. Detection of genotoxicity of metallic compounds by the bacterial bioluminescence test. J Biolumin Chemilumin 2:95-99.

*USGS. 1964. Public water supplies of the 100 largest cities in the United States, 1962. Geological survey water-Supply paper 1812. Washington, DC: U.S. Geological Survey, United States Department of the Interior. http://pubs.usgs.gov/wsp/1812/report.pdf. October 2, 2015.

*USGS. 1997. Methods of analysis by the U.S. Geological Survey. National water quality laboratory - Determination of molybdenum in water by graphite furnace atomic absorption spectrophotometry. U.S. Geological Survey, U.S. Department of the Interior. Open-File Report 97-198. http://pubs.usgs.gov/of/1997/0198/report.pdf. October 2, 2015.

*USGS. 2006. Review of trace element blank and replicate data collected in ground and surface water for the National Water-Quality Assessment Program, 1991-2002. U.S. Geological survey, U.S. Department of the Interior.

9. REFERENCES

*USGS. 2011. Trace elements and radon in groundwater across the United States, 1992-2003. Scientific Investigations Report 2011-5059. U.S. Geological Survey, U.S. Department of the Interior. http://pubs.usgs.gov/sir/2011/5059/pdf/sir2011-5059_report-covers_508.pdf. November 13, 2015.

*USGS. 2015a. 2013 Minerals yearbook. Molybdenum [advance release]. U.S. Geological Survey, U.S. Department of the Interior. http://minerals.usgs.gov/minerals/pubs/commodity/molybdenum/myb1-2013-molyb.pdf. October 2, 2015.

*USGS. 2015b. Molybdenum. Mineral commodity summaries, January 2015. U.S. Geological Survey, U.S. Department of the Interior. http://minerals.usgs.gov/minerals/pubs/commodity/molybdenum/index.html#mcs. November 24, 2015.

*USNRC. 2014. Part 20–Standards for protection against radiation. Appendix B to Part 20–Annual limits on intake (ALIs) and derived air concentrations (DACs) of radionuclides for occupational exposure; effluent concentrations; concentrations for release of sewerage. U.S. Nuclear Regulatory Commission. Code of Federal Regulations 10 CFR 20, Appendix B. http://www.gpo.gov/fdsys/pkg/CFR-2014-title10-vol1/pdf/CFR-2014-title10-vol1-part20-appB.pdf. November 6, 2015.

*USNRC. 2015. Molybdenum-99 production and its impact on the medical community. United States Nuclear Regulatory Commission. http://www.nrc.gov/reading-rm/doc-collections/commission/slides/2015/20150414/palestro-20150414.pdf. January 14, 2015.

*USNRC. 2016a. Part 20- Standards for protection against radiation. Subpart A to Subpart O. U.S. Nuclear Regulatory Commission. Code of Federal Regulations 10 CFR 20. http://www.nrc.gov/reading-rm/doc-collections/cfr/part020/full-text.html. May 24, 2016.

*USNRC. 2016b. Part 35- Medical use of byproduct material. U.S. Nuclear Regulatory Commission. Code of Federal Regulations 10 CFR 35. http://www.nrc.gov/reading-rm/doc-collections/cfr/part035/full-text.html. May 24, 2016.

+*Valli VE, McCarter A, McSherry BJ, et al. 1969. Hematopoiesis and epiphyseal growth zones in rabbits with molybdenosis. Am J Vet Res 30(3):435-445.

*Van Noorden R. 2013. The medical testing crisis. With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors. Nature (London) New Biol 504:202-204.

+*Van Reen R. 1959. The specificity of the molybdate-sulfate interrelationship in rats. J Nutr 68(2):243-250.

+*Van Reen R, Williams MA. 1956. Studies on the influence of sulfur compounds on molybdenum toxicity in rats. Arch Biochem Biophys 63(1):1-8.

+*Van Reen R, Ostrom CA, Berzinskas VJ. 1962. Studies of the possible cariostatic effect of sodium molybdate. Arch Oral Biol 7:351-356.

+*Vazquez-Salas RA, Lopez-Carrillo L, Menezes-Filho JA, et al. 2014. Prenatal molybdenum exposure and infant neurodevelopment in Mexican children. Nutr Neurosci 17(2):72-80. 10.1179/1476830513y.0000000076.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483.

*Vyskocil A, Viau C. 1999. Assessment of molybdenum toxicity in humans. J Appl Toxicol 19(3):185-192.

*Wahl B, Reichmann D, Niks D, et al. 2010. Biochemical and spectroscopic characterization of the human mitochondrial amidoxime reducing components hmARC-1 and hmARC-2 suggests the existence of a new molybdenum enzyme family in eukaryotes. J Biol Chem 285(48):37847-37859. 10.1074/jbc.M110.169532.

+*Walravens PA, Moure-Eraso R, Solomons CC, et al. 1979. Biochemical abnormalities in workers exposed to molybdenum dust. Arch Environ Health 34(5):302-308.

*Wang S, Ge H, Sun S, et al. 2015. A new molybdenum nitride catalyst with rhombohedral $MoS_2$ structure for hydrogenation applications. J Am Chem Soc 137:4815-4822.

*Welsh JA, Bigles CI, Valderrabano A. 2015. Future U.S. supply of Mo-99 production through fission based LEU/LEU technology. J Radioanal Nucl Chem 305:9-12.

*Werner E, Giussani A, Heinrichs U, et al. 1998. Biokinetic studies in humans with stable isotopes as tracers. Part 2: Uptake of molybdenum from aqueous solutions and labelled foodstuffs. Isotopes Environ Health Stud 34(3):297-301. 10.1080/10256019808234063.

*Werner E, Roth P, Heinrichs U, et al. 2000. Internal biokinetic behaviour of molybdenum in humans studied with stable isotopes as tracers. Isotopes Environ Health Stud 36(2):123-132. 10.1080/10256010008032938.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

*WHO. 2010. WHO guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. September 9, 2014.

*WHO. 2011. Guidelines for drinking-water quality. Geneva, Switzerland: World Health Organization. http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf?ua=1. September 9, 2014.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advance treatise. Volume II: The elements Part A. New York, NY: Academic Press, 1-247.

+*Widjajakusuma MC, Basrur PK, Robinson GA. 1973. Thyroid function in molybdenotic rabbits. J Endocrinol 57(3):419-424.

+*Williams MA, Van Reen R. 1956. Molybdenum toxicity in the rat. Proc Soc Exp Biol Med 91(4):638-641.

*WDNR. 2013. Caledonia groundwater molybdenum investigation- Southeast Wisconsin, January 2013. Wisconsin Department of Natural Resources. PUB-WA 1625. http://dnr.wi.gov/files/PDF/pubs/WA/WA1625.pdf. November 24, 2015.

+Yang MT, Yang SP. 1989. Effect of molybdenum supplementation on hepatic trace elements and enzymes of female rats. J Nutr 119(2):221-227.

*Yoo YC, Lee SK, Yang JY, et al. 2002. Organ distribution of heavy metals in autopsy material from normal Korean. J Health Sci 48(2):186-194.

+*Yorita Christensen KL. 2013. Metals in blood and urine, and thyroid function among adults in the United States 2007-2008. Int J Hyg Environ Health 216(6):624-632. I 10.1016/j.ijheh.2012.08.005.

*Yoshida M, Ota S, Fukunaga K, et al. 2006. Serum molybdenum concentration in healthy Japanese adults determined by inductively coupled plasma-mass spectrometry. J Trace Elem Med Biol 20(1):19-23. 10.1016/j.jtemb.2005.10.003.

*Zeiger E, Anderson B, Haworth S, et al. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 21:2-141.

*Zeisler R, Greenberg RR, Stone SF. 1988. Radiochemical and instrumental neutron activation analysis procedures for the determination of low level trace elements in human livers. J Radioanal Nucl Chem 124(1):47-63.

*Zeng Y, Feng W, Li J, et al. 2014. A prospective study concerning the relationship between metal allergy and post-operative pain following total hip and knee arthroplasty. Int Orthop 38(11):2231-2236. 10.1007/s00264-014-2367-1.

+*Zhai XW, Zhang YL, Qi Q, et al. 2013. Effects of molybdenum on sperm quality and testis oxidative stress. Syst Biol Reprod Med 59(5):251-255. 10.3109/19396368.2013.791347.

+*Zhang Y-L, Liu F-J, Chen X-L, et al. 2013. Dual effects of molybdenum on mouse oocyte quality and ovarian oxidative stress. Syst Biol Reprod Med 59(6):312-318. 10.3109/19396368.2013.826296. http://www.tandfonline.com/doi/abs/10.3109/19396368.2013.826296. 2015/09/24.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12(1):29-34.

9. REFERENCES

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# 10. GLOSSARY

**Absorption—**The taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure—**Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption—**The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ($K_{oc}$)—**The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio (Kd)—**The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD)—**Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a $BMD_{10}$ would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

**Benchmark Dose Model—**A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

**Bioconcentration Factor (BCF)—**The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers—**Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

**Cancer Effect Level (CEL)—**The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen—**A chemical capable of inducing cancer.

**Case-Control Study—** A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

**Case Report—**Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

**Case Series—**Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

**Ceiling Value—**A concentration that must not be exceeded.

**Chronic Exposure—**Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Cohort Study—**A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

**Cross-sectional Study—**A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

**Data Needs—**Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

**Developmental Toxicity—**The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship—**The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

**Embryotoxicity and Fetotoxicity—**Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

**Environmental Protection Agency (EPA) Health Advisory—**An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Epidemiology—**Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**Genotoxicity—**A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life—**A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

**Immediately Dangerous to Life or Health (IDLH)—**A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

**Immunologic Toxicity—**The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**Immunological Effects—**Functional changes in the immune response.

**Incidence—**The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure—**Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

**Lethal Concentration$_{(LO)}$ ($LC_{LO}$)—**The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration$_{(50)}$ ($LC_{50}$)—**A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose$_{(LO)}$ ($LD_{Lo}$)—**The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose$_{(50)}$ ($LD_{50}$)—**The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time$_{(50)}$ ($LT_{50}$)—**A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)—**The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects—**Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations—**Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)—**An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)—**A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity—**State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

**Mortality—**Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen—**A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy—**The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity—**The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

**No-Observed-Adverse-Effect Level (NOAEL)—**The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ($K_{ow}$)—**The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)—**A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**Organophosphate or Organophosphorus Compound—**A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)—**An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

**Pesticide—**General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics—**The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

**Pharmacokinetic Model—**A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model—**A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model—**Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence—**The number of cases of a disease or condition in a population at one point in time.

**Prospective Study—**A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

**$q_1$*—**The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The $q_1$* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/$m^3$ for air).

**Recommended Exposure Limit (REL)—**A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/$m^3$ or ppm.

**Reference Dose (RfD)—**An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)—**The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity—**The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study—**A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk—**The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

**Risk Factor—**An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio—**The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

**Short-Term Exposure Limit (STEL)—**A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**Standardized Mortality Ratio (SMR)—**A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity—**This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen—**A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)—**An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)—**An average exposure within a given time period.

**Toxic Dose$_{(50)}$ (TD$_{50}$)—**A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicokinetic—**The absorption, distribution, and elimination of toxic compounds in the living organism.

**Uncertainty Factor (UF)—**A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

**Xenobiotic—**Any substance that is foreign to the biological system.

# APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 8
Species: Mouse

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] mg molybdenum/$m^3$

Reference: NTP. 1997. Toxicology and carcinogenicity studies of molybdenum trioxide (CAS No. 1313-27-5) in F344/N rats and $B6C3F_1$ mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC. NT PTR 462.

Experimental design: Groups of male and female F344/N rats and B6C3F1 mice (50/sex/species/group) were exposed to target concentrations of 0, 10, 30, or 100 mg/$m^3$ molybdenum trioxide (0, 6.7, 20, and 67 mg Mo/$m^3$) 6 hours/day, 5 days/week for 106 (rats) or 105 (mice) weeks; actual concentrations were within 15% of the target level. The average particle sizes (mass median aerodynamic diameter) (and geometric standard deviation) were 1.5 (1.8), 1.6 (1.8), and 1.7 (1.8) μm for the 6.7, 20, and 67 mg/$m^3$ concentrations, respectively. The following parameters were used to assess toxicity: twice daily cage-side observations, body weights (weekly for 12 weeks, at 15 weeks, monthly thereafter, and at termination), and histopathological examination of major tissues and organs. In addition, bone density and femoral curvature studies were conducted in 10 animals/sex/species/group.

Effect noted in study and corresponding doses: No significant alterations in survival rates or body weight gain and no toxicologically significant alterations in bone density or curvature were found. Non-neoplastic lesions were only observed in the nose, larynx, and lungs; a summary of the type of lesions and incidences is presented in Table A-1. The severity of the respiratory lesions was concentration-related. Significant increases in the incidence of alveolar/bronchiolar carcinoma and/or adenoma were observed in mice: carcinoma in male mice at ≥6.7 mg/$m^3$, adenoma or carcinoma (combined) in male mice at 6.7 and 20 mg/$m^3$, adenoma in female mice at ≥20 and 67 mg/$m^3$, and adenoma or carcinoma (combined) in female mice at 67 mg/$m^3$. In rats, the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was increased in males; however, the incidences (0/50, 1/49, 1/49, 4/60) were within the range of historical controls and NTP considered this to be equivocal evidence of carcinogenic activity.

## Table A-1. Incidence of Non-Neoplastic Respiratory Tract Lesions in Rats and Mice Exposed to Molybdenum Trioxide for 2 Years

| | Concentration (mg molybdenum/$m^3$) | | | |
|---|---|---|---|---|
| | 0 | 6.7 | 20 | 67 |
| Male rats | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 2/50 | 7/49 | 48/49[a] | 49/50[a] |
| Squamous metaplasia of epiglottis | 0/49 | 11/48[a] | 16/49[a] | 39/49[a] |
| Chronic lung inflammation in alveolus | 2/50 | 3/50 | 25/50[a] | 47/50[a] |
| Female rats | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 1/48 | 13/49[a] | 50/50[a] | 50/50[a] |
| Hyaline degeneration of nasal olfactory epithelium | 39/48 | 47/49[b] | 50/50[a] | 50/50[a] |
| Squamous metaplasia of epiglottis | 0/49 | 18/49[a] | 29/49[a] | 49/50[a] |
| Chronic lung inflammation | 14/50 | 13/50 | 43/50[a] | 49/50[a] |
| Male mice | | | | |
| Nasal suppurative inflammation | 2/50 | 6/50 | 10/49[b] | 8/50[b] |
| Nasal olfactory epithelium atrophy | 3/50 | 5/50 | 3/49 | 10/50[b] |
| Hyaline degeneration of nasal respiratory epithelium | 11/50 | 13/50 | 11/49 | 41/50[a] |
| Squamous metaplasia of epiglottis | 0/50 | 26/49[a] | 37/48[a] | 49/50[a] |
| Laryngeal hyperplasia | 1/50 | 3/49 | 6/48 | 41/50 |
| Histiocyte infiltration in the lungs | 2/50 | 16/50[a] | 9/49[b] | 9/50[b] |
| Alveolar epithelial metaplasia | 0/50 | 32/50[a] | 36/49[a] | 49/50[a] |
| Female mice | | | | |
| Hyaline degeneration of nasal respiratory epithelium | 26/49 | 23/50 | 28/49 | 48/49[a] |
| Hyaline degeneration of nasal olfactory epithelium | 22/49 | 14/50 | 14/49 | 36/49[a] |
| Squamous metaplasia of epiglottis | 1/49 | 36/50[a] | 43/49[a] | 49/50[a] |
| Laryngeal hyperplasia | 1/49 | 1/50 | 7/49 | 35/50 |
| Alveolar epithelial metaplasia | 2/50 | 26/50[a] | 39/49[a] | 46/49[b] |

[a]Significantly different from controls; p≤0.01.
[b]Significantly different from controls; p≤0.05.

Source: NTP 1997

Dose and end point used for MRL derivation: The MRL was based on a BMCL of 0.19 mg molybdenum/$m^3$ for squamous metaplasia of the epiglottis in female mice

[ ] NOAEL [ ] LOAEL [X] BMCL

The incidence data (Table A-1) for respiratory tract lesions, which had significant increases in incidence at ≥6.7 mg/$m^3$ (squamous metaplasia of the epiglottis in male and female rats and mice, hyaline

degeneration of the nasal respiratory and olfactory epithelium in female rats, histiocyte infiltration in the lungs in male mice, and alveolar epithelial metaplasia in male and female mice), were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMC) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all lesion types, a BMR of 10% was used. Since the incidence of hyaline degeneration in the olfactory epithelium of female rats was essentially the same response level across groups, the data were not modeled since they provide limited information on the dose-response relationship. The incidence data for histiocyte infiltration in the lungs did not fit any of the available dichotomous models. The model prediction for the other end points are presented in Tables A-2 through A-8 and the fits of the selected models are presented in Figures A-1 through A-7. Although the data for squamous metaplasia of the epiglottis in female mice fit several BMD models, the high incidence in the lowest molybdenum group (72%) decreases the certainty in the modeling results.

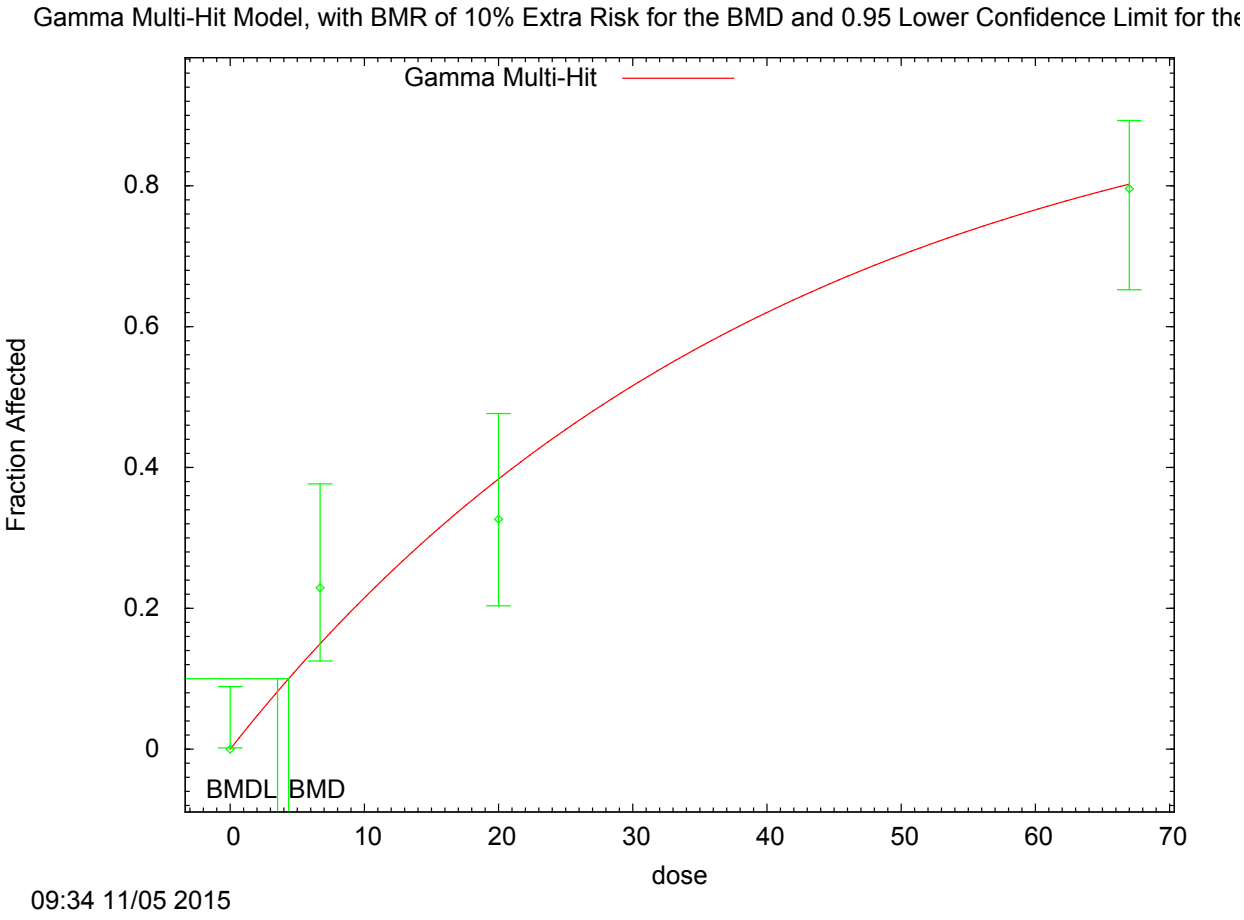
## Table A-2. Model Predictions for Squamous Metaplasia of the Epiglottis in Male Rats Exposed to Molybdenum Trioxide (NTP 1997)

| | | | $\chi^2$ | Scaled residuals[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Model | DF | $\chi^2$ | Goodness of fit p-value[a] | Dose below BMC | Dose above BMC | Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
| ***Gamma[c,d]*** | ***3*** | ***3.07*** | ***0.38*** | ***0.00*** | ***1.55*** | ***1.55*** | ***167.98*** | ***4.36*** | ***3.53*** |
| Logistic | 2 | 9.63 | 0.01 | 1.53 | 0.95 | -2.48 | 181.94 | ND | ND |
| LogLogistic[e] | 2 | 3.56 | 0.17 | 0.00 | 0.98 | -1.42 | 170.75 | 3.809 | 2.23 |
| LogProbit[e] | 2 | 11.85 | 0.01 | 3.00 | -1.39 | 3.00 | 174.85 | ND | ND |
| Multistage (1-degree)[f] | 3 | 3.07 | 0.38 | 0.00 | 1.55 | 1.55 | 167.98 | 4.36 | 3.53 |
| Multistage (2-degree)[f] | 3 | 3.07 | 0.38 | 0.00 | 1.55 | 1.55 | 167.98 | 4.36 | 3.53 |
| Multistage (3-degree)[f] | 3 | 3.07 | 0.38 | 0.00 | 1.55 | 1.55 | 167.98 | 4.36 | 3.53 |
| Probit | 2 | 9.35 | 0.01 | 1.62 | 0.92 | -1.38 | 181.23 | ND | ND |
| Weibull[c] | 3 | 3.07 | 0.38 | 0.00 | 1.55 | 1.55 | 167.98 | 4.36 | 3.53 |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-1. Fit of Gamma Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Male Rats Exposed to Molybdenum Trioxide (mg/m$^3$)**



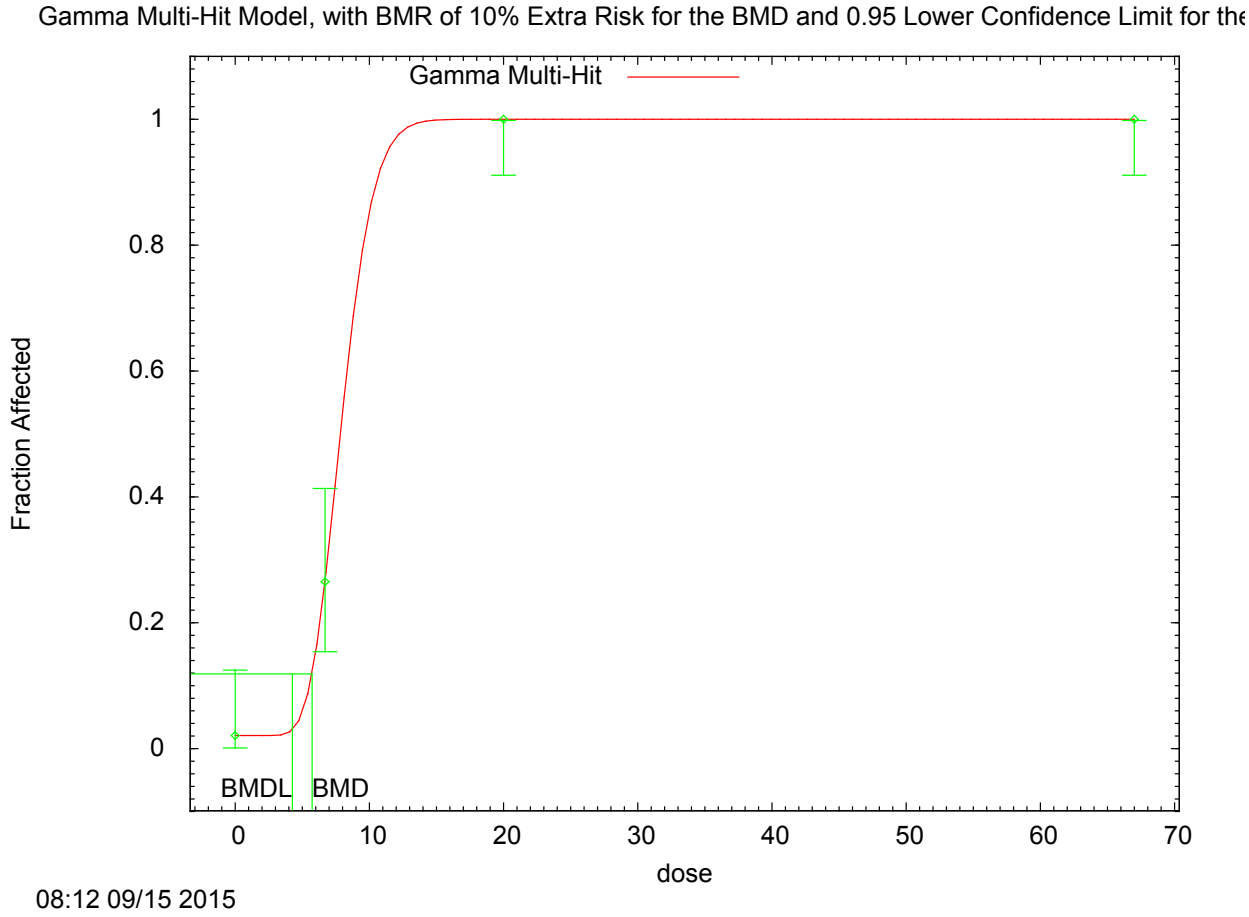
## Table A-3. Model Predictions for Hyaline Degeneration of the Nasal Respiratory Epithelium in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Dose above BMC | Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| ***Gamma[c,d]*** | ***2*** | ***0.00*** | ***1.00*** | ***0.00*** | ***0.00*** | ***0.01*** | ***70.42*** | ***5.73*** | ***4.26*** |
| Logistic | 2 | 0.40 | 0.82 | 0.44 | -0.17 | 0.44 | 70.97 | 4.47 | 3.46 |
| LogLogistic[e] | 2 | 0.00 | 1.00 | 0.00 | 0.00 | 0.00 | 70.42 | 6.30 | 4.83 |
| LogProbit[e] | 1 | 0.00 | 1.00 | 0.00 | 0.00 | 0.00 | 72.42 | 6.03 | 4.73 |
| Multistage (1-degree)[f] | 2 | 18.41 | 0.00 | 0.28 | -3.28 | -3.28 | 95.80 | ND | ND |
| Multistage (2-degree)[f] | 2 | 2.81 | 0.24 | 0.20 | -1.21 | -1.21 | 74.57 | 3.40 | 2.54 |
| Multistage (3-degree)[f] | 2 | 0.02 | 0.99 | 0.01 | -0.05 | 0.15 | 70.46 | 4.77 | 2.39 |
| Probit | 2 | 0.48 | 0.79 | 0.49 | -0.28 | 0.49 | 71.03 | 4.09 | 3.12 |
| Weibull[c] | 1 | 0.00 | 1.00 | 0.00 | 0.00 | 0.00 | 72.42 | 5.10 | 3.58 |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-2. Fit of Gamma Model to Data on Incidence of Hyaline Degeneration of the Nasal Respiratory Epithelium in Female Rats Exposed to Molybdenum Trioxide (mg/m$^3$)**



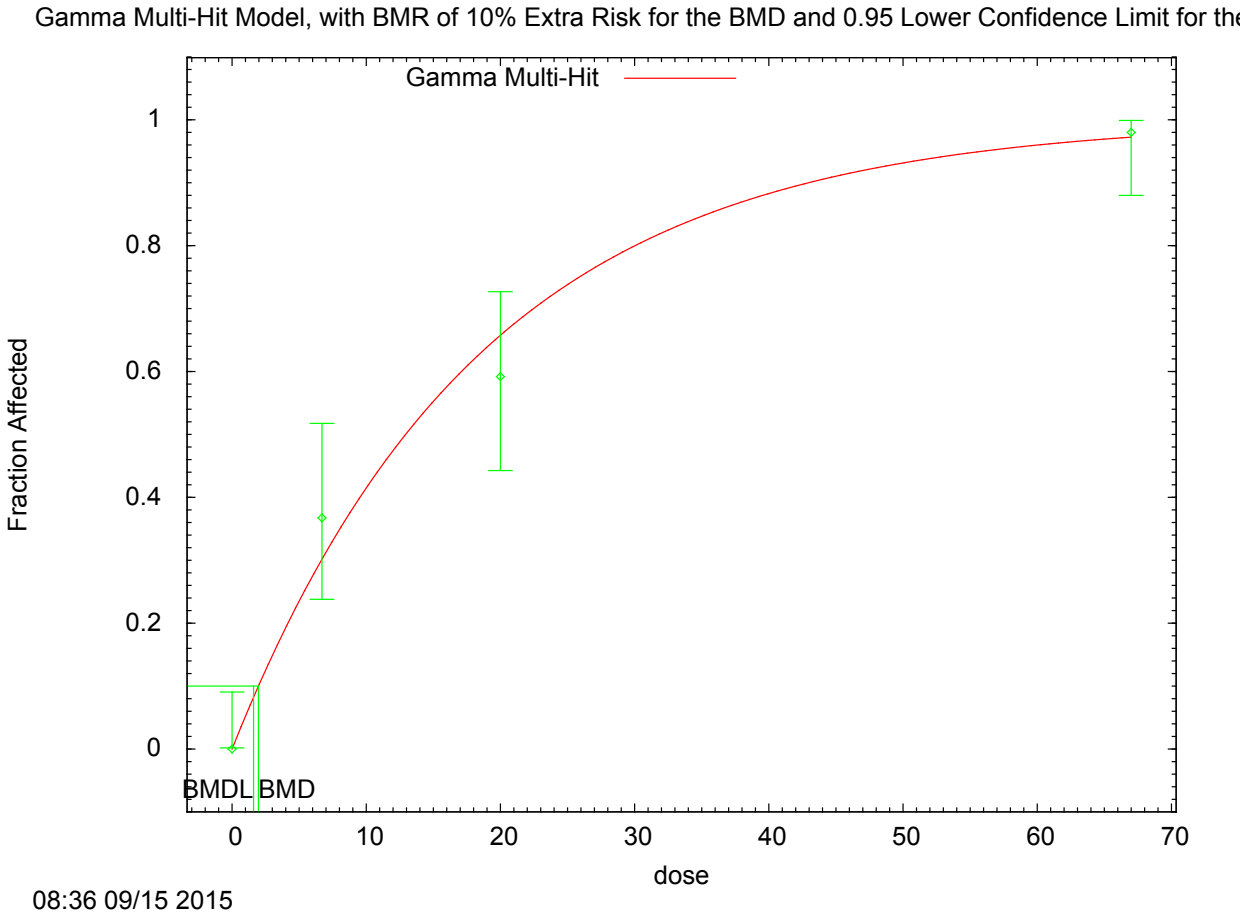
## Table A-4. Model Predictions for Squamous Metaplasia of the Epiglottis in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Scaled residuals[b] Dose above BMC | Scaled residuals[b] Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| ***Gamma[c,d]*** | ***3*** | ***2.05*** | ***0.56*** | ***0.00*** | ***1.00*** | ***1.00*** | ***144.51*** | ***1.97*** | ***1.60*** |
| Logistic | 2 | 15.55 | 0.00 | -2.67 | 2.17 | -2.67 | 163.85 | ND | ND |
| LogLogistic[e] | 2 | 5.02 | 0.08 | 0.00 | 0.82 | -1.58 | 150.04 | ND | ND |
| LogProbit[e] | 3 | 4.97 | 0.17 | 0.00 | 1.25 | -1.69 | 147.37 | 3.27 | 2.67 |
| Multistage (1-degree)[f] | 3 | 2.05 | 0.56 | 0.00 | 1.00 | 1.00 | 144.51 | 1.97 | 1.60 |
| Multistage (2-degree)[f] | 2 | 2.05 | 0.36 | 0.00 | 1.04 | 1.04 | 146.50 | 1.99 | 1.60 |
| Multistage (3-degree)[f] | 2 | 1.98 | 0.37 | 0.00 | 1.11 | 1.11 | 146.42 | 2.02 | 1.61 |
| Probit | 2 | 17.51 | 0.00 | -2.85 | 2.00 | -2.85 | 166.05 | ND | ND |
| Weibull[c] | 3 | 2.05 | 0.56 | 0.00 | 1.00 | 1.00 | 144.51 | 1.97 | 1.60 |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-3. Fit of Gamma Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Female Rats Exposed to Molybdenum Trioxide (mg/m$^3$)**



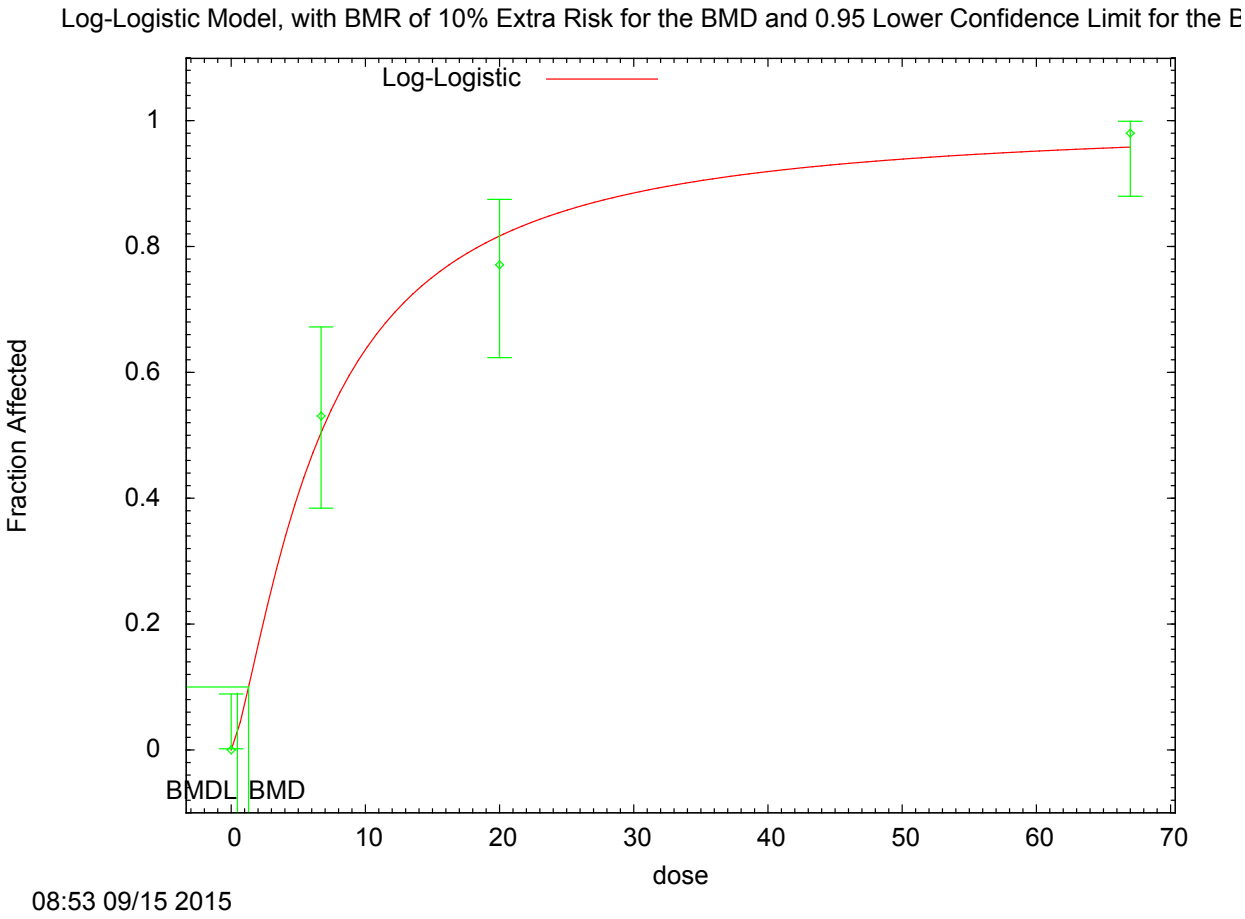
## Table A-5. Model Predictions for Squamous Metaplasia of the Epiglottis in Male Mice Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Scaled residuals[b] Dose above BMC | Scaled residuals[b] Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| Gamma[c] | 3 | 5.55 | 0.14 | 0.00 | 1.60 | -1.65 | 135.46 | 1.30 | 1.06 |
| Logistic | 2 | 61.77 | 0.00 | -3.19 | 2.80 | -6.62 | 164.85 | ND | ND |
| ***LogLogistic[d,e]*** | ***2*** | ***1.42*** | ***0.49*** | ***0.00*** | ***0.34*** | ***-0.85*** | ***134.73*** | ***1.29*** | ***0.47*** |
| LogProbit[d] | 3 | 2.74 | 0.43 | 0.00 | 1.11 | 1.19 | 133.83 | 2.10 | 1.69 |
| Multistage (1-degree)[f] | 3 | 5.55 | 0.14 | 0.00 | 1.60 | -1.65 | 135.46 | 1.30 | 1.06 |
| Multistage (2-degree)[f] | 3 | 5.55 | 0.14 | 0.00 | 1.60 | -1.65 | 135.46 | 1.30 | 1.06 |
| Multistage (3-degree)[f] | 3 | 5.55 | 0.14 | 0.00 | 1.60 | -1.65 | 135.46 | 1.30 | 1.06 |
| Probit | 2 | 90.03 | 0.00 | -3.63 | 2.65 | -8.24 | 171.89 | ND | ND |
| Weibull[c] | 3 | 5.55 | 0.14 | 0.00 | 1.60 | -1.65 | 135.46 | 1.30 | 1.06 |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-4. Fit of LogLogistic Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Male Mice Exposed to Molybdenum Trioxide (mg/m$^3$)**



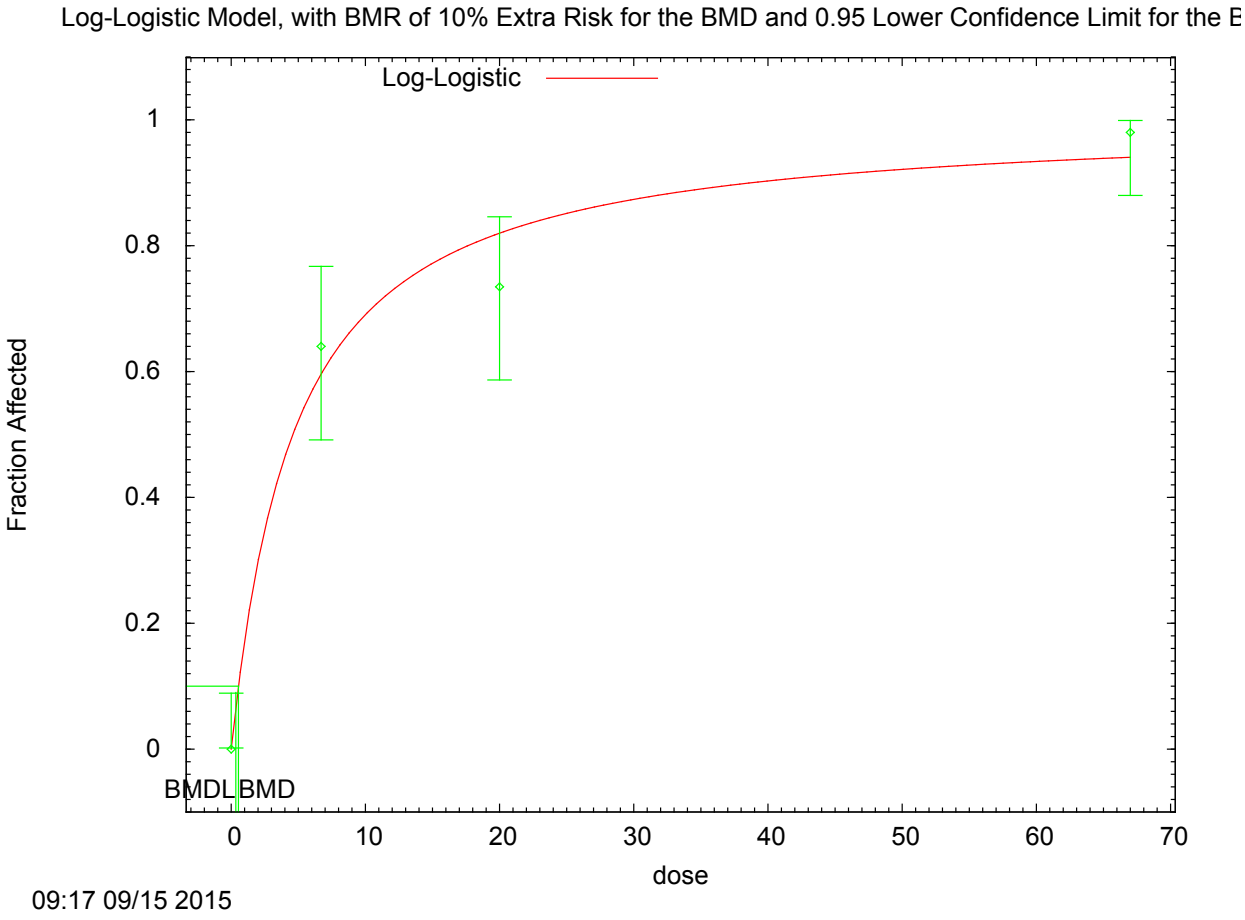
## Table A-6. Model Predictions for Alveolar Epithelial Metaplasia in Male Mice Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Scaled residuals[b] Dose above BMC | Scaled residuals[b] Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| Gamma[c] | 3 | 15.12 | 0.00 | 0.00 | 2.91 | 2.91 | 146.34 | ND | ND |
| Logistic | 2 | 44.97 | 0.00 | -3.71 | 3.74 | -4.41 | 177.74 | ND | ND |
| ***LogLogistic[d,e]*** | ***2*** | ***4.20*** | ***0.12*** | ***0.00*** | ***0.63*** | ***-1.55*** | ***140.27*** | ***0.54*** | ***0.35*** |
| LogProbit[d] | 3 | 10.82 | 0.01 | 0.00 | 2.15 | -2.43 | 143.68 | ND | ND |
| Multistage (1-degree)[f] | 3 | 15.12 | 0.00 | 0.00 | 2.91 | 2.91 | 146.34 | ND | ND |
| Multistage (2-degree)[f] | 3 | 15.12 | 0.00 | 0.00 | 2.91 | 2.91 | 146.34 | ND | ND |
| Multistage (3-degree)[f] | 3 | 15.12 | 0.00 | 0.00 | 2.91 | 2.91 | 146.34 | ND | ND |
| Probit | 2 | 54.33 | 0.00 | -4.10 | 3.67 | -4.84 | 183.04 | ND | ND |
| Weibull[c] | 3 | 15.12 | 0.00 | 0.00 | 2.91 | 2.91 | 146.34 | ND | ND |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The only model that provided adequate fit to the data was the Log-Logistic model.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-5. Fit of LogLogistic Model to Data on Incidence of Alveolar Epithelial Metaplasia in Male Mice Exposed to Molybdenum Trioxide (mg/m$^3$)**



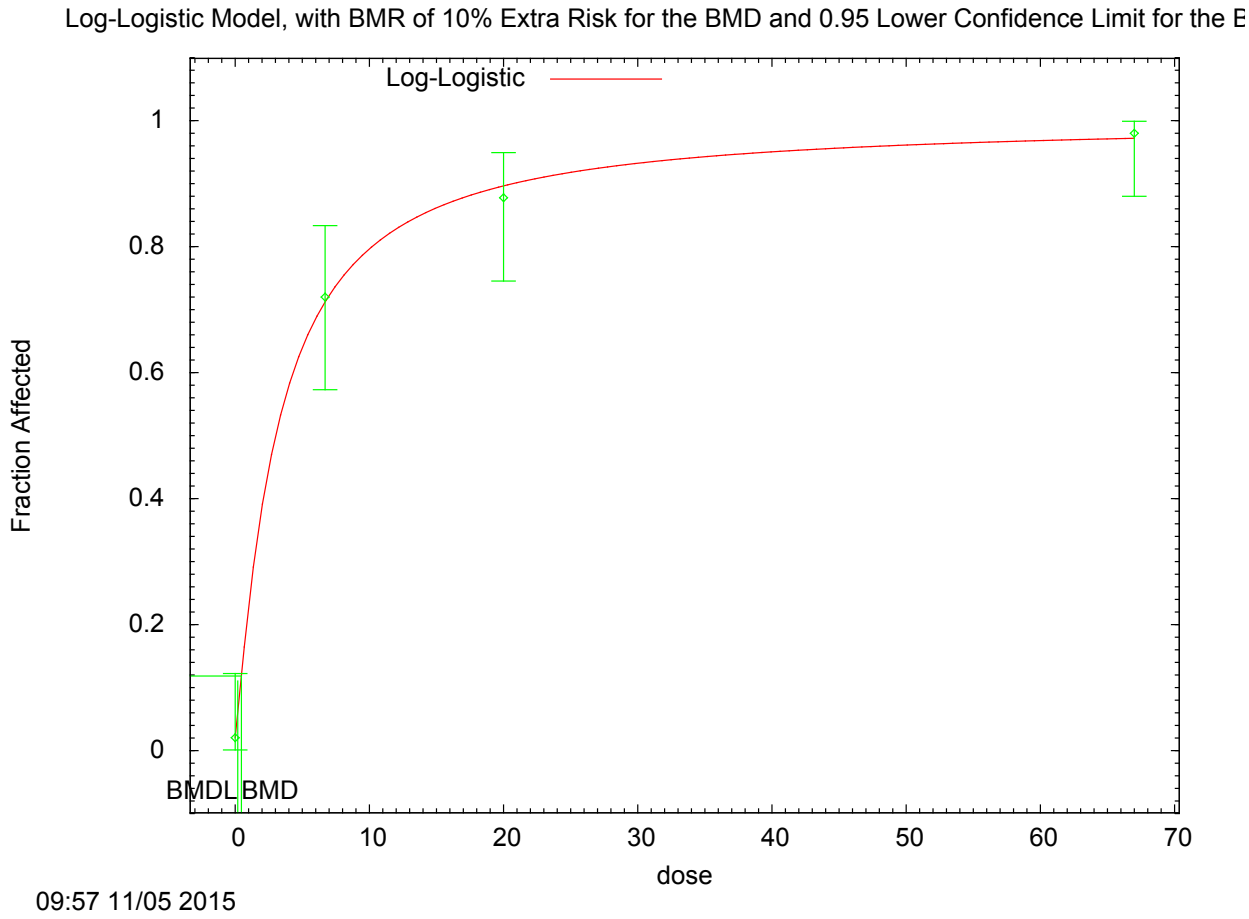
## Table A-7. Model Predictions for Squamous Metaplasia of the Epiglottis in Female Mice Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Scaled residuals[b] Dose above BMC | Scaled residuals[b] Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| Gamma[c] | 2 | 57.98 | 0.00 | -0.29 | 2.32 | -7.21 | 131.51 | ND | ND |
| Logistic | 2 | 413.85 | 0.00 | -3.51 | 3.42 | -19.74 | 159.94 | ND | ND |
| ***LogLogistic[d,e]*** | ***1*** | ***0.32*** | ***0.57*** | ***0.00*** | ***0.15*** | ***-0.41*** | ***121.62*** | ***0.46*** | ***0.19*** |
| LogProbit[d] | 2 | 5.96 | 0.05 | -0.08 | 1.26 | -1.71 | 123.72 | ND | ND |
| Multistage (1-degree)[f] | 2 | 57.98 | 0.00 | -0.29 | 2.32 | -7.21 | 131.51 | ND | ND |
| Multistage (2-degree)[f] | 2 | 57.98 | 0.00 | -0.29 | 2.32 | -7.21 | 131.51 | ND | ND |
| Multistage (3-degree)[f] | 2 | 57.98 | 0.00 | -0.29 | 2.32 | -7.21 | 131.51 | ND | ND |
| Probit | 2 | 511.74 | 0.00 | -4.31 | 3.51 | -21.88 | 172.08 | ND | ND |
| Weibull[c] | 2 | 57.98 | 0.00 | -0.29 | 2.32 | -7.21 | 131.51 | ND | ND |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The only model that provided adequate fit to the data was the Log-Logistic model.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-6. Fit of LogLogistic Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Female Mice Exposed to Molybdenum Trioxide (mg/m$^3$)**



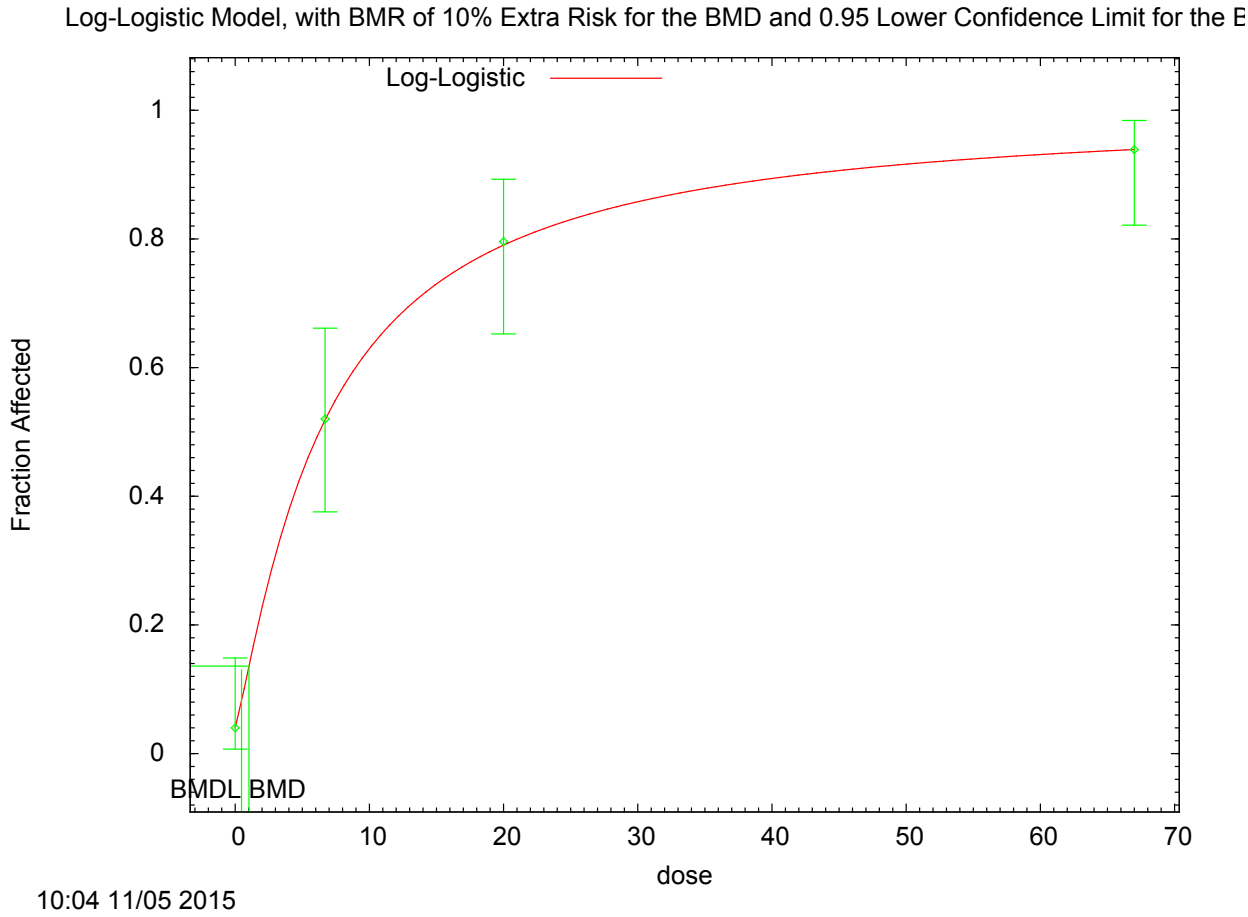
## Table A-8. Model Predictions for Alveolar Epithelial Metaplasia in Female Mice Exposed to Molybdenum Trioxide (NTP 1997)

| Model | DF | $\chi^2$ | $\chi^2$ Goodness of fit p-value[a] | Scaled residuals[b] Dose below BMC | Dose above BMC | Overall largest | AIC | $BMC_{10}$ ($mg/m^3$) | $BMCL_{10}$ ($mg/m^3$) |
|---|---|---|---|---|---|---|---|---|---|
| Gamma[c] | 2 | 15.17 | 0.0005 | -0.58 | 1.79 | -3.32 | 171.71 | ND | ND |
| Logistic | 2 | 37.47 | 0.00 | -3.49 | 2.02 | -4.18 | 194.28 | ND | ND |
| ***LogLogistic[d,e]*** | ***1*** | ***0.00*** | ***0.94*** | ***0.00*** | ***-0.02*** | ***0.05*** | ***164.20*** | ***1.03*** | ***0.47*** |
| LogProbit[d] | 2 | 6.53 | 0.04 | 0.22 | 1.25 | -2.20 | 166.91 | ND | ND |
| Multistage (1-degree)[f] | 2 | 15.17 | 0.0005 | -0.58 | 1.79 | -3.32 | 171.71 | ND | ND |
| Multistage (2-degree)[f] | 2 | 15.17 | 0.0005 | -0.58 | 1.79 | -3.32 | 171.71 | ND | ND |
| Multistage (3-degree)[f] | 2 | 15.17 | 0.0005 | -0.58 | 1.79 | -3.32 | 171.71 | ND | ND |
| Probit | 2 | 33.34 | 0.00 | -3.87 | 1.94 | -3.87 | 199.12 | ND | ND |
| Weibull[c] | 2 | 15.17 | 0.0005 | -0.58 | 1.79 | -3.32 | 171.71 | ND | ND |

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. The only model that provided adequate fit to the data was the Log-Logistic model.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

**Figure A-7. Fit of LogLogistic Model to Data on Incidence of Alveolar Epithelial Metaplasia in Female Mice Exposed to Molybdenum Trioxide (mg/m$^3$)**




Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: HECs were calculated for each potential POD by adjusting for intermittent exposure (6 hours/24 hours, 5 days/7 days) and multiplying the $POD_{ADJ}$ by the RDDR for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with reference body weights of 0.40, 0.25, 0.040, and 0.035 kg for the male rats, female rats, male mice, and female mice, respectively. The $POD_{HEC}$ values are presented in Table A-9.

## Table A-9. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs)

| End point | PODs (mg Mo/m$^3$) | RDDR values | HECs[a] (mg Mo/m$^3$) |
|---|---|---|---|
| Squamous metaplasia of the epiglottis in male rats | 3.53 (BMCL) | 0.459 | 0.28 |
| Hyaline degeneration of the respiratory epithelium in female rats | 4.26 (BMCL) | 0.248 | 0.19 |
| Hyaline degeneration of the olfactory epithelium in female rats | 6.7 (LOAEL) | 0.248 | 0.30 |
| Squamous metaplasia of the epiglottis in female rats | 1.60 (BMCL) | 0.248 | 0.071 |
| Squamous metaplasia of the epiglottis in male mice | 0.47 (BMCL) | 0.441 | 0.037 |
| Histiocyte infiltration in the lungs of male mice | 6.7 (LOAEL) | 1.046 | 1.3 |
| Alveolar epithelial metaplasia in male mice | 0.35 (BMCL) | 1.046 | 0.065 |
| Squamous metaplasia of the epiglottis in female mice | 0.19 (BMCL) | 0.367 | 0.012 |
| Alveolar epithelial metaplasia in female mice | 0.47 (BMCL) | 3.067 | 0.26 |

[a]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest observed adverse effect level; POD = point of departure; RDDR = regional deposited dose ratio for the specific region of the respiratory tract

Was a conversion used from intermittent to continuous exposure? As described above, the PODs were adjusted for intermittent exposure (6 hours/day, 5 days/week).

Other additional studies or pertinent information that lend support to this MRL: There are limited data on the toxicity of inhaled molybdenum in humans. A study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides, found no alterations in lung function, but did find increases in serum uric acid levels (Walravens et al. 1979); the TWA molybdenum concentration was 9.46 mg molybdenum/m$^3$. Another study of workers exposed to ultrafine molybdenum trioxide dust reported respiratory symptoms (dyspnea and cough), radiographic abnormalities, and impaired lung function (Ott et al. 2004); the study did not provide monitoring data. Confidence in these cohort studies was considered very low (see Appendix B for additional information). Data on the chronic toxicity of molybdenum in laboratory animals is limited to 2-year studies in rats and mice exposed to molybdenum trioxide (NTP 1997).

Agency Contacts (Chemical Managers): Dan Todd

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 5
Species: Mouse

Minimal Risk Level: 0.05 [X] mg molybdenum/kg/day [ ] ppm

The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

Reference: Zhang Y-L, Liu F-J, Chen X-L, et al. 2013. Dual effects of molybdenum on mouse oocyte quality and ovarian oxidative stress. Sys Bio Repro Med 59:312-318.

Experimental design: Groups of 25 female ICR mice (4–8 weeks of age) were exposed to 0, 5, 10, 20, or 40 mg/L molybdenum as sodium molybdate dihydrate in distilled drinking water for 14 days. Doses of 0, 1.3, 2.6, 5.3, and 11 mg molybdenum/kg/day were estimated using a reference body weight of 0.0246 kg and water intake of 0.0065 L/day. The copper content of the commercial pellet diet was not reported, but it was assumed to be adequate. The following parameters were used to assess reproductive toxicity: ovarian weight, number of ovulations, oocyte ultrastructure, and oocyte quality.

Effect noted in study and corresponding doses: A significant decrease in relative ovarian weight was observed at 11 mg molybdenum/kg/day; no information on body weight gain was reported. Hyperemia was noted in the ovaries of mice exposed to 5.3 or 11 mg molybdenum/kg/day; however, the incidence and statistical significance was not reported. A significant increase in the rate of abnormal MII oocytes (defined as the [number of total ovulations – number of normal MII oocytes]/number of total ovulations) was observed at 11 mg molybdenum/kg/day. At 1.3 mg molybdenum/kg/day, there was a significant decrease in the number of abnormal oocytes and increase in the number of ovulations, which were considered beneficial effects. The oocyte abnormality rates are presented in Table A-10. The study also found some significant alterations in superoxide dismutase (increased at 2.6 mg molybdenum/kg/day and decreased at 5.3 and 11 mg molybdenum/kg/day), glutathione peroxidase (increased at 1.3 and 2.6 mg molybdenum/kg/day and decreased at 11 mg molybdenum/kg/day), and malondialdehyde (increased at 5.3 and 11 mg molybdenum/kg/day) levels.

## Table A-10. MII Oocyte Morphology Alterations in Female Mice Exposed to Sodium Molybdate for 14 Days

| Dose (mg Mo/kg/day) | MII oocyte abnormality rate (%)[a] |
|---|---|
| 0 | 31.8542±2.3361 |
| 1.3 | 18.6753±0.8782[b] |
| 2.6 | 28.4928±1.9862 |
| 5.3 | 34.4304±3.0439 |
| 11 | 45.4952±3.3147[b] |

[a]Mean ± standard deviation; n = 25/group.
[b]Statistically different from controls, p<0.01.

Source: Zhang et al. 2013

Dose and end point used for MRL derivation: NOAEL of 5.3 and LOAEL of 11 mg molybdenum/kg/day for an increase in the rate of MII oocyte abnormalities.

[X] NOAEL [ ] LOAEL

BMD modeling was not used to identify a potential POD for the MRL. The plot of the rate of abnormal oocyte morphology versus dose has a U-shaped curve anchored by the beneficial effect observed at 1.3 mg molybdenum/kg/day and the adverse effect observed 11 mg molybdenum/kg/day. To accurately define the shape of the curve and allow for estimating a BMD for the adverse effect, additional data points would be needed. Thus, a NOAEL/LOAEL approach was used to identify the POD for the MRL.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated using the reported molybdenum concentration in the drinking water and reference drinking water intakes and body weight of 0.0065 L/day and 0.0246 kg, respectively.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Two other studies evaluated the reproductive toxicity of molybdenum following acute-duration oral exposure. Significant decreases in sperm concentration and motility and increases in sperm abnormalities were observed in male mice exposed to 25 mg molybdenum/kg/day as sodium molybdate in drinking water for 14 days (Zhai et al. 2013). Bersenyi et al. (2008) reported reductions in mature spermatocytes in rabbits exposed to 0.58 mg molybdenum/kg/day as ammonium heptamolybdate in carrots; however, the incidence and statistical significance of the finding were not reported. Bersenyi et al. (2008) also examined female rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet and found no histological alterations in the ovaries. Male and female reproductive effects have also been observed in

rats following intermediate-duration oral exposure (Fungwe et al. 1990; Lyubimov et al. 2004; Pandey and Singh 2002).

Limited data are available on the systemic toxicity of molybdenum following acute oral exposure. No alterations in uric acid levels were observed in volunteers administered 0.022 mg molybdenum/kg/day for 10 days (Deosthale and Gopalan 1974). No histological alterations were observed in the liver and kidneys of rabbits exposed to 1.2 mg molybdenum/kg/day in the diet for 14 days (Bersenyi et al. 2008); however, an increase in serum triglyceride levels was observed at this dose.

Agency Contacts (Chemical Managers): Dan Todd

# MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 24
Species: Rat

Minimal Risk Level: 0.008 [X] mg molybdenum/kg/day [ ] ppm

The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

Reference: Fungwe TV, Buddingh F, Demick DS, et al. 1990. The role of dietary molybdenum on estrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats. Nutr Res 10:515-524.

Experimental design: Groups of 21 female Sprague-Dawley rats (21 days of age) were exposed to drinking water containing 0, 5, 10, 50, or 100 mg/L molybdenum as sodium molybdate dihydrate; doses of 0.76, 1.5, 7.6, and 15 mg molybdenum/kg/day were estimated using a reference water intake of 0.031 L/day and body weight of 0.204 kg (EPA 1988). The diet contained 0.025 mg/kg molybdenum and 6.3 mg/kg copper. The investigators noted that the average molybdenum intake from the diet was 0.002 mg/kg/day (0.00028 mg/kg/day). After 6 weeks of exposure, the estrous cycle was determined through three cycles by vaginal cytology and microscopic examination. At the end of the third cycle, groups of 15 rats were mated with unexposed males.

Effect noted in study and corresponding doses: No alterations in body weight gain were observed. Exposure to 1.5 mg/kg/day resulted a significant prolonging of the length of the estrus cycle. The investigators noted that the estrus phase appeared to be the most affected stage of estrous; it was extended by 6–12 hours in the affected animals. In the published paper, the estrous cycle length was presented in a histogram; using GrabIt! software, Figure 1 of the Fungwe et al. (1990) paper was digitized; the estrous cycle lengths are summarized in Table A-11. No significant alterations in the conception rate were observed. This study also reported several developmental effects in the rats exposed to ≥10 mg/L molybdenum; effects included decreased total litter weight and increased number of resorption sites. Because the copper content of the diet was lower than the recommended level of 8 ppm for gestational exposure, this portion of the study was not considered suitable for MRL derivation.

## Table A-11. Estrous Cycle Length in Rats Exposed to Sodium Molybdate in the Drinking Water for 6 Weeks[a]

| Dose (mg Mo/kg/day) | Estrous cycle length[b] (days) |
|---|---|
| 0 | 4.48±0.29 |
| 0.76 | 4.49±0.27 |
| 1.5 | 5.06±0.26[c] |
| 7.6 | 5.45±0.24[c] |
| 15 | 5.43±0.31[c] |

[a]Data extracted using GrabIt! Software from Figure 1 in the Fungwe et al. (1990) study.
[b]Mean ± standard error.
[c]Statistically different from controls, p<0.05.

Source: Fungwe et al. 1990

Dose and end point used for MRL derivation: The NOAEL and LOAEL values of 0.76 and 1.5 mg molybdenum/kg/day were used as the POD for the MRL.

[X] NOAEL [ ] LOAEL

BMD modeling of the estrous cycle length data in Table A-11 was conducted with EPA's BMDS (version 2.5.0). The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. A BMR of 1 SD change from the control was selected. The data set for estrous cycle length was not adequate fit to the linear model under the assumption of constant variance or nonhomogenous variance. Thus, the NOAEL/LOAEL approach was used to identify the POD for the MRL.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated using the reported drinking water concentrations and references water intake and body weights of 0.031 L/day and 0.204 kg.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Several studies have reported reproductive effects following intermediate-duration; a summary of these studies is presented in Table A-12.

**Table A-12. Reproductive Effects Observed in Rats Orally Exposed to Molybdenum**

| Duration (route) | NOAEL (mg Mo/kg/day) | LOAEL (mg Mo/kg/day) | Effect | Reference (compound) |
|---|---|---|---|---|
| 8 weeks (drinking water) | 0.76 | 1.5 | Prolonged estrus phase; no effect on female fertility | Fungwe et al. 1990 (sodium molybdate) |
| ≥8 weeks (diet) | 7 | | No effect on fertility; male and female rats were exposed | Jeter and Davis 1954 (sodium molybdate) |
| 59–61 days (males), 22–35 days (females) (gavage) | 1.5 | 4.4 | Decreases in sperm motility and sperm count, and increased sperm morphology. No effects in females | Lyubimov et al. 2004 (ammonium tetrathiomolybdate) |
| 90 days (diet) | 17 | 60 | Decrease in percentage of progressive motile sperm. No significant alterations in other sperm parameters. No alterations in vaginal cytology, estrus cycle, or histology of male or female reproductive tissues | Murray et al. 2013 (sodium molybdate) |
| 60 days (gavage) | 3.4[a] | 10[a] | Decreases in sperm count and motility; increases in sperm abnormalities | Pandey and Singh 2002 (sodium molybdate) |
| 60 days (gavage) | | 10 | Decreases in male fertility | Pandey and Singh 2002 (sodium molybdate) |

[a]Adjusted for intermittent exposure (5 days/week).

Other effects that have been observed at higher doses include kidney damage at ≥60 mg molybdenum/kg/day (Bompart et al. 1990; Murray et al. 2013), neuromuscular effects at 54 mg molybdenum/kg/day (Arrington and Davis 1953), and body weight (most studies did not report alterations below 60 mg molybdenum/kg/day [Bompart et al. 1990; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956], although one study reported effects at 4.4 mg molybdenum/kg/day [Lyubimov et al. 2004]).

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# APPENDIX B. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR MOLYBDENUM

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to molybdenum, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to molybdenum:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

## B.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to molybdenum. The inclusion criteria used to identify relevant studies examining the health effects of molybdenum are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

## B.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of molybdenum. Studies for other sections of the toxicological profile were also identified in the literature search and screen step. Although these studies were not included in the systematic review process, the results of some studies (e.g., mechanistic studies, toxicokinetic studies) were considered in the final steps of the systematic review. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of molybdenum have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.

## Table B-1. Inclusion Criteria for the Literature Search and Screen

| |
|---|
| Species |
| Human |
| Laboratory mammals |
| Route of exposure |
| Inhalation |
| Oral |
| Dermal (or ocular) |
| Parenteral (these studies will be considered supporting data) |
| Health outcome |
| Death |
| Systemic effects |
| Respiratory effects |
| Cardiovascular effects |
| Gastrointestinal effects |
| Hematological effects |
| Musculoskeletal effects |
| Hepatic effects |
| Renal effects |
| Endocrine effects |
| Dermal effects |
| Ocular effects |
| Body weight effects |
| Metabolic effects |
| Other systemic effects |
| Immunological effects |
| Neurological effects |
| Reproductive effects |
| Developmental effects |
| Cancer |

### B.2.1 Literature Search

The following databases were searched, without date restrictions, in December 2014:

- PubMed
- National Library of Medicine's TOXLINE
- Scientist and Technical Information Network's TOXCENTER
- National Pesticide Information Retrieval System (NPIRS)
- Toxic Substances Control Act Test Submissions (TSCATS) and TSCATS2

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

The search strategy used the chemical name, CAS numbers (i.e., 7439-98-7; 1317-33-5; 12033-29-3; 12033-33-9; 11098-99-0; 18868-43-4; 1313-27-5; 1313-29-7; 11098-84-3; 27546-07-2; 12054-85-2; 15060-55-6; 7631-95-0; 10102-40-6; 7789-82-4; 12011-97-1; 11119-46-3; 11062-51-4; 10241-05-1; 1309-56-4; 7783-77-9; 13939-06-5; 14221-06-8; 13814-74-9), synonyms, and Medical Subject Headings (MeSH) terms for molybdenum. A total of 9,217 records were identified and imported into EndNote (version 5). After the identification and removal of 489 duplicates by EndNote, the remaining 8,728 records were moved to the literature screening step.

### B.2.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies examining the health effects of molybdenum:

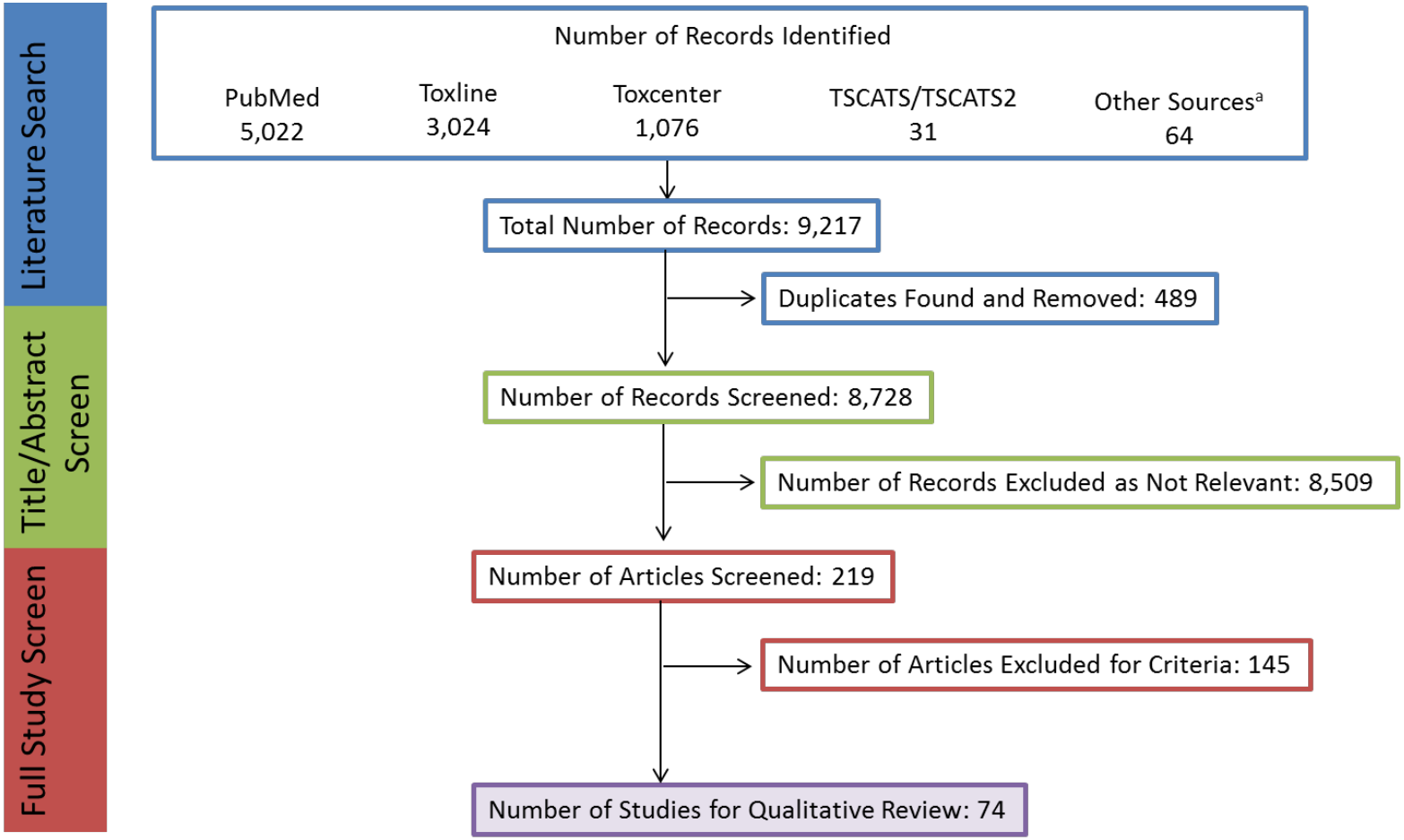
- Title and Abstract Screen
- Full Text Screen

***Title and Abstract Screen.*** Within the Endnote library, titles and abstracts were screened manually for relevance. Studies that were considered relevant were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study did not meet the inclusion criteria (Table B-1). In the Title and Abstract Screen step, 8,728 records were reviewed; 219 studies were considered relevant to Section 3.2 of the toxicological profile and were moved to the next step in the process.

***Full Text Screen.*** The second step in the literature screening process was a full text review of individual studies considered relevant in the Title and Abstract Screen step. Each study was reviewed to determine whether it met the inclusion criteria; however, the quality of the studies was not evaluated at this step of the process. Of the 219 studies undergoing Full Text Screen, 145 studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

A summary of the results of the literature search and screening is presented in Figure B-1.

**Figure B-1. Literature Search and Screen for Molybdenum Health Effect Studies**




[a]Red numbers will go up based on new records found during reference check (excluded not relevant will be new items cited but not in Section 3.2, articles screened will go up based on new references cited in Section 3.2).

## B.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms in Distiller. A summary of the type of data extracted from each study is presented in Table B-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Document for Molybdenum and overviews of the results of the inhalation, and oral exposure studies are presented in Section 3.2 of the profile and in the Levels Significant Exposures tables in Section 3.2 of the profile (Tables 3-1 and 3-2, respectively).

## B.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for molybdenum identified in human and animal studies are presented in Tables B-3 and B-4, respectively. The available human studies examined a limited number of end points and reported respiratory, hepatic, endocrine, other systemic (alterations in uric acid levels), reproductive, and developmental effects. Animal studies examined a number of end points following inhalation and oral exposure; no dermal exposure studies were identified. These studies examined most systemic end points and reported respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, and body weight effects. Additionally, animal studies have reported neurological, reproductive, and developmental effects. Although animal studies have identified a number of affected tissues and systems, interpretation of much of the data is limited by an inadequate amount of copper in the diet. Studies in which the diet did not contain adequate levels of copper were carried through Step 3 of the systematic review, but were not considered in the identification of potential health effect outcomes of concern. Additionally, body weight effects were not considered a primary effect especially since most studies did not provide data on food intake; thus, this end point was not considered in the assessment of potential human hazards.

## Table B-2. Data Extracted From Individual Studies

| |
|---|
| Citation |
| Chemical form |
| Route of exposure (e.g., inhalation, oral, dermal) |
| Specific route (e.g., gavage in oil, drinking water) |
| Species |
| Strain |
| Exposure duration category (e.g., acute, intermediate, chronic) |
| Exposure duration |
| Frequency of exposure (e.g., 6 hours/day, 5 days/week) |
| Exposure length |
| Number of animals or subjects per sex per group |
| Dose/exposure levels |
| Parameters monitored |
| Description of the study design and method |
| Summary of calculations used to estimate doses (if applicable) |
| Summary of the study results |
| Reviewer's comments on the study |
| Outcome summary (one entry for each examined outcome) |
| No-observed-adverse-effect level (NOAEL) value |
| Lowest-observed-adverse-effect level (LOAEL) value |
| Effect observed at the LOAEL value |

## Table B-3. Overview of the Health Outcomes for Molybdenum Evaluated In Human Studies

| | Systemic effects | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Endocrine | Dermal | Ocular | Body weight | Metabolic | Other | Immunological effects | Neurological effects | Reproductive effects | Developmental effects | Cancer |
| Inhalation studies | | | | | | | | | | | | | | | | | | |
| Cohort | 2<br>1 | | | | | | | | | | | | 1<br>1 | | | | | 1<br>1 |
| Case control | | | | | | | | | | | | | | | | | | |
| Population | | | | | | | | | | | | | | | | | | |
| Controlled exposure | | | | | | | | | | | | | | | | | | |
| Oral studies | | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | 1<br>1 | 1<br>1 | | | 2<br>2 | 2<br>1 | |
| Case control | | | | | | | | | | | | | | | | | | |
| Population | | | | | | 1<br>1 | | 3<br>3 | | | | | | | | | | |
| Controlled exposure | | | | | | | | | | | | | 1<br>0 | | | | | |
| Dermal studies | | | | | | | | | | | | | | | | | | |
| Cohort | | | | | | | | | | | | | | | | | | |
| Case control | | | | | | | | | | | | | | | | | | |
| Population | | | | | | | | | | | | | | | | | | |
| Controlled Exposure | | | | | | | | | | | | | | | | | | |

Number of studies examining end point: 0 | 1 | 2 | 3 | 4 | 5-9 | ≥10

APPENDIX B

Number of studies reporting outcome 0 1 2 3 4 5-9 ≥10

## Table B-4. Overview of the Health Outcomes for Molybdenum Evaluated in Experimental Animal Studies

| | Systemic effects | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Respiratory | Cardiovascular | Gastrointestinal | Hematological | Musculoskeletal | Hepatic | Renal | Endocrine | Dermal | Ocular | Body weight | Metabolic | Other | Immunological effects | Neurological effects | Reproductive effects | Developmental effects | Cancer |
| **Inhalation studies** | | | | | | | | | | | | | | | | | | |
| Acute-duration | 2<br>0 | | | | | | | | | | | | | | | | | |
| Intermediate-duration | 2<br>0 | | | | | | | | | | | | | | | | | |
| Chronic-duration | 2<br>2 | | | | | | | | | | | | | | | | | 2<br>2 |
| **Oral studies** | | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | 4<br>4 | 2<br>1 | 2<br>1 | | | | 5<br>0 | | | | | 4<br>3 | | |
| Intermediate-duration | 1<br>0 | 2<br>0 | 3<br>1 | 16<br>5 | 9<br>8 | 8<br>7 | 8<br>8 | 6<br>5 | 2<br>2 | 0<br>0 | 31<br>24 | 2<br>0 | 1<br>0 | | 2<br>1 | 10<br>7 | 8<br>4 | |
| Chronic-duration | | | | | | | | | | | | | | | | | | |
| **Dermal studies** | | | | | | | | | | | | | | | | | | |
| Acute-duration | | | | | | | | | | | | | | | | | | |
| Intermediate-duration | | | | | | | | | | | | | | | | | | |
| Chronic-duration | | | | | | | | | | | | | | | | | | |

Number of studies examining end point 0 1 2 3 4 5-9 ≥10
Number of studies reporting outcome 0 1 2 3 4 5-9 ≥10

## B.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

### B.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables B-5, B-6, and B-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

### Table B-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

| |
|---|
| **Selection bias** |
| Were the comparison groups appropriate? |
| **Confounding bias** |
| Did the study design or analysis account for important confounding and modifying variables? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |

## Table B-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

| |
|---|
| **Selection bias** |
| Was administered dose or exposure level adequately randomized? |
| Was the allocation to study groups adequately concealed? |
| **Performance bias** |
| Were the research personnel and human subjects blinded to the study group during the study? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |

## Table B-7. Risk of Bias Questionnaire for Experimental Animal Studies

| |
|---|
| **Selection bias** |
| Was administered dose or exposure level adequately randomized? |
| Was the allocation to study groups adequately concealed? |
| **Performance bias** |
| Were experimental conditions identical across study groups? |
| Were the research personnel blinded to the study group during the study? |
| **Attrition/exclusion bias** |
| Were outcome data complete without attrition or exclusion from analysis? |
| **Detection bias** |
| Is there confidence in the exposure characterization? |
| Is there confidence in outcome assessment? |
| **Selective reporting bias** |
| Were all measured outcomes reported? |
| **Other bias** |
| Did the study design or analysis account for important confounding and modifying variables? This question addresses whether the copper levels of the diet met nutritional requirements. |

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

***First Tier.*** Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

***Second Tier.*** A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

***Third Tier.*** Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of molybdenum health effects studies (observational epidemiology, human experimental, and animal experimental studies) are presented in Tables B-8, B-9, and B-10, respectively.

## Table B-8. Summary of Risk of Bias Assessment for Molybdenum—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate? | Confounding bias — Did the study design or analysis account for important confounding and modifying variables?* | Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis? | Detection bias — Is there confidence in the exposure characterization?* | Detection bias — Is there confidence in the outcome assessment?* | Selective reporting bias — Were all measured outcomes reported? | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| ***Outcome: Respiratory effects*** | | | | | | | |
| *Cohort studies* | | | | | | | |
| Ott et al. 2004 | – | – | + | na | + | ++ | Second |
| Walravens et al. 1979 | – | – | + | + | – | + | Second |
| ***Outcome: Hepatic effects*** | | | | | | | |
| *Cross-sectional studies* | | | | | | | |
| Mendy et al. 2012 | + | + | + | + | – | + | Second |
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | | | |
| *Cross-sectional studies* | | | | | | | |
| Koval'sky et al. 1961 | – | – | + | – | + | + | Second |
| *Cohort studies* | | | | | | | |
| Walravens et al. 1979 | – | – | + | + | – | + | Second |
| ***Outcome: Reproductive Effects*** | | | | | | | |
| *Cross-sectional studies* | | | | | | | |
| Lewis and Meeker 2015 | na | - | + | + | + | + | First |
| Meeker et al. 2008 | + | + | + | ++ | ++ | ++ | First |
| Meeker et al. 2010 | + | + | ++ | + | ++ | ++ | First |

## Table B-8. Summary of Risk of Bias Assessment for Molybdenum—Observational Epidemiology Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate? | Confounding bias — Did the study design or analysis account for important confounding and modifying variables?* | Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis? | Detection bias — Is there confidence in the exposure characterization?* | Detection bias — Is there confidence in the outcome assessment?* | Selective reporting bias — Were all measured outcomes reported? | Risk of bias tier |
|---|---|---|---|---|---|---|---|
| ***Outcome: Developmental Effects*** | | | | | | | |
| *Cross-sectional studies* | | | | | | | |
| Vazquez-Salas et al. 2014 | + | + | + | + | ++ | + | First |
| Shirai et al. 2010 | na | – | + | + | + | + | Second |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

## Table B-9. Summary of Risk of Bias Assessment for Molybdenum—Human-Controlled Exposure Studies

| | Risk of bias criteria and ratings | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Selection bias | | Performance bias | Attrition/ exclusion bias | Detection bias | | Selective reporting bias | |
| Reference | Was administered dose or exposure level adequately randomized? | Was the allocation to study groups adequately concealed? | Were the research personnel blinded to the study group during the study? | Were outcome data complete without attrition or exclusion from analysis? | Is there confidence in the exposure characterization? | Is there confidence in the outcome assessment?* | Were all measured outcomes reported? | Risk of bias tier |
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | | | | |
| *Oral acute exposure* | | | | | | | | |
| Deosthale and Gopalan 1974 | na | + | + | + | + | + | ++ | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized? | Selection bias — Was the allocation to study groups adequately concealed? | Performance bias — Were experimental conditions identical across study groups? | Performance bias — Were the research personnel blinded to the study group during the study? | Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis? | Detection bias — Is there confidence in the exposure characterization? | Detection bias — Is there confidence in the outcome assessment?* | Selective reporting bias — Were all measured outcomes reported? | Other bias — Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Outcome: Respiratory effects*** | | | | | | | | | | |
| *Inhalation acute exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| *Inhalation intermediate exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| *Inhalation chronic exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| ***Outcome: Hepatic effects*** | | | | | | | | | | |
| *Inhalation intermediate exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized? | Selection bias: Was the allocation to study groups adequately concealed? | Performance bias: Were experimental conditions identical across study groups? | Performance bias: Were the research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis? | Detection bias: Is there confidence in the exposure characterization? | Detection bias: Is there confidence in the outcome assessment?* | Selective reporting bias: Were all measured outcomes reported? | Other bias: Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| *Inhalation chronic exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| *Oral acute exposure* | | | | | | | | | | |
| Bersenyi et al. 2008 (rabbit) | – | + | + | – | ++ | – | + | + | + | First |
| Bersenyi et al. 2008 (rabbit) | – | + | + | – | ++ | – | + | + | + | First |
| *Oral intermediate exposure* | | | | | | | | | | |
| Murray et al. 2013 (rat) | ++ | + | ++ | – | ++ | ++ | ++ | ++ | ++ | First |
| Rana and Chauhan 2000 (rat) | – | + | + | – | ++ | + | – | ++ | – | Second |
| Rana and Kumar 1980b (rat) | – | + | + | – | ++ | – | – | + | – | Third |
| Rana and Kumar 1980c (rat) | + | + | – | – | ++ | – | + | ++ | – | First |
| Rana and Kumar 1983 (rat) | + | + | – | – | ++ | + | + | ++ | – | First |
| Rana and Prakash 1986 (rat) | – | + | + | – | ++ | – | + | + | + | First |

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized? | Selection bias: Was the allocation to study groups adequately concealed? | Performance bias: Were experimental conditions identical across study groups? | Performance bias: Were the research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis? | Detection bias: Is there confidence in the exposure characterization? | Detection bias: Is there confidence in the outcome assessment?* | Selective reporting bias: Were all measured outcomes reported? | Other bias: Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Rana et al. 1980 (rat) | – | + | + | – | + | – | + | + | + | First |
| Rana et al. 1985 (rat) | + | + | + | – | ++ | + | + | + | + | First |
| ***Outcome: Renal effects*** | | | | | | | | | | |
| *Inhalation intermediate exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| *Inhalation chronic exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| *Oral acute exposure* | | | | | | | | | | |
| Bersenyi et al. 2008 (rabbit, males) | – | + | + | – | ++ | – | + | + | + | First |
| Bersenyi et al. 2008 (rabbit, females) | – | + | + | – | ++ | – | + | + | + | First |

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized? | Selection bias: Was the allocation to study groups adequately concealed? | Performance bias: Were experimental conditions identical across study groups? | Performance bias: Were the research personnel blinded to the study group during the study? | Attrition/exclusion bias: Were outcome data complete without attrition or exclusion from analysis? | Detection bias: Is there confidence in the exposure characterization? | Detection bias: Is there confidence in the outcome assessment?* | Selective reporting bias: Were all measured outcomes reported? | Other bias: Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral intermediate exposure* | | | | | | | | | | |
| Bandyopadhyay et al. 1981 (rat) | – | + | + | – | ++ | – | + | ++ | ++ | First |
| Bompart et al. 1990 (rat) | + | + | + | – | ++ | + | + | ++ | + | First |
| Murray et al. 2013 (rat) | ++ | + | ++ | – | ++ | ++ | ++ | ++ | ++ | First |
| Rana et al. 1980 (rat) | – | + | + | – | + | – | + | + | + | First |
| Rana and Kumar 1980c | + | + | – | – | ++ | – | + | ++ | – | First |
| Rana and Kumar 1983 (rat) | + | + | – | – | ++ | + | + | ++ | – | First |
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | | | | | | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Murray et al. 2013 (rat) | ++ | + | ++ | - | ++ | ++ | ++ | ++ | ++ | First |
| ***Outcome: Reproductive effects*** | | | | | | | | | | |
| *Inhalation intermediate exposure* | | | | | | | | | | |
| NTP 1997 (rat) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |
| NTP 1997 (mouse) | ++ | + | ++ | + | ++ | ++ | ++ | ++ | + | First |

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized? | Selection bias: Was the allocation to study groups adequately concealed? | Performance bias: Were experimental conditions identical across study groups? | Performance bias: Were the research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis? | Detection bias: Is there confidence in the exposure characterization? | Detection bias: Is there confidence in the outcome assessment?* | Selective reporting bias: Were all measured outcomes reported? | Other bias: Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| *Oral acute exposure* | | | | | | | | | | |
| Zhang et al. 2013 (mouse) | – | + | ++ | – | ++ | – – | + | ++ | – | First |
| Zhai et al. 2013 (mouse) | – | + | ++ | – | ++ | – – | + | ++ | + | First |
| Bersenyi et al. 2008 (rabbit, males) | – | + | + | – | ++ | – | + | + | + | First |
| Bersenyi et al. 2008 (rabbit, females) | – | + | + | – | ++ | – | + | + | + | First |
| *Oral intermediate exposure* | | | | | | | | | | |
| Fungwe et al. 1990 (rat) | + | + | + | – | ++ | – | + | + | – – | First |
| Jeter and Davis 1954 (rat, adults) | – | + | + | – | ++ | – | + | + | – | First |
| Jeter and Davis 1954 (rat, weanling) | – | + | + | – | ++ | – | + | + | – – | First |
| Lyubimov et al. 2004 (rat) | + | + | ++ | – | ++ | + | + | ++ | ++ | First |
| Murray et al. 2013 (rat) | ++ | + | ++ | – | ++ | ++ | ++ | ++ | ++ | First |
| Pandey and Singh 2002 (rat) | – | + | ++ | – | ++ | + | + | ++ | – | First |

## Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

| Reference | Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized? | Selection bias: Was the allocation to study groups adequately concealed? | Performance bias: Were experimental conditions identical across study groups? | Performance bias: Were the research personnel blinded to the study group during the study? | Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis? | Detection bias: Is there confidence in the exposure characterization? | Detection bias: Is there confidence in the outcome assessment?* | Selective reporting bias: Were all measured outcomes reported? | Other bias: Did the study design or analysis account for important confounding and modifying variables? | Risk of bias tier |
|---|---|---|---|---|---|---|---|---|---|---|
| Pandey and Singh 2002 (rat fertility study) | – | + | ++ | – | ++ | + | + | ++ | – | First |
| ***Outcome: Developmental effects*** | | | | | | | | | | |
| *Oral intermediate exposure* | | | | | | | | | | |
| Jeter and Davis 1954 (rat, weanling) | – | + | + | – | ++ | – | + | + | – – | First |
| Lyubimov et al. 2004 (rat) | + | + | ++ | – | ++ | + | + | ++ | ++ | First |
| Murray et al. 2014 (rat) | ++ | + | + | – | ++ | ++ | + | ++ | + | First |
| Pandey and Singh 2002 (rat) | – | + | ++ | – | ++ | + | + | ++ | – | First |

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

## B.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to molybdenum and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

### B.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to molybendum and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in Tables B-11, B-12, and B-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

## Table B-11. Key Features of Study Design for Observational Epidemiology Studies

| |
|---|
| Exposure was experimentally controlled |
| Exposure occurred prior to the outcome |
| Outcome was assessed on individual level rather than at the population level |
| A comparison group was used |

## Table B-12. Key Features of Study Design for Human-Controlled Exposure Studies

| |
|---|
| A comparison group was used or the subjects served as their own control |
| A sufficient number of subjects were tested |
| Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported) |
| Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis |

## Table B-13. Key Features of Study Design for Experimental Animal Studies

| |
|---|
| A concurrent control group was used |
| A sufficient number of animals per group were tested |
| Appropriate parameters were used to assess a potential adverse effect |
| Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis |

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, gastrointestinal, renal, dermal, and ocular effects observed in the observational epidemiology, human experimental, and animal experimental studies are presented in Tables B-14, B-15, and B-16, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table B-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table B-17.

## Table B-14. Presence of Key Features of Study Design for Molybdenum—Observational Epidemiology Studies

| Reference | Key features | | | | Initial study confidence |
|---|---|---|---|---|---|
| | Controlled exposure | Exposure prior to outcome | Outcomes assessed on an individual level | Comparison group | |
| ***Outcome: Respiratory effects*** | | | | | |
| *Cohort studies* | | | | | |
| Ott et al. 2004 | No | Yes | Yes | No | Low |
| Walravens et al. 1979 | No | No | No | No | Very Low |
| ***Outcome: Hepatic effects*** | | | | | |
| *Cross-sectional studies* | | | | | |
| Mendy et al. 2012 | No | No | Yes | Yes | Low |
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | |
| *Cross-sectional studies* | | | | | |
| Koval'sky et al. 1961 | No | Yes | Yes | No | Low |
| *Cohort studies* | | | | | |
| Walravens et al. 1979 | No | No | No | No | Very Low |
| ***Outcome: Reproductive Effects*** | | | | | |
| *Cross-sectional studies* | | | | | |
| Lewis and Meeker 2015 | No | No | Yes | Yes | Low |
| Meeker et al. 2008 | No | No | Yes | Yes | Low |
| Meeker et al. 2010 | No | No | Yes | Yes | Low |
| ***Outcome: Developmental Effects*** | | | | | |
| *Cross-sectional studies* | | | | | |
| Vazquez-Salas et al. 2014 | No | No | Yes | Yes | Low |
| Shirai et al. 2010 | No | No | Yes | Yes | Low |

## Table B-15. Presence of Key Features of Study Design for Molybdenum—Human-Controlled Exposure Studies

| Reference | Key feature: Concurrent control group or self-control | Key feature: Sufficient number of subjects tested | Key feature: Appropriate methods to measure outcome | Key feature: Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | |
| *Oral acute exposure* | | | | | |
| Deosthale and Gopalan 1974 | Yes | No | Yes | No | Low |

## Table B-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| ***Outcome: Respiratory effects*** | | | | | |
| *Inhalation acute exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Inhalation intermediate exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Inhalation chronic exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| ***Outcome: Hepatic effects*** | | | | | |
| *Inhalation intermediate exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Inhalation chronic exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Oral acute exposure* | | | | | |
| Bersenyi et al. 2008 (rabbit, males) | Yes | No | Yes | Yes | Moderate |
| Bersenyi et al. 2008 (rabbit, females) | Yes | No | Yes | Yes | Moderate |
| *Oral intermediate exposure* | | | | | |
| Murray et al. 2013 (rat) | Yes | Yes | Yes | Yes | High |
| Rana and Chauhan 2000 (rat) | Yes | Yes | No | Yes | Moderate |
| Rana and Kumar 1980b (rat) | Yes | Yes | No | Yes | Moderate |
| Rana and Kumar 1980c (rat) | Yes | Yes | No | Yes | Moderate |
| Rana and Kumar 1983 (rat) | Yes | Yes | No | Yes | Moderate |
| Rana and Prakash 1986 (rat) | Yes | Yes | No | Yes | Moderate |
| Rana et al. 1980 (rat) | Yes | Yes | No | No | Low |
| Rana et al. 1985 (rat) | Yes | Yes | No | Yes | Moderate |
| ***Outcome: Renal effects*** | | | | | |
| *Inhalation intermediate exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |

## Table B-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

| Reference | Key feature: Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
|---|---|---|---|---|---|
| *Inhalation chronic exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Oral acute exposure* | | | | | |
| Bersenyi et al. 2008 (rabbit, males) | Yes | No | Yes | Yes | Moderate |
| Bersenyi et al. 2008 (rabbit, females) | Yes | No | Yes | Yes | Moderate |
| *Oral intermediate exposure* | | | | | |
| Bandyopadhyay et al. 1981 (rat) | Yes | No | Yes | No | Low |
| Bompart et al. 1990 (rat) | Yes | No | Yes | Yes | Moderate |
| Murray et al. 2013 (rat) | Yes | Yes | Yes | Yes | High |
| Rana et al. 1980 (rat) | Yes | Yes | No | No | Low |
| Rana and Kumar 1980c | Yes | Yes | No | Yes | Moderate |
| Rana and Kumar 1983 (rat) | Yes | Yes | No | Yes | Moderate |
| ***Outcome: Alterations in Uric Acid Levels*** | | | | | |
| *Oral intermediate exposure* | | | | | |
| Murray et al. 2013 (rat) | Yes | Yes | Yes | Yes | High |
| ***Outcome: Reproductive effects*** | | | | | |
| *Inhalation intermediate exposure* | | | | | |
| NTP 1997 (rat) | Yes | Yes | Yes | Yes | High |
| NTP 1997 (mouse) | Yes | Yes | Yes | Yes | High |
| *Oral acute exposure* | | | | | |
| Zhang et al. 2013 (mouse) | Yes | Yes | No | Yes | Moderate |
| Zhai et al. 2013 (mouse) | Yes | Yes | No | Yes | Moderate |
| Bersenyi et al. 2008 (rabbit, males) | Yes | No | No | Yes | Low |
| Bersenyi et al. 2008 (rabbit, females) | Yes | No | No | No | Very Low |
| *Oral intermediate exposure* | | | | | |
| Fungwe et al. 1990 (rat) | Yes | No | Yes | Yes | Moderate |
| Jeter and Davis 1954 (rat, adult) | Yes | No | No | No | Very Low |
| Jeter and Davis 1954 (rat, weanlings) | Yes | No | No | No | Very Low |
| Lyubimov et al. 2004 (rat) | Yes | Yes | Yes | Yes | High |
| Murray et al. 2013 (rat) | Yes | Yes | Yes | Yes | High |
| Pandey and Singh 2002 (rat) | Yes | Yes | No | Yes | Moderate |
| Pandey and Singh 2002 (rat, fertility study) | Yes | Yes | Yes | Yes | High |

## Table B-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

| Reference | Key feature | | | | |
|---|---|---|---|---|---|
| | Concurrent control group | Sufficient number of animals per group | Appropriate parameters to assess potential effect | Adequate data for statistical analysis | Initial study confidence |
| ***Outcome: Developmental effects*** | | | | | |
| *Oral intermediate exposure* | | | | | |
| Jeter and Davis 1954 (rat, weanling) | Yes | No | No | No | Very Low |
| Lyubimov et al. 2004 (rat) | Yes | Yes | Yes | Yes | High |
| Murray et al. 2014 (rat) | Yes | Yes | Yes | Yes | High |
| Pandey and Singh 2002 (rat) | Yes | Yes | Yes | Yes | High |

## Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| ***Outcome: Respiratory effects*** | | |
| *Inhalation acute exposure* | | |
| Human studies | | |
| Cohort studies | | |
| Ott et al. 2004 | Low | Low |
| Walravens et al. 1979 | Very Low | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Inhalation intermediate exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Inhalation chronic exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| ***Outcome: Hepatic effects*** | | |
| Human studies | | |
| *Cross-sectional studies* | | |
| Mendy et al. 2012 | Low | Low |
| *Inhalation intermediate exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Inhalation chronic exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Bersenyi et al. 2008 (rabbit, males) | Moderate | Moderate |
| Bersenyi et al. 2008 (rabbit, females) | Moderate | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Murray et al. 2013 (rat) | High | High |
| Rana and Chauhan 2000 (rat) | Moderate | |
| Rana and Kumar 1980b (rat) | Moderate | |
| Rana and Kumar 1980c (rat) | Moderate | |
| Rana and Kumar 1983 (rat) | Moderate | |
| Rana and Prakash 1986 (rat) | Moderate | |
| Rana et al. 1980 (rat) | Low | |
| Rana et al. 1985 (rat) | Moderate | |

## Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| ***Outcome: Renal effects*** | | |
| *Inhalation intermediate exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Inhalation chronic exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Bersenyi et al. 2008 (rabbit, males) | Moderate | Moderate |
| Bersenyi et al. 2008 (rabbit, females) | Moderate | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Bandyopadhyay et al. 1981 (rat) | Low | High |
| Bompart et al. 1990 (rat) | Moderate | |
| Murray et al. 2013 (rat) | High | |
| Rana et al. 1980 (rat) | Low | |
| Rana and Kumar 1980c | Moderate | |
| Rana and Kumar 1983 (rat) | Moderate | |
| ***Outcome: Alterations in Uric Acid Levels*** | | |
| Human studies | | |
| *Cross-sectional studies* | | |
| Koval'sky et al. 1961 | Low | Low |
| *Cohort studies* | | |
| Walravens et al. 1979 | Very Low | Very Low |
| *Oral acute exposure* | | |
| Human studies | | |
| *Controlled exposure* | | |
| Deosthale and Gopalan 1974 | Low | Low |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Murray et al. 2013 (rat) | High | High |
| ***Outcome: Reproductive Effects*** | | |
| Human studies | | |
| *Cross-sectional studies* | | |
| Lewis and Meeker 2015 | Low | Low |
| Meeker et al. 2008 | Low | |
| Meeker et al. 2010 | Low | |

## Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

| | Initial study confidence | Initial confidence rating |
|---|---|---|
| *Inhalation intermediate exposure* | | |
| Animal studies | | |
| NTP 1997 (rat) | High | High |
| NTP 1997 (mouse) | High | |
| *Oral acute exposure* | | |
| Animal studies | | |
| Zhang et al. 2013 (mouse) | Moderate | Moderate |
| Zhai et al. 2013 (mouse) | Moderate | |
| Bersenyi et al. 2008 (rabbit) | Low | |
| Bersenyi et al. 2008 (rabbit) | Very Low | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Fungwe et al. 1990 (rat) | Moderate | High |
| Jeter and Davis 1954 (rat, adult) | Very Low | |
| Jeter and Davis 1954 (rat, weanling) | Very Low | |
| Lyubimov et al. 2004 (rat) | High | |
| Murray et al. 2013 (rat) | High | |
| Pandey and Singh 2002 (rat) | Moderate | |
| Pandey and Singh 2002 (rat, fertility study) | High | |
| ***Outcome: Developmental Effects*** | | |
| Human studies | | |
| *Cross-sectional studies* | | |
| Vazquez-Salas et al. 2014 | Low | Low |
| Shirai et al. 2010 | Low | |
| *Oral intermediate exposure* | | |
| Animal studies | | |
| Jeter and Davis 1954 (rat, weanling) | Very Low | High |
| Lyubimov et al. 2004 (rat) | High | |
| Murray et al. 2014 (rat) | High | |
| Pandey and Singh 2002 (rat) | High | |

### B.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hepatic, renal, alterations in uric acid levels, reproductive and developmental effects are presented in Table B-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with molybdenum exposure is presented in Table B-19.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables B-14, B-15, and B-16). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the end points to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect

  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure

scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level if there is a high degree of consistency in the database

## Table B-18. Adjustments to the Initial Confidence in the Body of Evidence

| | Initial confidence | Adjustments to the initial confidence rating | Final confidence |
|---|---|---|---|
| **Outcome: Respiratory Effects** | | | |
| Cohort studies | Low | -1 risk of bias; -1 imprecision | Very low |
| Animal studies | High | +1 magnitude | High |
| **Outcome: Hepatic Effects** | | | |
| Cross-sectional studies | Low | -1 risk of bias | Very low |
| Animal studies | High | -1 indirectness (secondary outcomes); | Moderate |
| **Outcome: Renal Effects** | | | |
| Animal studies | High | None | High |
| **Outcome: Alterations in Uric Acid Levels** | | | |
| Cross-sectional studies | Low | -1 risk of bias | Very low |
| Cohort studies | Very Low | -1 risk of bias | Very low |
| Human controlled exposure studies | Low | None | Low |
| Animal studies | High | None | High |
| **Outcome: Reproductive Effects** | | | |
| Cross-sectional studies | Low | None | Low |
| Animal studies | High | -1 inconsistency | Moderate |
| **Outcome: Developmental Effects** | | | |
| Cross-sectional studies | Low | None | Low |
| Animal studies | High | -1 inconsistency | Moderate |

## Table B-19. Confidence in the Body of Evidence for Molybdenum

| | Confidence in body of evidence | |
|---|---|---|
| Outcome | Human studies | Animal studies |
| Respiratory effects | Very low | High |
| Hepatic effects | Very low | Moderate |
| Renal effects | No data | High |
| Alterations in uric acid levels | Low | High |
| Reproductive Effects | Low | Moderate |
| Developmental effects | Low | Moderate |

### B.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for molybdenum, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome or very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for molybdenum is presented in Table B-20.

## Table B-20. Level of Evidence of Health Effects for Molybdenum

| Outcome | Confidence in body of evidence | Direction of health effect | Level of evidence for health effect |
|---|---|---|---|
| **Human studies** | | | |
| Respiratory effects (inhalation only) | Very low | Health effect | Inadequate |
| Hepatic effects | Very low | Health effect | Inadequate |
| Renal effects | No data | No data | No data |
| Alterations in uric acid levels | Low | Health effect | Inadequate |
| Reproductive effects | Low | Health effect | Low |
| Developmental effects | Low | Health effect | Low |
| **Animal studies** | | | |
| Respiratory effects (inhalation only) | High | Health effect | High |
| Hepatic effects | Moderate | Health effect | Moderate |
| Renal effects | High | Health effect | High |
| Alterations in uric acid levels | High | No effect | Evidence of no health effect |
| Reproductive effects | Moderate | Health effect | Moderate |
| Developmental effects[a] | Moderate | Health effect<br>No health effect | High<br>Evidence of no health effect |

[a]Mixed results were found in animal studies reporting developmental effects; three studies reported no effects and one study reported an effect.

### B.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure B-2 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.

- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for molybdenum are listed below and summarized in Table B-21.

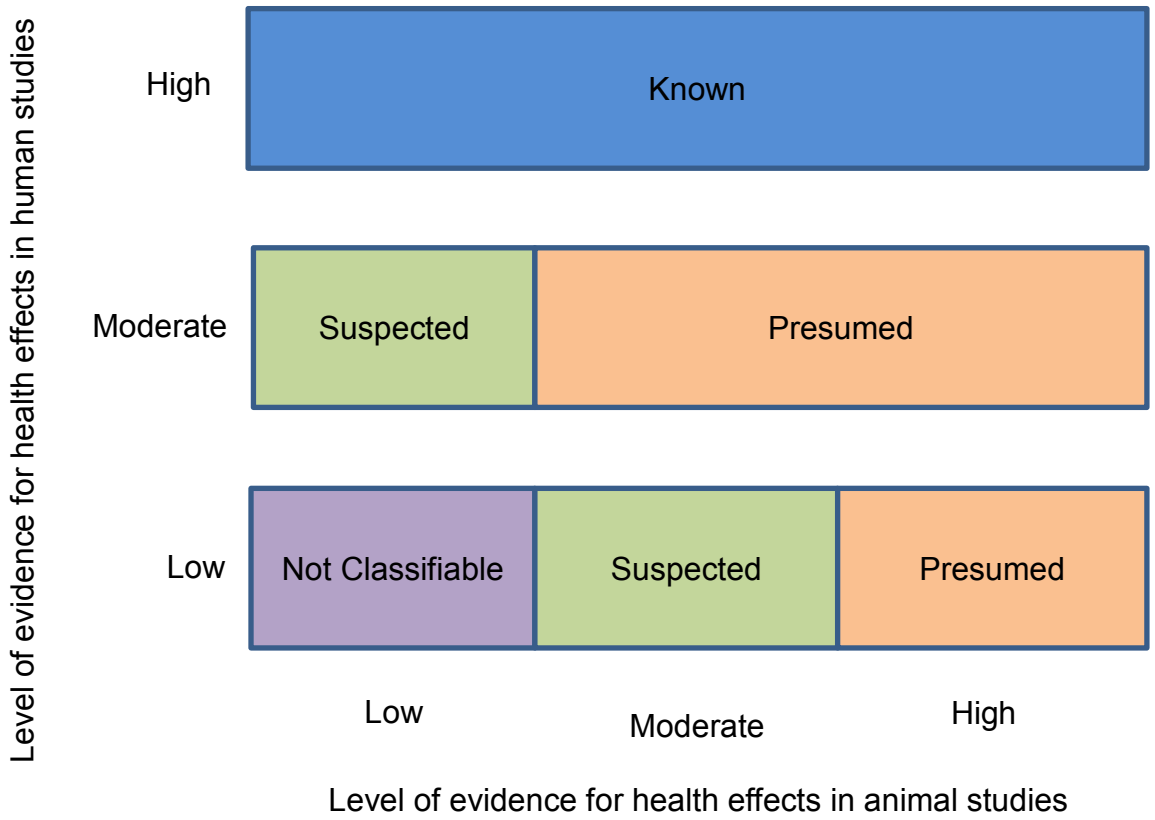
**Presumed Health Effects**

- Respiratory effects following inhalation exposure to molybdenum oxides
  - Inadequate evidence from studies of molybdenum oxide workers (Ott et al. 2004; Walravens et al. 1979).
  - High level of evidence from chronic exposure studies in rats and mice (NTP 1997).
- Renal effects
  - No data in humans.
  - High level of evidence of histological alterations in kidneys, alterations in renal function, and/or increased lipid levels in the kidneys in orally exposed rats (Bandyopadhyay et al. 1981; Bompart et al. 1990; Murray et al. 2013; Rana and Kumar 1980c, 1983; Rana et al. 1980).

## Table B-21. Hazard Identification Conclusions for Molybdenum

| Outcome | Hazard identification |
|---|---|
| Respiratory effects | Presumed health effect following inhalation exposure |
| Hepatic effects | Suspected health effect |
| Renal effects | Presumed health effect |
| Alterations in uric acid levels | Not classifiable as a hazard to humans |
| Reproductive effects | Suspected health effect |
| Developmental effects | Not classifiable as a hazard to humans |

**Figure B-2. Hazard Identification Scheme**



**Suspected Health Effects**

- Hepatic effects
  - Inadequate evidence of increased risk of self-reported liver conditions from a cross-sectional study (Mendy et al. 2012).
  - Moderate evidence of increases in clinical chemistry parameters and/or liver lipid levels in rabbits following acute oral exposure (Bersenyi et al. 2008) or rats exposed orally exposed to high doses (Rana and Chauhan 2000; Rana and Kumar 1980b, 1980c, 1983; Rana and Prakash 1986; Rana et al. 1980, 1985).
- Reproductive effects
  - Low level of evidence of male reproductive effects in cross-sectional studies (Lewis and Meeker 2015; Meeker et al. 2008, 2010).
  - Moderate level of evidence of male and/or female reproductive effects in orally exposed rats (Fungwe et al. 1990; Lyubimov et al. 2004; Murray et al. 2013; Pandey and Singh 2002), mice (Zhai et al. 2013; Zhang et al. 2013), and rabbits (Bersenyi et al. 2008).

**Not Classifiable as a Hazard to Humans**

- Alterations in uric acid levels
  - Low evidence of an effect in cross-sectional studies (Koval'skiy et al. 1961; Walravens et al. 1979).
  - High confidence in an animal study not finding an effect (Murray et al. 2013).
- Developmental effects
  - Low evidence of an effect in a cross-sectional study. Two cross-sectional studies reported no alterations in newborn body weight (Shirai et al. 2010; Vazquez-Salas et al. 2014); one study reported decreases in psychomotor development indices (Vazquez-Salas et al. 2014).
  - Three studies in rats did not find alterations in resorptions, post-implantation losses, or fetal body weights (Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014); the initial confidence levels for these studies were high, high, and very low. A fourth study (initial high confidence level) involving male-only exposure found decreases in number of live fetuses and fetal body weights (Pandey and Singh 2002).
  - The animal studies had different study designs (male only, female only, male and female exposure) making a comparison across studies difficult. Additionally, none of the animal studies evaluated potential neurodevelopmental effects, which were observed in an epidemiology study. Thus, the available data were not considered adequate for drawing a conclusion on the potential developmental toxicity of molybdenum in humans.

# APPENDIX C. USER'S GUIDE

## Chapter 1

### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

## Chapter 2

### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

### Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

## Chapter 3

## Health Effects

### Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**LEGEND**

**See Sample LSE Table 3-1 (page C-6)**

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND**

**See Sample Figure 3-1 (page C-7)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in $mg/m^3$ or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ($q_1$*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

**SAMPLE**

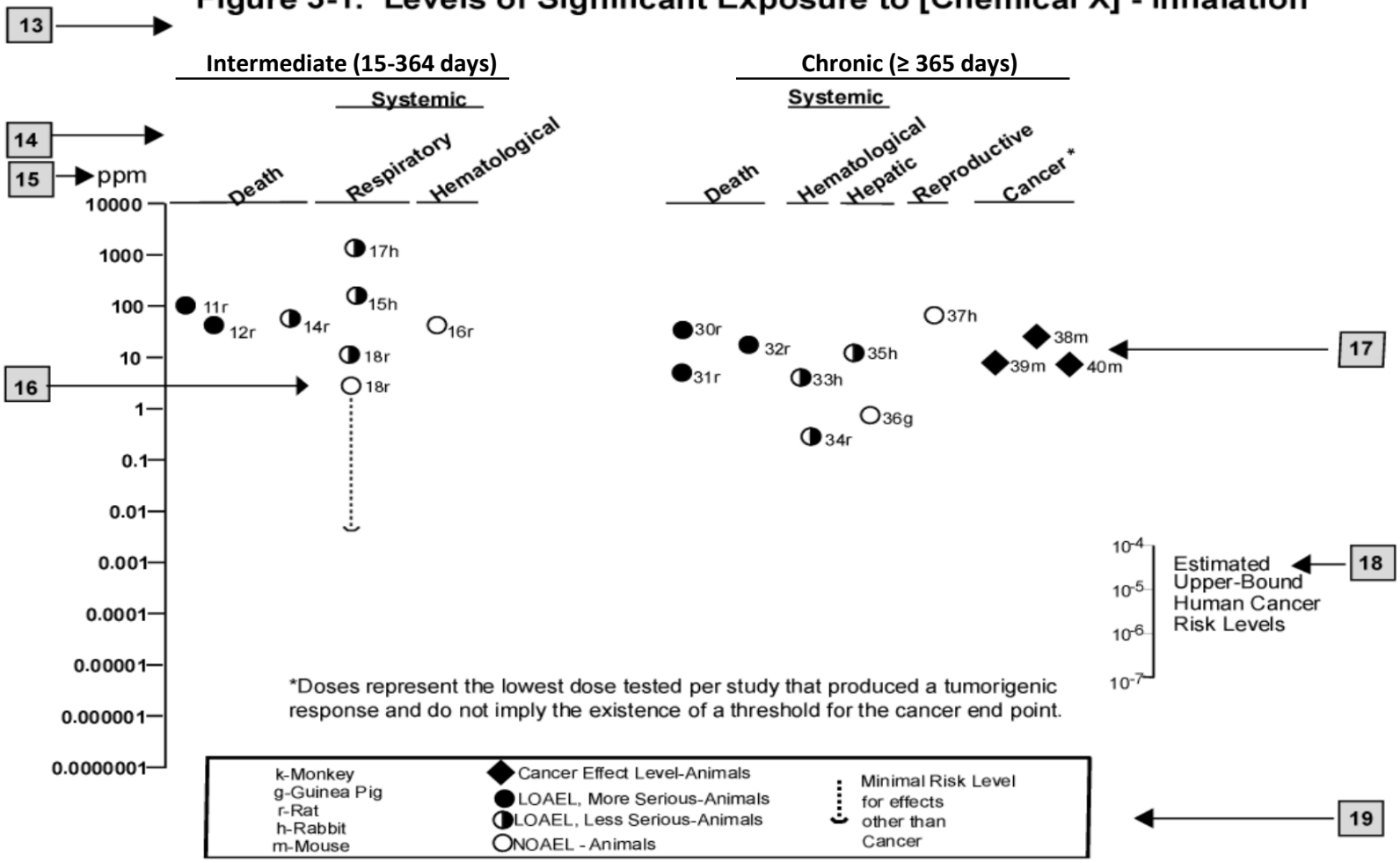
**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

| Key to figure[a] | Species | Exposure frequency/ duration | System | NOAEL (ppm) | LOAEL (effect) Less serious (ppm) | Serious (ppm) | Reference |
|---|---|---|---|---|---|---|---|
| INTERMEDIATE EXPOSURE | | | | | | | |
| Systemic | | | | | | | |
| 18 | Rat | 13 wk<br>5 d/wk<br>6 hr/d | Resp | 3[b] | 10 (hyperplasia) | | Nitschke et al. 1981 |
| CHRONIC EXPOSURE | | | | | | | |
| Cancer | | | | | | | |
| 38 | Rat | 18 mo<br>5 d/wk<br>7 hr/d | | | 20 | (CEL, multiple organs) | Wong et al. 1982 |
| 39 | Rat | 89–104 wk<br>5 d/wk<br>6 hr/d | | | 10 | (CEL, lung tumors, nasal tumors) | NTP 1982 |
| 40 | Mouse | 79–103 wk<br>5 d/wk<br>6 hr/d | | | 10 | (CEL, lung tumors, hemangiosarcomas) | NTP 1982 |

[a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5 \times 10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

**SAMPLE**

## Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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# APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AED | atomic emission detection |
| AFID | alkali flame ionization detector |
| AFOSH | Air Force Office of Safety and Health |
| ALT | alanine aminotransferase |
| AML | acute myeloid leukemia |
| AOAC | Association of Official Analytical Chemists |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| APHA | American Public Health Association |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BAT | best available technology |
| BCF | bioconcentration factor |
| BEI | Biological Exposure Index |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BSC | Board of Scientific Counselors |
| C | centigrade |
| CAA | Clean Air Act |
| CAG | Cancer Assessment Group of the U.S. Environmental Protection Agency |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CELDS | Computer-Environmental Legislative Data System |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| CLP | Contract Laboratory Program |
| cm | centimeter |
| CML | chronic myeloid leukemia |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DHEW | Department of Health, Education, and Welfare |
| DHHS | Department of Health and Human Services |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DOL | Department of Labor |
| DOT | Department of Transportation |

| | |
|---|---|
| DOT/UN/ NA/IMDG | Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code |
| DWEL | drinking water exposure level |
| ECD | electron capture detection |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EEGL | Emergency Exposure Guidance Level |
| EPA | Environmental Protection Agency |
| F | Fahrenheit |
| $F_1$ | first-filial generation |
| FAO | Food and Agricultural Organization of the United Nations |
| FDA | Food and Drug Administration |
| FEMA | Federal Emergency Management Agency |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FPD | flame photometric detection |
| fpm | feet per minute |
| FR | Federal Register |
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GLC | gas liquid chromatography |
| GPC | gel permeation chromatography |
| HPLC | high-performance liquid chromatography |
| HRGC | high resolution gas chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| ILO | International Labor Organization |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactic dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Levels of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| MA | *trans,trans*-muconic acid |
| MAL | maximum allowable level |
| mCi | millicurie |
| MCL | maximum contaminant level |

| | |
|---|---|
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| MFO | mixed function oxidase |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| mppcf | millions of particles per cubic foot |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NATICH | National Air Toxics Information Clearinghouse |
| NATO | North Atlantic Treaty Organization |
| NCE | normochromatic erythrocytes |
| NCEH | National Center for Environmental Health |
| NCI | National Cancer Institute |
| ND | not detected |
| NFPA | National Fire Protection Association |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |
| NIOSH | National Institute for Occupational Safety and Health |
| NIOSHTIC | NIOSH's Computerized Information Retrieval System |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NOES | National Occupational Exposure Survey |
| NOHS | National Occupational Hazard Survey |
| NPD | nitrogen phosphorus detection |
| NPDES | National Pollutant Discharge Elimination System |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NSPS | New Source Performance Standards |
| NTIS | National Technical Information Service |
| NTP | National Toxicology Program |
| ODW | Office of Drinking Water, EPA |
| OERR | Office of Emergency and Remedial Response, EPA |
| OHM/TADS | Oil and Hazardous Materials/Technical Assistance Data System |
| OPP | Office of Pesticide Programs, EPA |
| OPPT | Office of Pollution Prevention and Toxics, EPA |
| OPPTS | Office of Prevention, Pesticides and Toxic Substances, EPA |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| OSW | Office of Solid Waste, EPA |
| OTS | Office of Toxic Substances |

| | |
|---|---|
| OW | Office of Water |
| OWRS | Office of Water Regulations and Standards, EPA |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PCE | polychromatic erythrocytes |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| pg | picogram |
| PHS | Public Health Service |
| PID | photo ionization detector |
| pmol | picomole |
| PMR | proportionate mortality ratio |
| ppb | parts per billion |
| ppm | parts per million |
| ppt | parts per trillion |
| PSNS | pretreatment standards for new sources |
| RBC | red blood cell |
| REL | recommended exposure level/limit |
| REL-C | recommended exposure level-ceiling value |
| RfC | reference concentration (inhalation) |
| RfD | reference dose (oral) |
| RNA | ribonucleic acid |
| RQ | reportable quantity |
| RTECS | Registry of Toxic Effects of Chemical Substances |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |
| SIM | selected ion monitoring |
| SMCL | secondary maximum contaminant level |
| SMR | standardized mortality ratio |
| SNARL | suggested no adverse response level |
| SPEGL | Short-Term Public Emergency Guidance Level |
| STEL | short term exposure limit |
| STORET | Storage and Retrieval |
| $TD_{50}$ | toxic dose, 50% specific toxic effect |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| TOC | total organic carbon |
| TPQ | threshold planning quantity |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |
| VOC | volatile organic compound |
| WBC | white blood cell |

| | |
|---|---|
| WHO | World Health Organization |

| | |
|---|---|
| > | greater than |
| ≥ | greater than or equal to |
| = | equal to |
| < | less than |
| ≤ | less than or equal to |
| % | percent |
| α | alpha |
| β | beta |
| γ | gamma |
| δ | delta |
| μm | micrometer |
| μg | microgram |
| $q_1^*$ | cancer slope factor |
| – | negative |
| + | positive |
| (+) | weakly positive result |
| (–) | weakly negative result |