

Assessment of Corrective Measures Closure Area

Prairie Creek Generating Station
Cedar Rapids, Iowa

Prepared for:

Alliant Energy



SCS ENGINEERS

25218201.00 | September 12, 2019

2830 Dairy Drive
Madison, WI 53718-6751
608-224-2830

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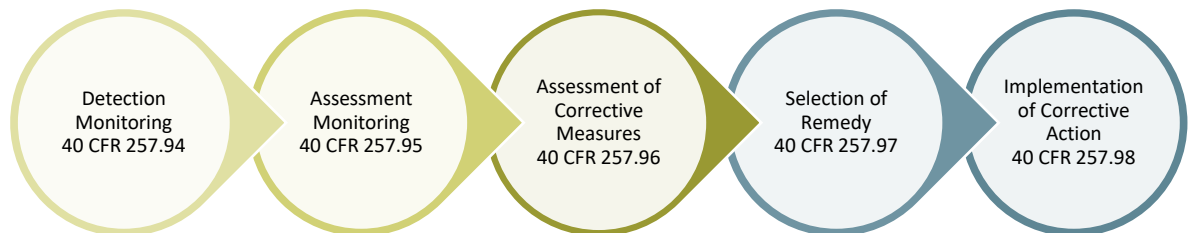
EXECUTIVE SUMMARY

Interstate Power and Light Company (IPL), an Alliant Energy company, operated eight ash ponds and two ash piles at the Prairie Creek Generating Station (PCS). The ponds and piles were used to manage coal combustion residuals (CCR) and wastewater from the power plant, which burns coal and natural gas to generate electricity and steam.

In 2018, IPL consolidated the CCR from the ash ponds and piles into a single closure area that was capped according to a permit from the Iowa Department of Natural Resources (IDNR) and U.S. Environmental Protection Agency (USEPA) standards for the Disposal of CCR from Electric Utilities, or the “CCR Rule” (Rule).

IPL samples and tests the groundwater in the area of the former ponds/piles and the closure area to comply with the Rule. Groundwater samples from some of the wells installed to monitor the closure area contained two metals, arsenic and molybdenum, at levels higher than the Groundwater Protection Standards (GPS) defined in the Rule. These metals occur naturally, and both can be present in coal and CCR.

IPL has prepared this Assessment of Corrective Measures (ACM) Report in response to the groundwater sampling results at the PCS facility. The ACM process is one step in a series of steps defined in the Rule and shown below.



To prepare the ACM, IPL has worked to understand the following:

- Types of soil and rock deposits in the area of the PCS facility.
- Depth of groundwater.
- Direction that groundwater is moving.
- Potential sources of the arsenic and molybdenum in groundwater.
- The area where arsenic and molybdenum levels are higher than the USEPA standards.
- The people, plants, and animals that may be affected by levels of arsenic and molybdenum in groundwater that are above the GPS.

IPL has installed new wells to help identify where arsenic and molybdenum levels are higher than the USEPA standards. Because the time allowed by the Rule to prepare the ACM is limited, work to improve the understanding of the items listed above is still ongoing.

IPL has identified appropriate options, or Corrective Measures, to bring the levels of arsenic and molybdenum in groundwater below USEPA standards. These corrective measures include:

- No Further Action

- Monitored Natural Attenuation (MNA)
- Cover Upgrade with MNA
- Gradient Control with MNA
- Excavate and Dispose CCR in Off-site Landfill with MNA

The ACM includes a preliminary evaluation of all five options using factors identified in the Rule.

Based on what is currently known, the groundwater impacts at PCS are limited, but are not completely understood. IPL will continue to work on understanding groundwater impacts at PCS, and will use this information to select one of the Corrective Measures identified above.

IPL will provide semiannual updates on its progress in evaluating Corrective Measures to address the groundwater impacts at PCS.

Before a remedy is selected, IPL will hold a public meeting with interested and affected parties to discuss the ACM.

For more information on Alliant Energy, view our 2019 Corporate Sustainability Report at <http://www.alliantenergy.com/sustainability>.

1.0 INTRODUCTION AND PURPOSE

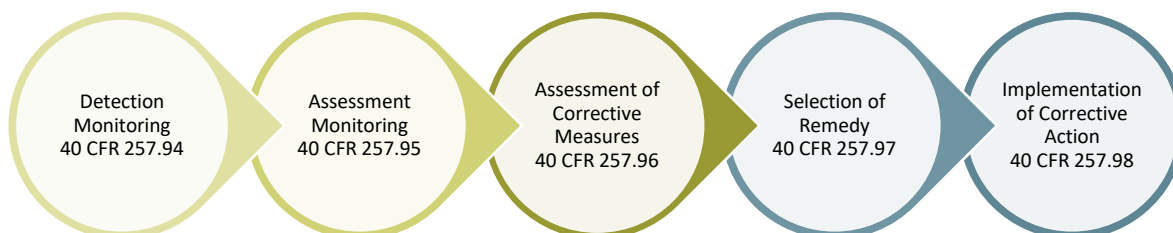
The Assessment of Corrective Measures (ACM) for the Interstate Power and Light Company (IPL) Prairie Creek Generating Station (PCS) was prepared to comply with U.S. Environmental Protection Agency (USEPA) regulations regarding the Disposal of Coal Combustion Residuals from Electric Utilities [40 CFR 257.50-107], or the “CCR Rule” (Rule). Specifically, the ACM was initiated and this report was prepared to fulfill the requirements of 40 CFR 257.96, including:

- Prevention of further releases
- Remediation of release
- Restoration of affected areas

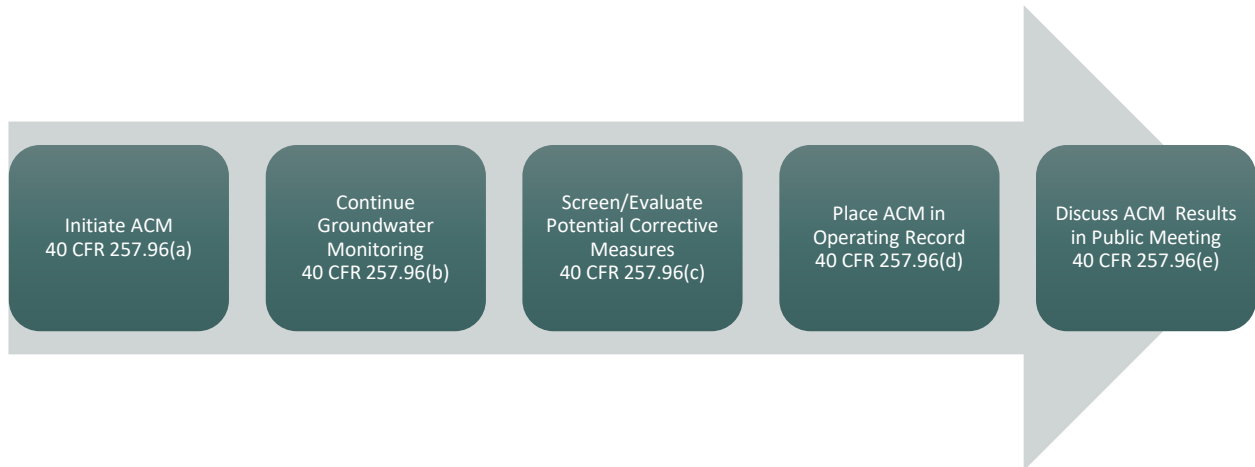
This ACM Report summarizes the remedial alternatives for addressing the Groundwater Protection Standard (GPS) exceedances observed in the October 2018 sampling event and identified in the Notification of Groundwater Protection Standard Exceedance dated February 13, 2019.

1.1 ASSESSMENT OF CORRECTIVE MEASURES PROCESS

As discussed above, this ACM Report has been prepared in response to GPS exceedances observed in groundwater samples collected to monitor the PCS facility. The ACM process is one step in a series of steps defined in the CCR Rule and depicted in the graphic below. To date, IPL has implemented a detection monitoring program per 40 CFR 257.94 and completed assessment monitoring at PCS per 40 CFR 257.95. An ACM is now required based on the groundwater monitoring results obtained through October 2018. With the ACM completed, IPL is required to select a corrective measure (remedy) according to 40 CFR 257.97. The remedy selection process must be completed as soon as feasible, and, once selected, IPL is required to start the corrective action process within 90 days.



The process for developing the ACM is defined in 40 CFR 257.96 and is shown in the graphic below. IPL is required to discuss the ACM results in a public meeting at least 30 days before selecting a remedy. To facilitate the selection of a remedy for the GPS exceedances at PCS, IPL continues to investigate and assess the nature and extent of the groundwater impacts. Information about the site, the groundwater monitoring completed, the groundwater impacts as they are currently understood, and the ongoing assessment activities are discussed in the sections that follow.



1.2 SITE INFORMATION AND MAP

PCS is located to the south of Prairie Creek and to the west of the Cedar River, on the south side of the City of Cedar Rapids in Linn County, Iowa (**Figure 1**). The address of the plant is 3300 C Street Southwest, Cedar Rapids, Iowa. In addition to the coal-fired generating station, the property also contains a closure area located within the original footprint of the Coal Combustion Residuals (CCR) impoundments, a coal stockpile, and a hydrated fly ash beneficial reuse stockpile.

The groundwater monitoring system at PCS monitors the Closure Area, which was created when the following CCR units were closed:

- PCS Pond 1
- PCS Pond 2
- PCS Pond 3
- PCS Pond 4
- PCS Pond 5
- PCS Pond 6
- PCS Pond 7
- PCS Discharge Pond (Pond 8)
- PCS Beneficial Use Storage Area
- PCS Bottom Ash Pile

All CCR material from these units was consolidated into a single closure area in accordance with 40 CFR 257.102 and a Closure Permit issued by the Iowa Department of Natural Resources (IDNR). The closure was completed on December 19, 2018. This ACM was initiated following detection monitoring and assessment monitoring activities that occurred prior to, during, and following the closure activities, including the October 2018 sampling event when Groundwater Protection Standard exceedances were observed. A map showing the closure area, the former locations of the closed CCR units, and all background (or upgradient) and downgradient monitoring wells with identification numbers for the CCR groundwater monitoring program is provided as **Figure 2**.

2.0 BACKGROUND

2.1 REGIONAL GEOLOGIC INFORMATION

The uppermost geologic formation beneath PCS that meets the definition of the “uppermost aquifer,” as defined under 40 CFR 257.53, is the surficial alluvial aquifer. The alluvial aquifer comprises Cedar River Valley sand, gravel, silt, and clay deposits. This deposit is present in the Cedar River Valley. A map of the regional glacial geology in the area is included in **Appendix A**.

The alluvial aquifer is underlain by Devonian and Silurian limestone bedrock. A bedrock geology map of the area is located in **Appendix A**. The limestone bedrock is also an aquifer and is likely hydraulically connected to the alluvial aquifer above.

2.2 SITE GEOLOGIC INFORMATION

Monitoring wells MW-301 through MW-310 were installed to intersect the alluvial aquifer at the site. The unconsolidated material at these well locations is generally sand and silt with some clay and gravel. The total monitoring well boring depths are between 15.5 and 30.5 feet. The depth to bedrock at the site is variable; drilling logs for private supply wells at the site indicate that the alluvial deposits extend up to 77 feet below ground surface (bgs), and bedrock was encountered as shallow as 6 feet bgs in investigative borings installed prior to monitoring well installation. The boring logs for MW-301 through MW-310 are included in **Appendix B**.

Shallow groundwater at the site generally flows to the north, toward Prairie Creek. The groundwater flow pattern in April 2019 is shown on **Figure 3**. The groundwater elevation data for the CCR monitoring wells are provided in **Table 1**.

A geologic cross section was prepared for PCS. The cross section line runs through upgradient well MW-302, crosses the closure area, then runs through downgradient monitoring well MW-305 and assessment monitoring well MW-310. The cross section location is provided on **Figure 2** and the geologic cross section is provided on **Figure 4**. Unconsolidated geologic material and estimated water table levels are identified on the cross section.

2.3 CCR RULE MONITORING SYSTEM

The groundwater monitoring system established in accordance with the CCR Rule consists of two upgradient (background) monitoring wells and six downgradient (compliance) monitoring wells. The CCR Rule wells are installed in the upper portion of the alluvial aquifer. Well depths range from approximately 14.5 to 29.5 feet bgs.

The two background wells, MW-301 and MW-302, and four downgradient wells, MW-303, MW-304, MW-305, and MW-306, were installed between October 2016 and December 2016. Two additional downgradient monitoring wells, MW-307 and MW-308, were installed in November 2018 following the closure of PCS Pond 1 and PCS Pond 2. Prior to the pond closure, the area downgradient of Ponds 1 and 2 was not accessible for well installation. Two additional downgradient monitoring wells, MW-309 and MW-310, were installed in August 2019 in accordance with the assessment monitoring requirements of 40 CFR 257.95(g)(1).

3.0 NATURE AND EXTENT OF GROUNDWATER IMPACTS

3.1 SOURCE EVALUATION

The potential sources of groundwater impacts are the former CCR units at PCS. Based on a review of existing site documents, potential sources of groundwater impacts include former PCS Ponds 1 through 8, the Bottom Ash Pile, and the Beneficial Reuse Storage Area. These CCR units were closed in 2018, and all CCR material from these units was consolidated into a single Closure Area (**Figure 2**). The information provided here is summarized from the Closure Plan for Existing CCR Surface Impoundments and CCR Landfills dated August 28, 2018, and the Construction Documentation Report dated December 18, 2018.

Approximately 90,000 cubic yards of CCR was present in PCS Ponds 1 through 8, the Bottom Ash Pile, and the Beneficial Use Storage Area prior to closure. During closure, PCS Ponds 1 through 8 were dewatered. CCR was removed from PCS Ponds 1, 2, 8, and portions of PCS Ponds 3, 4, and 7, and was consolidated in the former footprints of PCS Ponds 3 through 7 during closure. A portion of the hydrated fly ash pile was also consolidated in the Closure Area. A final cover system consisting of 18 inches of compacted clay and 6 inches of soil capable of sustaining a vegetative cover was installed over the consolidated CCR.

3.2 GROUNDWATER ASSESSMENT

3.2.1 Groundwater Depth and Flow Direction

Groundwater flow at the site is generally to the north. Depth to groundwater varies from 0 to 16 feet bgs due to topographic variations across the facility and seasonal fluctuations in the groundwater surface. The downgradient area where MW-303 through MW-306 are located is prone to flooding when water levels in Prairie Creek and the Cedar River are high.

3.2.2 Groundwater Protection Standard Exceedances Identified

The ACM process was triggered by the detection of arsenic and molybdenum at statistically significant levels exceeding the GPSs in samples from the following compliance wells:

- Arsenic: MW-303 and MW-304
- Molybdenum: MW-306

The initial statistical evaluation of the assessment monitoring results was based on the first four sampling events for the Appendix IV assessment monitoring parameters, including sampling events in May, August, and October 2018, and a resampling event for selected parameters at selected wells in March 2019. The complete results for these sampling events are summarized in **Table 3**. Some additional compliance monitoring wells had individual results exceeding the GPSs for these parameters, but the exceedances were not determined to be at statistically significant levels. The evaluation of statistically significant levels exceeding the GPSs was summarized in an Alternative Source Demonstration (ASD) completed in April 2019. The ASD identified a reduced list of wells with parameters exceeding the GPS and recommended that IPL initiate the ACM.

Based on the results of sampling conducted through the April 2019 sampling event, statistically significant levels exceeding the GPSs have been identified for the following wells and parameters:

Assessment Monitoring Appendix IV Parameters	Location of GPS Exceedance(s)	Historic Range of Detections at Wells Exceeding GPS	Groundwater Protection Standards (GPS)
Arsenic (µg/L)	MW-303 and MW-304	11-44.5	10
Molybdenum (µg/L)	MW-306	200-271	100

Arsenic was also detected at a concentration exceeding the GPS in the April 2019 sample from MW-308; however, additional sample results are needed to determine if arsenic is at a statistically significant level above the GPS at this well. MW-308 was installed in November 2018, and the April

2019 sampling event was the first event to include this well. The statistical evaluation of GPS exceedances is based on comparison of the GPS to the lower confidence limit of the mean concentration based on a minimum of four samples. Although the statistical significance of the arsenic result exceeding the GPS at MW-308 cannot yet be evaluated, this result was treated as a significant GPS exceedance for purposes of this ACM.

3.2.3 Expanding the Groundwater Monitoring Network

Two additional monitoring wells, MW-309 and MW-310, were installed in the area between MW-303 through MW-306 and Prairie Creek to fulfill the requirements of 40 CFR 257.95(g)(1), which requires additional characterization to support a complete and accurate assessment of corrective measures. The installation of these wells was originally scheduled for late winter or early spring 2019, but due to permitting requirements and persistent flooding along Prairie Creek, the installation of these wells was completed in August 2019. Monitoring wells MW-309 and MW-310 will be initially sampled in late August or September 2019 after both wells are developed and instrumented with dedicated, low-flow sampling pumps. The results of the initial sampling event for MW-309 and MW-310 were not available as of the date of this report, but will be considered prior to selecting a remedy in accordance with 40 CFR 257.97.

3.3 CONCEPTUAL SITE MODEL

The following conceptual site model describes the compounds and nature of constituents above the GPS, discusses potential exposure pathways affecting human health and the environment, and presents a cursory review of their potential impacts. The conceptual site model for PCS has been prepared in general conformance with the Standard Guide for Developing Conceptual Site Models for Contaminated Sites (ASTM E1689-95). This conceptual site model is the basis for assessing the efficacy of likely corrective measures to address the source, release mechanisms, and exposure routes.

3.3.1 Nature of Constituents above GPS

To describe the nature of the constituents in groundwater at PCS, we have reviewed a number of sources for information regarding arsenic and molybdenum in groundwater, and how that groundwater may impact potential receptors through the exposure pathways discussed in **Section 3.3.2**.

Arsenic

Arsenic (As) is a metalloid that is naturally present in rocks, soil, and water. Arsenic is naturally present in coal and is present as a trace metal in CCR after the coal is combusted.

Arsenic has historically had numerous industrial and commercial uses, including as copper chromated arsenate (CCA), a wood preservative. Arsenic is also used in pesticides, semiconductors and light-emitting diodes, and it is added to other metals to form alloys for industrial use, including in lead-acid batteries.

Primary food sources of arsenic include seafood, however much of the arsenic in food sources is in the form of relatively nontoxic organic arsenic compounds. In some areas, drinking water also contains arsenic. Human intake varies depending on location and diet.

A summary of the properties and occurrences of arsenic is provided in the Public Health Statement and ToxFAQs factsheet prepared by the Agency for Toxic Substances and Disease Registry (ATSDR),

which is an agency of the U.S. Department of Health and Human Services. Copies of the ATSDR Public Health Statement and ToxFAQs factsheet are provided in **Appendix C**.

Arsenic Exposure

A summary of the potential exposures and health effects of arsenic is provided in the Public Health Statement and ToxFAQs factsheet prepared by ATSDR. Copies of the ATSDR Public Health Statement and ToxFAQs factsheet are provided in **Appendix C**.

The concentrations of arsenic detected to date in samples from the site monitoring wells range from below the detection limit to 50.4 µg/L. (Note: 1 µg/L in water is equal to 1 ppb.). The GPS for arsenic is 10 µg/L. The GPS for arsenic is equivalent to the USEPA maximum contaminant level (MCL) for arsenic in drinking water.

Molybdenum

Molybdenum (Mo) is a transitional metal that is naturally present in soil. Molybdenum is naturally present in coal and is present as a trace metal in CCR after the coal is combusted.

Molybdenum has industrial uses in metal alloys and chemical applications [LME 2007]. Molybdenum is also an essential trace dietary element [Schwarz, et. al. 2013]. Significant dietary sources of molybdenum include meats, green beans, eggs, sunflower seeds, wheat flour, lentils, cucumbers, and cereal grain [Emsley 2001].

Acute toxicity has not been seen in humans, and the toxicity depends on the chemical state. Although human toxicity data is unavailable, animal studies have shown that chronic ingestion of more than 10 mg/day (10,000 µg/day) of molybdenum can cause diarrhea, growth retardation, infertility, low birth weight, and gout; it can also affect the lungs, kidneys, and liver [Coughlan, 1983][Barceloux, Barcerloux 1999].

Molybdenum Exposure

ATSDR prepared a Toxicological Profile for Molybdenum, draft for public comment dated April 2017. A copy of the draft profile is provided in **Appendix C**. The report offered the following with respect to molybdenum in surface water and groundwater:

- It has been reported that concentrations of molybdenum in surface waters are generally less than 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 to 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.
- USEPA has determined that exposure to drinking water containing 0.08 mg/L (80 µg/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 (40 µg/L) is not likely to cause adverse health effects.

The concentrations of molybdenum detected to date in samples from the site monitoring wells range from below the detection limit to 271 µg/L. The GPS for molybdenum is 100 µg/L. The GPS for molybdenum is based on non-carcinogenic, child-based limits.

3.3.2 Potential Receptors and Pathways

As described in **Section 3.3**, ASTM E1689-95 provides a framework for identifying potential receptors (people or other organisms potentially affected by the groundwater impacts at PCS) and pathways (the ways groundwater impacts might reach receptors). In accordance with ASTM E1689-95, we have considered potential human and ecological exposures to groundwater impacted by the constituents identified in **Section 3.2.2**:

Human Health

In general human health exposure routes to contaminants in the environment include ingestion, inhalation, and dermal contact with the following environmental media:

- Groundwater
- Surface Water and Sediments
- Air
- Soil
- Biota/Food

If people might be exposed to the impacts described in **Section 3.0** via one of the environmental media listed above, a potential exposure route exists and is evaluated further. For the groundwater impacts at PCS, the following potential exposure pathways have been identified with respect to human health:

- Groundwater – Ingestion and Dermal Contact: The potential for ingestion of, or dermal contact with, impacted groundwater from PCS exists if water supply wells are present in the area of impacted groundwater and are used as a potable water supply. Based on a review of the IDNR GeoSam well database, and information provided by PCS:
 - No off-site water supply wells have been identified immediately downgradient or sidegradient in the vicinity of the CCR Units.
 - The nearest identified off-site water supply well is at Jones Park, approximately 500 feet from the closure area and on the opposite side of Prairie Creek. This well is 430 feet deep and is cased to a depth of approximately 89 feet. According to the City of Cedar Rapids this well is used only for irrigation.
 - The on-site water supply wells are not used as a source of potable water. Potable water at PCS is provided by the City of Cedar Rapids. According to the City of Cedar Rapids website, the City obtains its water from the alluvial aquifer along the Cedar River. The City's wells are located upstream of PCS.
- Surface Water and Sediments – Ingestion and Dermal Contact: The potential for ingestion of or dermal contact with impacted surface water and sediments exists if impacted groundwater from the facility has interacted with adjacent surface water and sediments, to the extent that the constituents identified in **Section 3.2.2** are present in these media at concentrations that represents a risk to human health.
- Biota/Food – Ingestion: The potential for ingestion of impacted food exists if impacted groundwater from the PCS facility has interacted with elements of the human food chain. Based on discussions with PCS facility staff, no hunting or farming occurs within the current area of known groundwater impacts. Elements of the food chain may also be exposed indirectly through groundwater-to-surface interactions, which are subject to additional assessment.

These potential human health exposure pathways will be evaluated further after results are obtained from new assessment monitoring wells MW-309 and MW-310. The implementation of potential corrective measures may introduce secondary exposure pathways that are discussed in **Section 6.0** and will be evaluated further as a corrective measure is selected for PCS.

Ecological Health

In addition to human exposures to impacted groundwater, potential ecological exposures are also considered. If ecological receptors might be exposed to impacted groundwater, the potential exposure routes are evaluated further. Ecological receptors include living organisms, other than humans, the habitat supporting those organisms, or natural resources potentially adversely affected by CCR impacts. This includes:

- Transfer from an environmental media to animal and plant life. This can occur by bioaccumulation, bioconcentration, and biomagnification:
 - Bioaccumulation is the general term describing a process by which chemicals are taken up by a plant or animal either directly from exposure to impacted media (soil, sediment, water) or by eating food containing the chemical.
 - Bioconcentration is a process in which chemicals are absorbed by an animal or plant to levels higher than the surrounding environment; and
 - Biomagnification is a process in which chemical levels in plants or animals increase from transfer through the food web (e.g., predators have greater concentrations of a particular chemical than their prey)
- Benthic invertebrates within adjacent waters.

Based on the information presented in **Sections 3.2.2** and **3.2.3** and the location of Prairie Creek downgradient of PCS, both of these ecological exposure routes need to be evaluated further, pending further evaluation of the extent of groundwater impacts.

The surface water/sediment, biota/food, and ecological exposure assessment is presently incomplete as the extent of groundwater impacts is still being evaluated. If groundwater impacts extend to the creek, then these exposure pathways will be evaluated further.

4.0 POTENTIAL CORRECTIVE MEASURES

In this section, we identify potential corrective measures to meet the ACM goals identified in 40 CFR 257.96(a), which are to:

- Prevent further releases
- Remediate releases
- Restore affected areas to original conditions

The development of corrective measure alternatives is described further in the following sections. Corrective measure alternatives developed to address the groundwater impacts at PCS are described in **Section 5.0**. The alternatives selected are qualitatively evaluated in **Section 6.0**.

4.1 IDENTIFICATION OF CORRECTIVE MEASURES

As described in the USEPA Solid Waste Disposal Facility Criteria Technical Manual (USEPA 1998), corrective measures are generally composed of up to three components, including:

- Source Control
- Containment
- Restoration

Within each component, there are alternative measures that may be used to accomplish the component objectives. The measures from one or more components are then combined to form corrective measure alternatives (discussed in **Section 5.0**) intended to address the observed groundwater impacts. Potential corrective measures were identified based on site information available during development of the ACM for the purpose of meeting the goals described in **Section 4.0**,

Each component and associated corrective measures are further identified in subsequent paragraphs. The corrective measures are evaluated for feasibility and combined to create the corrective action alternatives identified in this section, and further evaluated in **Section 5.0**. We continue to evaluate site conditions and may identify additional corrective measures based on new information regarding the nature and extent of the impacts.

4.1.1 Source Control

The source control component of a corrective measure is intended to identify and locate the source of impacts and provide a mechanism to prevent further releases from the source. For the PCS site, source control has already been provided through the closure of the existing CCR units at the facility, which included the consolidation of CCR materials from multiple units into a single closure area and the installation of a vegetated low permeability soil cover. Closure activities at PCS were completed in 2018, and were already underway when the groundwater impacts that required IPL to initiate the ACM were identified in October 2018. Although more time may be required to see a groundwater quality response to the closure activities completed in 2018, additional source control measures, or enhancements to existing source control measures, are identified below:

- **Cover Upgrade.** A cap upgrade would further reduce infiltration and prevent transport of CCR constituents from unsaturated CCR materials into the groundwater.
- **Excavate and dispose at a licensed off-site disposal area.** Remove all CCR from the site and haul to a licensed landfill to prevent further releases from the closure area.

Water movement through the CCR materials is the mechanism for CCR impacts to groundwater, including surface water that moves vertically through the CCR materials via infiltration of precipitation and surface water runoff. Based on the available information for this site, both the source control measures have potential to prevent further releases caused by infiltration if GPSs are not achieved by the closure activities completed in 2018, thus are retained for incorporation into alternatives for further evaluation. However, IPL continues to monitor and investigate the nature and extent of groundwater impacts and, with new information, source control measures may be added or removed from consideration.

4.1.2 Containment

The objective of containment is to limit the spread of the groundwater impacts beyond the source. The need for containment depends on the nature and extent of impacts, exposure pathways, and risks to receptors. Containment may also be implemented in combination with restoration as described in **Section 4.1.3**.

Containment may be a recommended element of a corrective measure if needed to:

- Prevent off-site migration of groundwater impacts
- Cease completion of a confirmed exposure pathway (e.g., water supply well)

Containment may also be used in lieu of active restoration if an active approach is needed. However, containment with active treatment is not warranted when:

- Water in the affected aquifer is naturally unsuited for human consumption
- Contaminants are present in low concentration with low mobility
- Low potential for exposure pathways to be completed and low risk associated with exposure
- Low transmissivity and low future user demand

The following containment measures have potential to limit the spread of the existing groundwater impacts at the site, if necessary:

- **Gradient Control with Pumping.** Gradient control includes a measure to alter the groundwater velocity and direction to slow or isolate impacts. This can be accomplished with pumping wells and/or a trench/sump collection system. If groundwater pumping is considered for capturing an impacted groundwater plume, the impacted groundwater must be managed in conformance with all applicable Federal and State requirements.
- **Gradient Control with Phytotechnology.** Gradient control with phytotechnology relies on the ability of vegetation to evapotranspire sources of surface water and groundwater. Water interception capacity by the aboveground canopy and subsequent evapotranspiration through the root system can limit vertical migration of water from the surface downward. The horizontal migration of groundwater can be controlled or contained using deep-rooted species, such as prairie plants and trees, to intercept, take up, and transpire the water. Trees classified as phreatophytes are deep-rooted, high-transpiring, water-loving organisms that send their roots into regions of high moisture and can survive in conditions of temporary saturation.

Based on the currently available information for this site, gradient control is included in the proposed alternatives. We will continue to investigate the nature and extent of the groundwater impacts at PCS and may add containment measures as warranted by data.

4.1.3 Restoration

Restoration is the process through which groundwater quality is restored to meet GPSs. This can be accomplished by way of Monitored Natural Attention (MNA) or intensively addressed by groundwater treatment with or without extraction.

MNA can be a viable remedy or component of a remedial alternative for groundwater impacted with metals. MNA requires ongoing involvement and potentially intense characterization of the geochemical environment to understand the attenuation processes involved and to justify reliance on them and regular, long-term monitoring to ensure the attenuation processes are meeting remedial goals.

MNA is not a “do-nothing” alternative; rather it is an effective knowledge-based remedy where a thorough engineering analysis provides the basis for understanding, monitoring, predicting, and documenting natural processes. To properly employ this remedy, there needs to be a strong scientific basis supported by appropriate research and site-specific monitoring implemented in accordance with quality controls. The compelling evidence needed to support proper evaluation of the remedy requires that the processes that lower metal concentrations in groundwater be well understood.

If active treatment is implemented, water may be treated in situ, on site, or off site. The need for active treatment depends on the nature and extent of impacts, exposure pathways, and risks to receptors. If there are no receptors, or when active treatment is not required for the reasons discussed in **Section 4.1.2**, then MNA is an appropriate option. If existing or future impacts require a more rapid restoration of groundwater quality, then active restoration may be needed.

Treated groundwater may be re-injected, sent to a local publicly owned treatment works (POTW), or discharged to a local body of surface water, depending on local, State, and Federal requirements. Typical on-site treatment practices for metals include coagulation and precipitation, ion exchange, or reverse osmosis. Off-site wastewater treatment may include sending the impacted groundwater that is extracted to a local POTW or to a facility designed to treat the contaminants of concern.

The removal rate of groundwater constituents such as arsenic and molybdenum will depend on the rate of groundwater extraction, the cation exchange capacity of the soil, and partition coefficients of the constituents sorbed to the soil. As the concentration of metals in groundwater is reduced, the rate at which constituents become partitioned from the soil to the aqueous phase may also be reduced. The amount of flushing of the aquifer material required to remove the metals and reduce their concentrations in groundwater below GPSs will generally determine the time frame required for restoration. This time frame is site-specific.

In-situ methods may be appropriate, particularly where pump and treat technologies may present adverse effects. In-situ methods may include biological restoration requiring pH control, addition of specific micro-organisms, and/or addition of nutrients and substrate to augment and encourage degradation by indigenous microbial populations. Bioremediation requires laboratory treatability studies and pilot field studies to determine the feasibility and the reliability of full-scale treatment.

Based on current information, MNA is retained for incorporation into alternatives for further evaluation. Other restoration measures are not currently required for this site, but may be added following continued investigation of the nature and extent of groundwater impacts.

5.0 CORRECTIVE MEASURE ALTERNATIVES

We have preliminarily identified the following corrective measure alternatives for the groundwater impacts at PCS:

- Alternative 1 – No Further Action
- Alternative 2 – MNA

- Alternative 3 – Cover Upgrade with MNA
- Alternative 4 – Gradient Control with MNA
- Alternative 5 – Excavate and Dispose Off-site with MNA

These alternatives were developed by selecting components from the reasonable and appropriate corrective measures components discussed above. Each of the corrective measure alternatives meet the requirements in 40 CFR 257.97(b)(1) through (5) based on the information available at the current time. We may identify additional alternatives based on the continued evaluation of site conditions.

5.1 ALTERNATIVE 1 – NO FURTHER ACTION

Closure of the CCR units at PCS was already underway when the groundwater impacts that required IPL to initiate the ACM process were identified. Closure activities at PCS included consolidation and capping of CCR from various CCR units into a single closure area (**Figure 2**) in accordance with the requirements for closure in place in 40 CFR 257.102(d). The closure was consistent with landfill cover systems that prevent infiltration of surface water into the CCR as described in **Section 4.1.1**. The cap limits exposure of CCR material to precipitation/surface water infiltration, which is currently believed to be the primary mechanism for mobilization of constituents to the environment and resulting GPS exceedances.

Closure activities were completed in October 2018, and additional time is required to monitor the response in groundwater conditions to the closure activities and determine whether the final cover system results in decreases in constituent concentrations below the GPS. This alternative assumes that post-closure monitoring of groundwater will continue as described in Section 2.4 of the Post-Closure Plan for the CCR units at PCS issued in August 2018.

5.2 ALTERNATIVE 2 – MNA

Alternative 2 includes no additional source control component or containment component. Closure of the CCR units at PCS with CCR in place under a cap has already been completed. The cap limits exposure of CCR material to precipitation/surface water infiltration, which is currently believed to be the primary mechanism for mobilization of constituents to the environment and resulting GPS exceedances. Under Alternative 2, the current post-closure groundwater monitoring program will be supplemented with MNA. MNA may include the analysis of groundwater samples for additional parameters and increased sampling frequency over and above the minimum program. Additional monitoring is intended to assist IPL with understanding, monitoring, predicting, and documenting natural processes affecting groundwater quality. MNA will track groundwater impacts and the effects of degradation mechanisms, if present, on groundwater concentrations over time.

5.3 ALTERNATIVE 3 – COVER UPGRADE WITH MNA

Alternative 3 includes an upgrade to the existing cover that was constructed over the closure area in 2018 in accordance with the criteria set forth in 40 CFR 257.102(d). Closure of the CCR units at PCS with CCR in place under a cap has already been completed. Under Alternative 3, the existing cap will be enhanced to further reduce the overall permeability of the final cover in the event the final cover system design prescribed in the CCR Rule and implemented in 2018 does not attain the GPS for arsenic and molybdenum. Cover upgrades include one, or a combination, of the following:

- Increase the thickness of the infiltration layer (low-permeability clay layer)
- Increase the overall thickness of cover to promote evapotranspiration

- Installation of a geomembrane over the existing infiltration layer (i.e., upgrade to composite cover)
- Installation of a drainage layer (e.g., geocomposite or granular soil layer) above the infiltration layer

The closure areas will also be subject to enhanced groundwater monitoring via MNA.

This alternative is expected to further reduce infiltration of surface water into the closure area. Leaching of metals and migration within groundwater may be reduced, which may eliminate GPS exceedances over time or accelerate the time required to obtain GPSs. MNA will assist to track if the groundwater impacts are reduced.

5.4 ALTERNATIVE 4 – GRADIENT CONTROL WITH MNA

Alternative 4 includes gradient control measures to cease completion of any confirmed exposure pathways, and limit the spread of groundwater impacts. Under Alternative 4, gradient control measures will be installed to supplement the closure activities completed in 2018 in the event the final cover system prescribed in the CCR Rule and implemented in 2018 does not attain the GPS for arsenic and molybdenum. Gradient control measure may be used to prevent the completion of an exposure pathway for groundwater containing arsenic or molybdenum concentrations above the GPS to impact downgradient receptors. MNA is included with this alternative and will monitor groundwater impacts and the effects of degradation mechanisms, if present, on groundwater concentrations over time.

5.5 ALTERNATIVE 5 – EXCAVATE AND DISPOSE OFF-SITE WITH MNA

Alternative 5 includes the removal of the existing final cover and excavation of all CCR within the closure area. Under Alternative 5, CCR from the closure area will be excavated and transported to an approved off-site landfill after the removal of the existing final cover in the event the final cover system prescribed in the CCR Rule and implemented in 2018 does not attain the GPS for arsenic and molybdenum. Further on site releases from the CCR sources will be prevented by removing the source materials from the site, which eliminates the potential for ongoing on site leaching of constituents into groundwater. MNA is included with this alternative and will monitor groundwater impacts and the effects of degradation mechanisms, if present, on groundwater concentrations over time.

6.0 EVALUATION OF CORRECTIVE MEASURE ALTERNATIVES

As required by 40 CFR 257.96(c), the following sections provide an evaluation of the effectiveness of corrective measure alternatives in meeting the requirements and objectives outlines in 40 CFR 257.97. The evaluation addresses the requirements and objectives identified in 40 CFR 257.96(c)(1) through (3), which include:

- The performance, reliability, ease of implementation, and potential impacts of appropriate potential remedies, including safety impacts, cross-media impacts, and control of exposure to residual contamination;
- The time required to begin and complete the remedy; and
- The institutional requirements, such as state or local permit requirements or other environmental or public health requirements that may substantially affect implementation of the remedy.

In addition to the discussion of the items listed above, **Table 4** provides a summary of the initial evaluation of the alternatives including each of the criteria listed in 40 CFR 257.97.

6.1 ALTERNATIVE 1 – NO FURTHER ACTION

As described in **Section 5.1**, Alternative 1 includes no further corrective action. Ongoing activities include post-closure monitoring of groundwater as described in Section 2.4 of the Post-Closure Plan for the CCR units at PCS issued in August 2018.

- **Performance, Reliability, Implementation, and Impacts.**
 - **Performance** – Ceasing wastewater discharges and closing the impoundments by capping as completed in 2018 is expected to address infiltration, which is a key contributor to groundwater impacts. In combination with the closure activities completed to date, Alternative 1 is capable of and expected to attain the GPS for arsenic and molybdenum.
 - **Reliability** – The expected reliability of capping is good. Capping is a common practice and standard remedial method for closure in place in remediation and solid waste management. There is significant industry experience with the design and construction of this method, which was incorporated into the requirements of 40 CFR 257.102(d). A deed notation is in place for closure with CCR left in place, which is a reliable means of communicating the onsite conditions.
 - **Implementation** – Nothing is required to implement Alternative 1.
 - **Impacts** – No additional safety or cross-media impacts are expected with Alternative 1. This alternative does not control current suspected routes of exposure to residual contamination.
- **Timing.** No time is required to begin. The time required to attain the GPS for arsenic and molybdenum will be evaluated further during the remedy selection process, but is expected to take between 5 and 10 years after closure construction is complete. Alternative 1 can provide full protection within the 30 year post-closure monitoring period.
- **Institutional Requirements.** IPL must maintain the IDNR Closure Permit. The current IDNR Closure Permit expires in 2047.

6.2 ALTERNATIVE 2 – MNA

As described in **Section 5.2**, Alternative 2 includes no further corrective action. Ongoing post-closure monitoring of groundwater will be supplemented with MNA.

- **Performance, Reliability, Implementation, and Impacts.**
 - **Performance** – Ceasing wastewater discharges and closing the impoundments by capping as completed in 2018 is expected to address infiltration, which is a key contributor to groundwater impacts. MNA monitoring will identify, if active, the natural attenuation processes that reduce mass, toxicity, mobility, volume, or concentrations of the constituents of concern in groundwater. In combination with the closure activities completed to date, Alternative 2 is capable of and expected to attain the GPS for arsenic and molybdenum.
 - **Reliability** – The expected reliability of capping is good. Capping is a common practice and standard remedial method for closure in place in remediation and solid waste management. There is significant industry experience with the design and construction of this method, which was incorporated into the requirements of 40 CFR

257.102(d). A deed notation is in place for closure with CCR left in place, which is a reliable means of communicating the onsite conditions.

- **Implementation** – Implementing MNA requires additional study to understand the site-specific attenuation processes that are influencing groundwater quality.
- **Impacts** – No additional safety or cross-media impacts are expected with Alternative 2. The potential for exposure to residual contamination is low since residual CCR is capped.
- **Timing.** The attenuation study could be initiated shortly after selection of this alternative. The time required to attain the GPS for arsenic and molybdenum will be evaluated further during the remedy selection process, but is expected to take between 5 and 10 years after closure construction is complete. Alternative 2 can provide full protection within the 30 year post-closure monitoring period.
- **Institutional Requirements.** IPL must maintain the IDNR Closure Permit. The current IDNR Closure Permit expires in 2047.

6.3 ALTERNATIVE 3 – COVER UPGRADE WITH MNA

As described in **Section 5.3**, Alternative 3 includes an upgrade to the existing cover that was constructed over the closure area in 2018 in accordance with the criteria set forth in 40 CFR 257.102(d).

- **Performance, Reliability, Implementation, and Impacts.**
 - **Performance** – Enhancing the existing cap may further limit post-construction infiltration through the cap, which is a key contributor to groundwater impacts. MNA monitoring will identify, if active, the natural attenuation processes that reduce mass, toxicity, mobility, volume, or concentrations of the constituents of concern in groundwater. In combination with the closure activities completed to date, Alternative 3 is capable of and expected to attain the GPS for arsenic and molybdenum.
 - **Reliability** – The expected reliability of an enhanced cap is good. The potential cap enhancements described in **Section 5.3** are in common use for closure in place for remediation and solid waste management. There is significant industry experience with the design and construction of this method, which was incorporated into the requirements of 40 CFR 257.102(d). A deed notation is in place for closure with CCR left in place, which is a reliable means of communicating the onsite conditions.
 - **Implementation** – The complexity of constructing the cap is low. The logistics of designing and installing a cap upgrade increases the complexity of the alternative due to the limited space available at the facility. The local availability of cap upgrade materials will be evaluated further during remedy selection. The equipment and personnel required to implement Alternative 3 are not specialized and are generally readily available with the exception of the resources needed to install an upgrade that involves geosynthetic components, which may not be available locally.
 - **Impacts** – Safety impacts associated with the implementation of Alternative 3 are not significantly different than other heavy civil construction projects. The level of disturbance required to upgrade the cap may represent some increase in safety risk due to site conditions and incoming/outgoing construction traffic. Cross-media impacts are not expected because it is unlikely that CCR must be exposed to upgrade the cap. The potential for exposure to residual contamination is low since CCR will remain capped.
- **Timing.** An upgrade to the existing cap can be completed within 1 year of remedy selection and issuance of required permits. The time required to attain the GPS for arsenic and molybdenum will be evaluated further during the remedy selection process,

but is expected to take between 5 and 10 years after closure construction is complete. The cap upgrade may decrease the time to reach GPS due to reduced cover permeability. Alternative 3 can provide full protection within the 30 year post-closure monitoring period.

- **Institutional Requirements.** An amendment to the IDNR Closure Permit is likely required to implement Alternative 3.

6.4 ALTERNATIVE 4 – GRADIENT CONTROL WITH MNA

As described in **Section 5.4**, Alternative 4 includes the installation of gradient control measures to cease completion of any confirmed exposure pathways, and limit the spread of groundwater impacts.

- **Performance, Reliability, Implementation, and Impacts.**
 - **Performance** – Gradient control measures can prevent the completion of an exposure pathway for groundwater containing arsenic or molybdenum concentrations above the GPS. MNA monitoring will identify, if active, the natural attenuation processes that reduce mass, toxicity, mobility, volume, or concentrations of the constituents of concern in groundwater. In combination with the closure activities completed to date, Alternative 4 is capable of and expected to attain the GPS for arsenic and molybdenum.
 - **Reliability** – Depending on the method selected, the reliability of gradient control is good. There is significant industry experience with some gradient control methods used in groundwater remediation. A deed notation is in place for closure with CCR left in place, which is a reliable means of communicating the onsite conditions.
 - **Implementation** – The complexity of constructing a gradient control system is moderate. There is a high degree of logistic complexity due to the presence of a high-traffic rail corridor adjacent to the Closure Area and off-site property owner access. The materials, equipment, and personnel required to implement Alternative 4 may vary based on the method of gradient control selected. Some methods may be more specialized with limited local availability. There is no on-site capacity to treat gradient control system discharge. If required, on-site capacity will need to be developed. Off-site ability/willingness to accept discharge is currently unknown.
 - **Impacts** – No additional safety or cross-media impacts are expected with Alternative 4. The potential for exposure to residual contamination is low since residual CCR is capped.
- **Timing.** Gradient control may be completed within 1 to 3 years of remedy selection and issuance of required permits, depending on the method of gradient control used and treatment/discharge requirements. The time required to initiate this alternative and attain the GPS for arsenic and molybdenum will be evaluated further during the remedy selection process, but is expected to take between 5 and 10 years once implemented. Gradient control may decrease the time to reach GPS due to groundwater removal. Alternative 4 can provide full protection within the 30 year post-closure monitoring period.
- **Institutional Requirements.** The following permits and approvals are expected to be required to implement Alternative 4:
 - IDNR Closure Permit
 - Downgradient property owner access agreements
 - Federal, state, and local floodplain permits
 - Receiving treatment facility approval or agency approval to construct the necessary treatment facility

State and local erosion control/construction stormwater management permits may also be required depending on the level of disturbance required to implement the alternative.

6.5 ALTERNATIVE 5 – EXCAVATE AND DISPOSE OFF-SITE WITH MNA

As described in **Section 5.5**, Alternative 5 includes removal of the existing final cover, excavation of all CCR within the closure area, and transporting CCR offsite for disposal.

- **Performance, Reliability, Implementation, and Impacts.**
 - **Performance** – Removing and re-disposing CCR offsite will eliminate the source material. The offsite disposal of CCR prevents further releases at PCS, but introduces the possibility of releases at the receiving facility. MNA monitoring will identify, if active, the natural attenuation processes that reduce mass, toxicity, mobility, volume, or concentrations of the constituents of concern in groundwater. Alternative 5 is capable of and expected to attain the GPS for arsenic and molybdenum.
 - **Reliability** – The expected reliability of excavation and offsite disposal is good. Offsite disposal facilities are required to meet the requirements in 40 CFR 257.70 or other similar requirements, and have been used for solid waste disposal including municipal and industrial waste for numerous years. There is significant industry experience with the design and construction of these disposal facilities.
 - **Implementation** – The complexity of excavating CCR for offsite disposal is low. The scale of CCR excavation, offsite transportation, and the permitting/development of offsite disposal facility airspace makes this alternative logistically complex. Significant dewatering will be required to excavate CCR. Conditioning (e.g., drying) of excavated CCR is expected to facilitate offsite transportation and re-disposal. Alternative 5 can likely be achieved through standard dewatering and conditioning methods, but may be impacted by the space available for these activities. Although the source area at PCS is eliminated, the development of offsite disposal airspace will put a high demand on the receiving disposal facility, which may not have the current physical or logistical capacity to receive large volumes of CCR in a short period of time. The equipment and personnel required to implement onsite and offsite aspects of Alternative 5 are not specialized and are generally readily available, with the exception of the resources needed to install the geosynthetic portions of the offsite composite liner and cover, which are not locally available.
 - **Impacts** – Safety impacts associated with the implementation of Alternative 5 are not significantly different than other heavy civil construction projects. However, the level of disturbance required to excavate, transport, and re-dispose CCR and the traffic required to import composite liner and cap material at the receiving disposal facility are not typical and likely represent an increase in safety risk due to large volumes of incoming/outgoing offsite construction traffic at both sites. A risk of cross-media impacts is possible due to the large volume of CCR to be excavated and transported from the site. The potential for exposure to residual contamination onsite is very low since CCR will be removed, however the offsite potential for exposure to CCR is increased due to the relocation of the source material.
- **Timing.** Removal of CCR from the existing closure area can likely be completed within 1 to 2 years of remedy selection. However, the time required to secure the offsite disposal airspace required to complete this alternative, including potential procurement, permitting, and construction, may extend this schedule significantly. The time required to attain the GPS for arsenic and molybdenum will be evaluated further during the remedy selection process, but is expected to take between 5 and 10 years after closure construction is complete. The level of source disturbance during construction may

increase the time required to reach GPS. The removal of CCR from PCS may decrease the time to reach GPS. Alternative 5 can provide full protection within the 30 year post-closure monitoring period.

- **Institutional Requirements.** The following permits and approvals are expected to be required to implement Alternative 5:
 - IDNR Closure Permit
 - Approval of offsite disposal facility owner or landfill permit for new offsite facility
 - State and local erosion control/construction stormwater management permits
 - Transportation agreements and permits (local roads and railroads)

State solid waste comprehensive planning approvals may also be required.

7.0 SUMMARY OF ASSESSMENT

Each of the identified corrective measure alternatives exhibit favorable and unfavorable outcomes with respect to the assessment factors that must be evaluated in accordance with 40 CFR 257.97(c). At the present time, limited impacts have been identified as described in **Section 3.0**. The nature and extent of those impacts are the subject of ongoing assessment and IPL continues to assess remedies to meet the requirements and objectives described in 40 CFR 257.97.

8.0 REFERENCES

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Tables

- 1 Water Level Summary
- 2 CCR Rule Groundwater Samples Summary
- 3 Groundwater Analytical Results Summary - CCR Program - Assessment Monitoring
- 4 Preliminary Evaluation of Corrective Measure Alternatives

Table 1. Water Level Summary
IPL - Prairie Creek / SCS Engineers Project #25218201

Ground Water Elevation in feet above mean sea level (amsl)								
Well Number	MW-301	MW-302	MW-303	MW-304	MW-305	MW-306	MW-307	MW-308
Top of Casing Elevation (feet amsl)	732.55	722.27	709.46	709.66	709.61	712.54	721.16	719.67
Screen Length (ft)	10.00	10.00	10.00	10.00	10.00	5.00	10.00	10.00
Total Depth (ft from top of casing)	25.10	16.98	17.01	17.09	17.00	31.91	23.27	23.21
Top of Well Screen Elevation (ft)	717.45	715.29	702.45	702.57	702.61	685.63	707.89	706.46
Measurement Date								
December 20, 2016	716.05	715.39	703.36	703.42	703.46	703.32	NI	NI
January 23, 2017	716.05	715.77	704.64	704.56	704.59	704.49	NI	NI
February 23, 2017	715.87	715.55	704.46	704.65	704.67	704.59	NI	NI
March 28, 2017	715.80	715.45	703.81	703.99	704.09	703.99	NI	NI
April 27, 2017	716.70	716.07	705.07	705.08	705.04	704.98	NI	NI
May 25, 2017	717.08	716.27	705.37	705.37	705.29	705.34	NI	NI
June 28, 2017	716.10	715.22	703.96	704.16	704.11	703.94	NI	NI
August 17, 2017	715.35	714.47	702.83	702.96	702.91	702.74	NI	NI
October 17, 2017	714.36	713.92	702.95	703.17	703.21	703.16	NI	NI
May 8, 2018	713.95	713.53	705.36	705.54	705.61	705.51	NI	NI
August 6, 2018	714.30	713.83	702.64	702.62	702.56	702.68	NI	NI
October 9, 2018	715.74	716.72	707.86	707.81	707.73	707.88	NI	NI
March 11, 2019	NM	NM	NM	704.24	704.05	NM	NI	NI
April 22-23, 2019	716.44	715.69	703.83	703.93	703.93	704.23	709.86	706.19
Bottom of Well Elevation (ft)	707.45	705.29	692.45	692.57	692.61	680.63	697.89	696.46

Created by: KAK
 Last rev. by: JSN
 Checked by: NDK

Date: 5/1/2017
 Date: 4/30/2019
 Date: 4/30/2019

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**Table 2. CCR Rule Groundwater Samples Summary
Prairie Creek Generating Station /SCS Engineers Project #25218201**

Sample Dates	Downgradient Wells						Background Wells	
	MW-303	MW-304	MW-305	MW-306	MW-307	MW-308	MW-301	MW-302
12/20-21/2016	B	B	B	B	--	--	B	B
1/23-24/2017	B	B	B	B	--	--	B	B
2/23/2017	B	B	B	B	--	--	B	B
3/28/2017	B	B	B	B	--	--	B	B
4/26-27/2017	B	B	B	B	--	--	B	B
5/25/2017	B	B	B	B	--	--	B	B
6/28/2017	B	B	B	B	--	--	B	B
8/17/2017	B	B	B	B	--	--	B	B
10/17/2017	D	D	D	D	--	--	D	D
05/08/18	A	A	A	A	--	--	A	A
8/6/2018	A	A	A	A	--	--	A	A
10/9/2018	A	A	A	A	--	--	A	A
3/11/2019	--	R	R	--	--	--	--	--
4/22/2019	A	A	A	A	A	A	A	A

Abbreviations:

B = Background Sample

D = Required by Detection Monitoring Program

A = Required by Assessment Monitoring Program R = Resample Event

-- = Not Applicable

Created by: NDK Date: 1/4/2019

Last revision by: MDB Date: 8/7/2019

Checked by: NDK Date: 8/7/2019

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Table 3. Groundwater Analytical Results Summary - CCR Program - Assessment Monitoring
 Prairie Creek Generating Station / SCS Engineers Project #25218201

Parameter Name	UPL	Background Wells										Compliance Wells																									
		MW-301					MW-302					MW-303				MW-304				MW-305				MW-306		MW-307	MW-308										
		10/17/2017	5/8/2018	8/6/2018	10/9/2018	4/22/2019	10/17/2017	5/8/2018	8/6/2018	10/9/2018	4/22/2019	10/17/2017	5/8/2018	8/6/2018	10/9/2018	4/22/2019	10/17/2017	5/8/2018	8/6/2018	10/9/2018	3/11/2019	4/22/2019	10/17/2017	5/8/2018	8/6/2018	10/9/2018	3/11/2019	4/22/2019	10/17/2017	5/8/2018	8/6/2018	10/9/2018	4/22/2019	4/22/2019	4/22/2019		
Appendix III																																					
Boron, ug/L	67	26.8 J	22.8 J	30.9 J	30.6 J	<110	36.5 J	22.4 J	38.1 J	65.0 J	<110	598	772	753	932	800	386	384	841	661	NA	770	462	437	589	634	NA	790	2,910	2,930	2,770	2,890	3000	840	5700		
Calcium, mg/L	148	139	155	154	163	130	109	125	106	63.3	67	59.9	102	85.4	99.9	130	49.3	73.5	93.0	89.0	NA	130	51.4	61.0	71.1	82.7	NA	94	48.1	56.2	58.7	65.1	59	22	59		
Chloride, mg/L	36.7	33.6	51.4	57.4	62.0	43	36.4	69.4	33.6	20.2	19	19.9	26.1	20.2	23.9	33	23.4	24.6	36.6	33.6	NA	27	18.6	18.9	18.9	18.3	NA	17	28.7	28.6	28.9	30.3	25.0	15	15		
Fluoride, mg/L	0.23	0.17 J	0.20 J	0.16 J	0.22	<0.23	0.19 J	0.23	0.17 J	0.21	<0.23	0.80	0.5	0.60	0.71	0.35 J	0.78	0.58	0.55	0.61	NA	0.41 J	0.63	0.61	0.62	0.61	NA	0.45 J	0.30	0.30	0.26	0.32	<0.23	0.54	0.77		
Field pH, Std. Units	8	7.46	7.51	6.81	7.63	6.99	7.71	6.98	6.55	6.50	6.64	7.94 H6	7.23 H6	7.20	7.13	7.40	8.16 H6	7.31 H6	6.92	7.50	NA	7.08	8.08	7.65	7.12	7.05	NA	7.12	8.45	7.47	7.45	7.40	7.58	10.05	9.24		
Sulfate, mg/L	108	95.5	117	113	131	100	82.9	69.6	72.2	55.1	56	60	146	83.3	74.7	88	55.1	77.3	193	167	NA	140	44	61.9	98.2	98.9	NA	150	139	151	195	233	160	52	190		
Total Dissolved Solids, mg/L	642	621	784	747	743	610	505	718	503	314	320	329	580	475	515	650	298	423	630	541	NA	680	307	348	434	424	NA	520	403	454	506	494	440	150	450		
Appendix IV																																					
Antimony, ug/L	0.55	6	NA	0.041 J	<0.15	<0.078	<0.53	NA	0.048 J	0.17 JB	0.092 J	<0.53	NA	0.61 J	1.1 B	0.72 J	<0.53	NA	1.3	1.3 B	1.4	NA	1.2	NA	1.6	1.6 B	1.1	NA	0.92 J	NA	<0.026	<0.15	<0.078	<0.53	0.92 J	1.4	
Arsenic, ug/L	3.6	10	NA	0.54 J	1.1 B	0.67 J	<0.75	NA	0.79 J	9.0	4.5	2.1	NA	26.9	35.1	44.5	26	NA	15.0	12.3	14.4	12.9	11	NA	14.3	13.0	6.6	11.6	5.9	NA	0.58 J	0.70 JB	0.72 J	1.9 J	3.8	45	
Barium, ug/L	332.4	2000	NA	282	281 M1	261	230	NA	213	254	141	130	NA	87.5	82.7	94.3	150	NA	95.0	121	110	NA	140	NA	63.7	90.3	95.6	NA	110	NA	54.4	59.3	62.1	110	30	39	
Beryllium, ug/L	0.16	4	NA	<0.012	NA	<0.089	<0.27	NA	<0.012	NA	<0.089	<0.27	NA	<0.012	NA	<0.089	<0.27	NA	<0.012	NA	<0.089	NA	<0.27	NA	<0.012	NA	<0.089	NA	<0.27	NA	<0.012	NA	<0.089	<0.27	<0.27	<0.27	
Cadmium, ug/L	0.11	5	NA	0.069 J	0.096 JB	0.075 J	<0.077	NA	0.041 J	0.084 JB	<0.033	<0.077	NA	<0.018	0.24 JB	<0.033	<0.077	NA	<0.018	<0.070	<0.033	NA	<0.077	NA	0.032 J	<0.070	0.040 J	NA	0.081 J	NA	0.043 J	0.085 JB	0.075 J	<0.077	<0.077	<0.077	
Chromium, ug/L	8.6	100	NA	4.1	5.8	5.2	3.6 J	NA	1.2	4.4	0.78 J	<0.98	NA	0.19 JB	0.62 JB	0.55 J	<0.98	NA	0.15 JB	0.34 JB	0.31 J	NA	<0.98	NA	0.18 J	0.28 JB	0.14 J	NA	<0.98	NA	0.21 J	0.55 JB	0.11 J	<0.98	<0.98	<0.98	
Cobalt, ug/L	24.5	6	NA	0.028 J	0.52 JB	0.084 J	0.12 J	NA	3.2	1.6 B	3.2	2.1	NA	0.31 J	0.66 JB	0.43 J	1.3	NA	0.57 J	1.1 B	0.75 J	NA	1.4	NA	0.42 J	0.64 JB	0.60 J	NA	0.63	NA	0.071 J	0.43 JB	0.079 J	0.49 J	0.091 J	<0.091	
Fluoride, mg/L	0.23	4	NA	0.20 J	0.16 J	0.22	<0.23	NA	0.23	0.17 J	0.21	<0.23	NA	0.5	0.60	0.71	0.35 J	NA	0.58	0.55	0.61	NA	0.41 J	NA	0.61	0.62	0.61	NA	0.45 J	NA	0.30	0.26	0.32	<0.23	0.54	0.77	
Lead, ug/L	2	15	NA	<0.033	0.66 JB	0.17 J	<0.27	NA	0.035 J	1.2 B	0.13 J	<0.27	NA	0.078 J	0.48 JB	0.31 J	0.30 J	NA	0.045 J	0.24 JB	<0.13	NA	<0.27	NA	<0.033	0.42 JB	<0.13	NA	<0.27	NA	0.075 J	1.0 B	<0.13	0.40 J	<0.27	<0.27	
Lithium, ug/L	19.1	40	NA	13.6	5.4 J	13.3	8.5 J	NA	5.4 J	<4.6	4.6 J	4.7 J	NA	19.0	15.4	19.9	17	NA	10.8	6.9 J	13.4	NA	17	NA	10.7	9.5 J	13.3	NA	15	NA	<4.6	<4.6	<4.6	3.0 J	10	29	
Mercury, ug/L	LOQ	2	NA	<0.090	NA	<0.090	<0.10	NA	<0.090	NA	<0.090	<0.10	NA	<0.090	NA	<0.090	<0.10	NA	<0.090	NA	<0.090	NA	<0.10	NA	<0.090	NA	<0.090	NA	<0.10	NA	<0.090	NA	<0.090	<0.10	<0.10	<0.10	
Molybdenum, ug/L	0.73	100	NA	0.35 J	0.44 JB	<0.57	<1.1	NA	0.99 J	0.78 JB	0.67 J	<1.1	NA	23.1	20.7	21.7	12	NA	19.8	25.4	27.6	NA	23	NA	27.9	29.0	32.0	NA	26	NA	271	234	235	200	5.8	58	
Selenium, ug/L	1.5	50	NA	1.3	1.3 B	0.95 J	1.1 J	NA	0.54 J	1.4 B	0.37 J	<1.0	NA	0.24 J	0.46 JB	0.21 J	<1.0	NA	0.12 J	0.23 JB	0.16 J	NA	<1.0	NA	0.22 J	0.24 JB	0.23 J	NA	<1.0	NA	<0.086	<0.16	<0.085	<1.0	<1.0	<1.0	
Thallium, ug/L	0.47	2	NA	<0.036	NA	<0.099	<0.27	NA	0.039 J	NA	<0.099	<0.27	NA	<0.036	NA	<0.099	<0.27	NA	<0.036	NA	<0.099	NA	<0.27	NA	<0.036	NA	<0.099	NA	<0.27	NA	<0.036	NA	<0.099	<0.27	<0.27	<0.27	
Radium 226/228 Combined, pCi/L	1.9	5	NA	1	1.07	1.09	0.596	NA	0.699	3.61	1.09	0.0742	NA	1.26	0.847	1.08	0.632	NA	1.26	0.768	1.31	NA	0.628	NA	2.07	1.38	1.38	NA	0.109	NA	0.645	1.21	1.42	1.040	0.166	0.301	

4.4 Blue highlighted cell indicates the compliance well result exceeds the UPL and the LOQ
 30.8 Yellow highlighted cell indicate the compliance well results exceeds the GPS and the LOQ

Abbreviations:
 UPL = Upper Prediction Limit GPS = Groundwater Protection Standard
 NA = Not Available LOQ = Limit of Quantification LOD = Limit of Detection

Notes:
 B = Analyte was detected in the associated Method Blank.
 M1 = Matrix spike recovery exceeded QC limits. Batch accepted based on laboratory control sample (LCS) recovery.
 J = Estimated concentration at or above the LOD and below the LOQ.
 1. GPS is the United States Environmental Protection Agency (US EPA) Maximum Contamination Level (MCLs), if established.

**Table 4. Preliminary Evaluation of Corrective Measure Alternatives
Prairie Creek Generating Station / SCS Engineers Project #25218201.00**

	Alternative #1 No Further Action	Alternative #2 Monitored Natural Attenuation (MNA)	Alternative #3 Cover Upgrade with MNA	Alternative #4 Gradient Control with MNA	Alternative #5 Excavate and Dispose in Offsite Landfill
CORRECTIVE ACTION ASSESSMENT - 40 CFR 257.97(b)					
257.97(b)(1) Is remedy protective of human health and the environment?	Yes	Yes	Yes	Yes	Yes
257.97(b)(2) Can the remedy attain the groundwater protection standard?	Yes	Yes	Yes	Yes	Yes
257.97(b)(3) Can the remedy control the source(s) of releases so as to reduce or eliminate, to the maximum extent feasible, further releases of constituents in appendix IV to this part into the environment?	Yes	Yes	Yes	Yes	Yes
257.97(b)(4) Can the remedy remove from the environment as much of the contaminated material that was released from the CCR unit as is feasible?	Not Applicable - No release of CCR	Not Applicable - No release of CCR	Not Applicable - No release of CCR	Not Applicable - No release of CCR	Not Applicable - No release of CCR
257.97(b)(5) Can the remedy comply with standards for management of wastes as specified in §257.98(d)?	Yes	Yes	Yes	Yes	Yes
LONG- AND SHORT-TERM EFFECTIVENESS - 40 CFR 257.97(c)(1)					
257.97(c)(1)(i) Magnitude of reduction of existing risks	Existing risk reduced by achieving GPS	Same as Alternative #1	Same as Alternative #1	Same as Alternative #1	Same as Alternative #1
257.97(c)(1)(ii) Magnitude of residual risks in terms of likelihood of further releases due to CCR remaining following implementation of a remedy	No reduction of existing risk for additional releases Residual risk is limited for all alternatives due to limited extent of impacts and lack of receptors	Same as Alternative #1	Same as Alternative #1 with potential further reduction in release risk due to the reduced permeability of the final cover However, limited as no additional overall risk reduction is provided due to lack of current/anticipated future receptors for groundwater impacts	Same as Alternative #1	Same as Alternative #1 with further reduction in release risk due to removal of impounded CCR from site However, limited as no additional overall risk reduction is provided due to lack of current/anticipated future receptors for groundwater impacts
257.97(c)(1)(iii) The type and degree of long-term management required, including monitoring, operation, and maintenance	30-year post-closure groundwater monitoring Groundwater monitoring network maintenance and as-needed repair/replacement Final cover maintenance (e.g., mowing and as-needed repair) Periodic final cover inspections Additional corrective action as required based on post-closure groundwater monitoring	Same as Alternative #1 with increased monitoring for MNA parameters	Same as Alternative #1 with increased monitoring for MNA parameters	Same as Alternative #1 with increased monitoring for MNA parameters and monitoring, operation, and maintenance of the gradient control system and any discharge-related water treatment	No on-site long-term management required Limited on-site post-closure groundwater monitoring until GPSs are achieved Receiving disposal facility will have same/similar long-term monitoring, operation, and maintenance requirements as Alternative #1

**Table 4. Preliminary Evaluation of Corrective Measure Alternatives
Prairie Creek Generating Station / SCS Engineers Project #25218201.00**

	Alternative #1 No Further Action	Alternative #2 Monitored Natural Attenuation (MNA)	Alternative #3 Cover Upgrade with MNA	Alternative #4 Gradient Control with MNA	Alternative #5 Excavate and Dispose in Offsite Landfill
LONG- AND SHORT-TERM EFFECTIVENESS - 40 CFR 257.97(c)(1) (continued)					
257.97(c)(1)(iv) Short-term risks - Implementation					
Excavation	None	None	Increased risk over Alternative #1 due to general construction activities that are not anticipated to expose CCR	None	Increased risk to environment over Alternative #3 due to CCR excavation volumes (~148K cy) required for removal and off-site re-disposal
Transportation	None	None	Increased risk over Alternative #1 from construction traffic due to final cover disturbance and import of cover upgrade materials	None	Highest level of community and environmental risk due to CCR volume export (~148K cy)
Re-Disposal	None	None	None	None	Increased risk to community and environment due to re-disposal of large CCR volume (~148K cy) at another facility Re-disposal risks are managed by the receiving disposal facility
257.97(c)(1)(v) Time until full protection is achieved	To be evaluated further during remedy selection Closure and capping was completed in 2018 Groundwater protection timeframe to reach GPS potentially 5 to 10 years following closure construction, achievable within 30-year post-closure monitoring period	Similar to Alternative #1 with the potential for increased understanding of timeframe based on MNA monitoring results	Similar to Alternative #2 with some potential for decrease in time to reach GPS due to reduced cover permeability.	Similar to Alternative #2 with potential for decrease in time to reach GPS due to groundwater removal	Similar to Alternative #2 Potential for increase in time to reach GPS due to significant source disturbance during construction Potential decrease in time to reach GPS due to CCR source removal
257.97(c)(1)(vi) Potential for exposure of humans and environmental receptors to remaining wastes, considering the potential threat to human health and the environment associated with excavation, transportation, re-disposal, or containment	No change in potential exposure	Same as Alternative #1	Same as Alternative #1	Same as Alternative #1	No potential for on-site exposure to remaining waste since no waste remains on site Risk of potential exposure is transferred to receiving disposal facility and is likely similar to Alternative #2
257.97(c)(1)(vii) Long-term reliability of the engineering and institutional controls	Long-term reliability of existing cap is good Significant industry experience with methods/controls Capping is common practice/industry standard for closure in place for remediation and solid waste management Deed notation in place for closure with CCR left in place	Long-term reliability of existing cap is good Significant industry experience with methods/controls Capping is common practice/industry standard for closure in place for remediation and solid waste management Deed notation in place for closure with CCR left in place	Long-term reliability of enhanced cap is good Significant industry experience with methods/controls Capping is common practice/industry standard for closure in place for remediation and solid waste management Deed notation in place for closure with CCR left in place	Similar to Alternatives 1 through 3 Depending on the gradient control method selected, the long-term reliability can be good There is significant industry experience with some potential gradient control methods used in remediation of groundwater impacts	Success of remedy at PCS does not rely on long-term reliability of engineering or institutional controls Overall success relies on reliability of the engineering and institutional controls at the receiving facility
257.97(c)(1)(viii) Potential need for replacement of the remedy	Limited potential need for replacement of original cap placed in 2018 if maintained.	Same as Alternative #1	Same as Alternative #1	Same as Alternative #1	No potential need for remedy replacement
SOURCE CONTROL TO MITIGATE FUTURE RELEASES - 40 CFR 257.97(c)(2)					
257.97(c)(2)(i) The extent to which containment practices will reduce further releases	Cap installed in 2018 will reduce further releases by minimizing infiltration through CCR	Same as Alternative #1	Same as Alternative #1 with possible reduction in further release risk due to lower cap permeability/ reduced infiltration through CCR	Same as Alternative #1	Removal of CCR prevents further releases at PCS Receiving disposal site risk similar to Alternative #3
257.97(c)(2)(ii) The extent to which treatment technologies may be used	Alternative does not rely on treatment technologies for source control	Alternative does not rely on treatment technologies for source control	Alternative does not rely on treatment technologies for source control	Alternative does not rely on treatment technologies for source control	Alternative does not rely on treatment technologies for source control

**Table 4. Preliminary Evaluation of Corrective Measure Alternatives
Prairie Creek Generating Station / SCS Engineers Project #25218201.00**

	Alternative #1 No Further Action	Alternative #2 Monitored Natural Attenuation (MNA)	Alternative #3 Cover Upgrade with MNA	Alternative #4 Gradient Control with MNA	Alternative #5 Excavate and Dispose in Offsite Landfill
IMPLEMENTATION - 40 CFR 257.97(c)(3)					
257.97(c)(3)(i) Degree of difficulty associated with constructing the technology	No construction involved	No construction involved	Low complexity construction Moderate degree of design and logistical complexity to complete cap upgrade	Moderate complexity construction High degree of logistical complexity due to off-site property owner access	Low complexity construction High degree of logistical complexity including the excavation and off-site transport of ~148K cy of CCR and permitting/development of off-site disposal facility airspace Moderate to high level of dewatering effort - dewatering required for excavation of full CCR volume
257.97(c)(3)(ii) Expected operational reliability of the technologies	Not Applicable	Not Applicable	High reliability based on historic use of capping as corrective measure	Operational reliability depends on method of gradient control required/selected, the level of extracted groundwater treatment required, and the location of groundwater treatment Overall expected reliability is good based on industry experience	Success at PCS does not rely on operational reliability of technologies Overall success relies on off-site disposal facility, which is likely same/similar to Alternative #3
IMPLEMENTATION - 40 CFR 257.97(c)(3) (continued)					
257.97(c)(3)(iii) Need to coordinate with and obtain necessary approvals and permits from other agencies	No further approvals or permits required	Same as Alternative #1	Need is low in comparison to other alternatives State Closure Permit amendment likely required	Need is high in comparison to other alternatives State Closure Permit amendment likely required Approval of downgradient site owner required Approval of facility receiving gradient control discharge for treatment required, or agency approval to construct the necessary treatment facility is required	Need is highest in comparison to other alternatives State Closure Permit amendment likely required Approval of off-site disposal site owner required May require State solid waste comprehensive planning approval Local road use permits likely required
257.97(c)(3)(iv) Availability of necessary equipment and specialists	Not Applicable	Lowest level of demand for MNA implementation	Low level of demand for cap construction material	Moderate level of demand expected Level of demand may vary based on method of gradient control selected	Availability of necessary equipment to develop necessary off-site disposal facility airspace and transport ~148K cy of CCR to new disposal facility will be a limiting factor in the schedule for executing this alternative No liner or cover material demands for on-site implementation of remedy
257.97(c)(3)(v) Available capacity and location of needed treatment, storage, and disposal services	Not Applicable	Not Applicable	Not Applicable	There is no on-site capacity to treat gradient control system discharge If required, on-site capacity will need to be developed Off-site capacity to treat gradient control system discharge may exist at City of Cedar Rapids WWTP, but ability/willingness to accept discharge is currently unknown	Off-site disposal capacity, facility logistical capacity, or the time required to develop the necessary off-site disposal and logistical capacity is a significant limiting factor
COMMUNITY ACCEPTANCE - 40 CFR 257.97(c)(4)					
257.97(c)(4) The degree to which community concerns are addressed by a potential remedy (Anticipated)	To be determined based on input obtained through public meetings/outreach to be completed	To be determined based on input obtained through public meetings/outreach to be completed	To be determined based on input obtained through public meetings/outreach to be completed	To be determined based on input obtained through public meetings/outreach to be completed	To be determined based on input obtained through public meetings/outreach to be completed

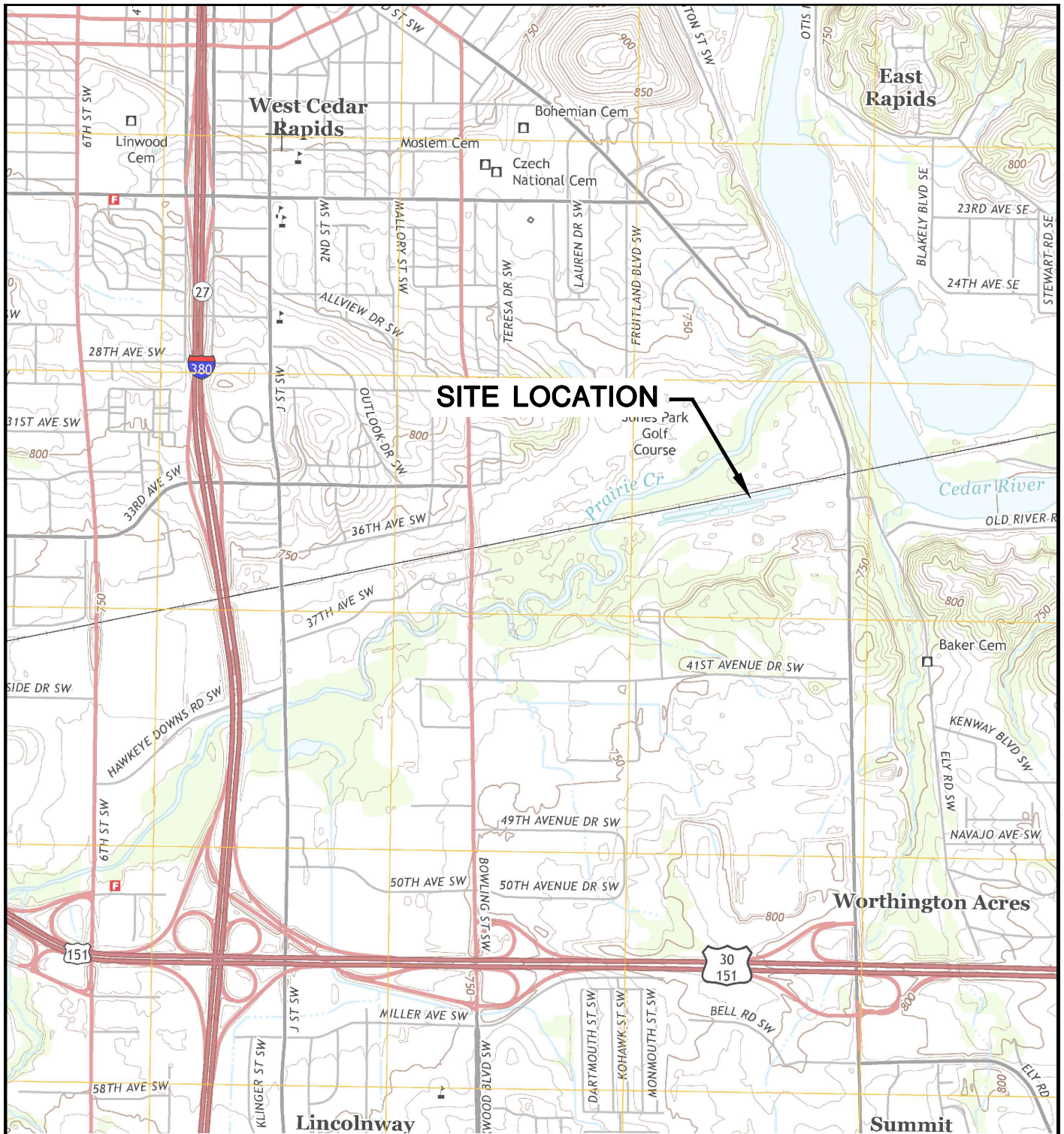
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Last revision by: EJN
Checked by: TK/SC

Date: 6/20/2019
Date: 8/12/2019
Date: 8/13/2019

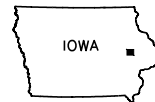
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Figures

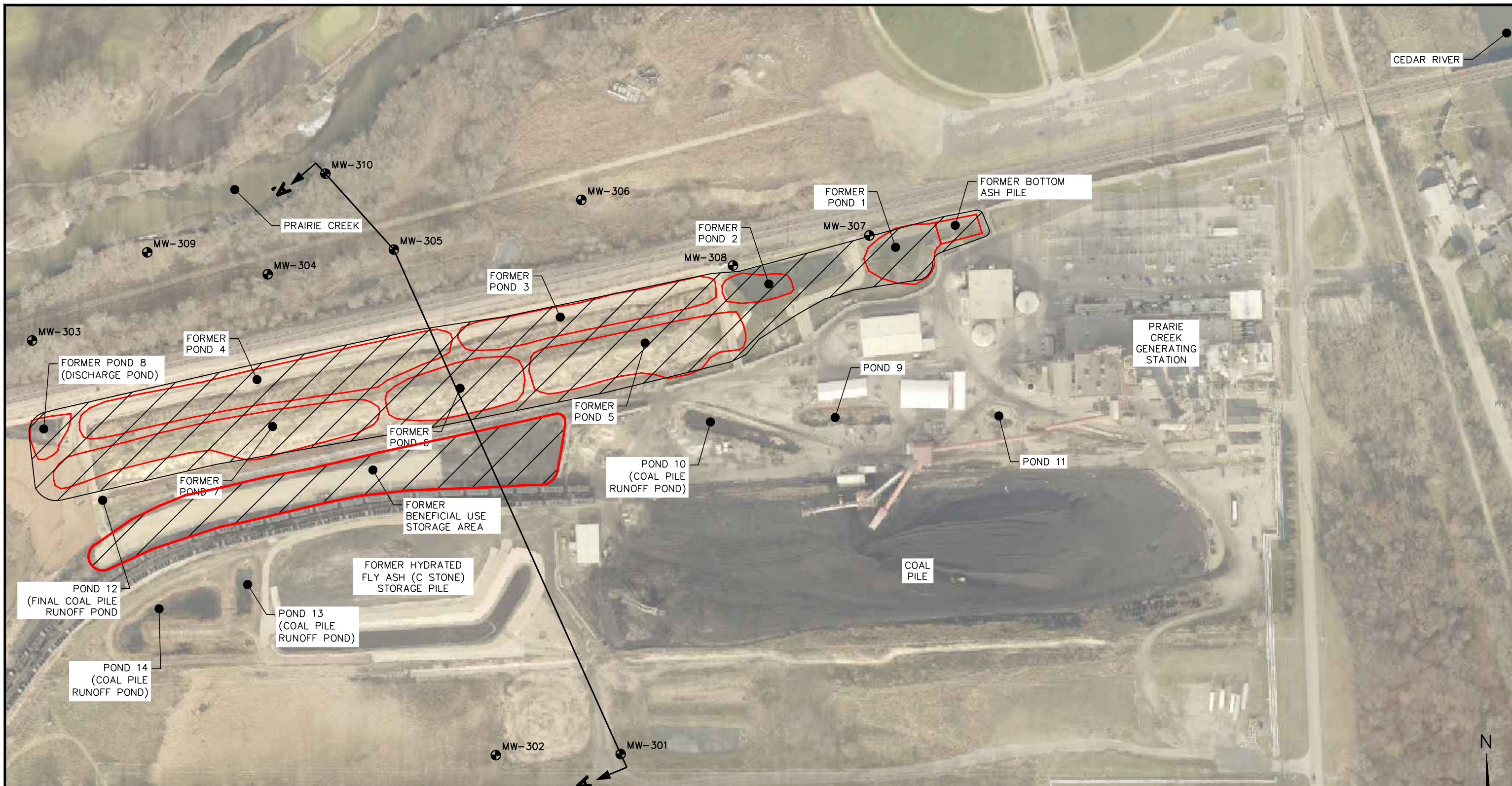
- 1 Site Location Map
- 2 Site Plan and Monitoring Well Locations Map
- 3 Water Table Map – April 2019
- 4 Cross Section A-A'







CEDAR RAPIDS SOUTH QUADRANGLE
 IOWA-LINN CO.
 7.5 MINUTE SERIES (TOPOGRAPHIC)
 2013
 SCALE: 1" = 2,000'



CLIENT	ALLIANT ENERGY 4902 N. BILTMORE LANE, MADISON, WI 53718	SITE	IPL- PRAIRIE CREEK GENERATING STATION 3300 C ST. SW CEDAR RAPIDS, IA 52404	ENGINEER	SCS ENGINEERS 2830 DAIRY DRIVE MADISON, WI 53718-6751 PHONE: (608) 224-2830	FIGURE	1					
	PROJECT NO.		25218201.00				DRAWN BY:	AHB	DRAWN:	05/28/15	CHECKED BY:	KK

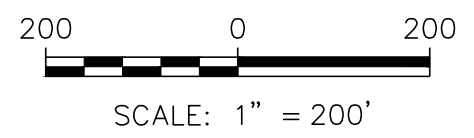


LEGEND

-  MONITORING WELL
-  CLOSURE AREA (APPROXIMATE)
-  FORMER POND OR CCR UNIT LIMITS (APPROXIMATE)
-  GEOLOGIC CROSS SECTION LOCATION

NOTES:

1. PCS PONDS 1-8, THE BOTTOM ASH PILE, AND THE BENEFICIAL USE STORAGE AREA WERE CLOSED IN DECEMBER 2018.
2. AERIAL PHOTO IMPORTED FROM THE ARCMAP BASEMAP (CEDAR RAPIDS, IOWA GIS - DECEMBER 22, 2018).



PROJECT NO.	25218201.00	DRAWN BY:	BSS
DRAWN:	07/03/19	CHECKED BY:	MDB
REVISED:	08/17/19	APPROVED BY:	TJK 09/10/19

ENGINEER

SCS ENGINEERS
 2830 DAIRY DRIVE MADISON, WI 53718-6751
 PHONE: (608) 224-2830

CLIENT

ALLIANT ENERGY
 4902 N. BILTMORE LANE
 MADISON, WI 53718

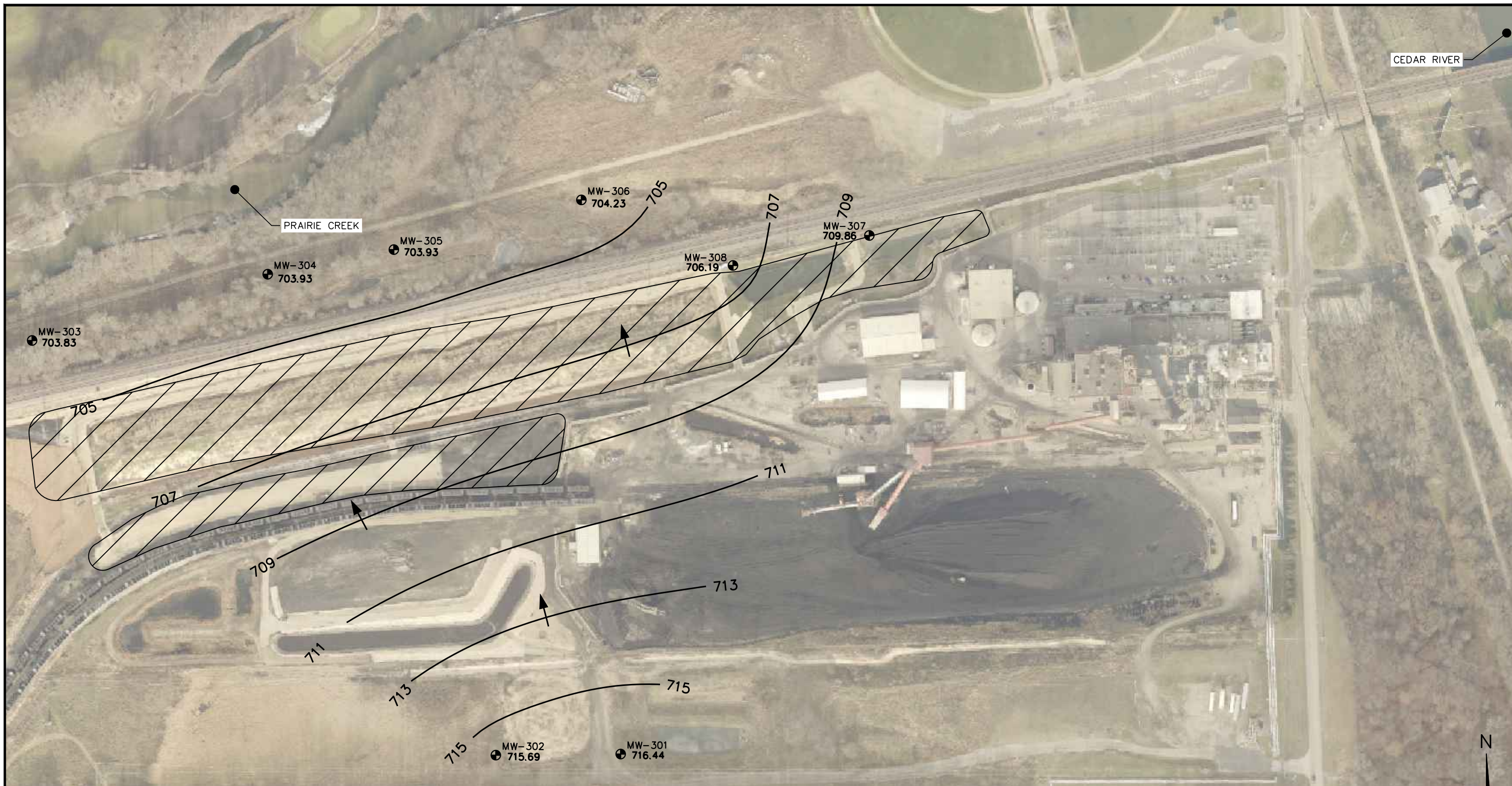
SITE

IPL-PRAIRIE CREEK GENERATING STATION
 3300 C ST. SW
 CEDAR RAPIDS, IA 52404

SITE PLAN AND
 MONITORING WELL LOCATION MAP

FIGURE
 2

I:\25218201.00\Drawings\Prairie Creek\2 Prairie Creek Site Plan and Monitoring Well Location.dwg, 9/10/2019 1:31:35 PM

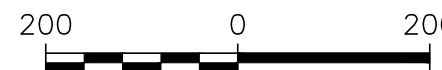


LEGEND

- MONITORING WELL
- WATER TABLE CONTOUR
- CLOSURE AREA (APPROXIMATE)
- 716.44 WATER TABLE ELEVATION (APRIL 22-23, 2019)
- APPROXIMATE GROUNDWATER FLOW DIRECTION

NOTES:

1. AERIAL PHOTO IMPORTED FROM THE ARCMAP BASEMAP (CEDAR RAPIDS, IOWA GIS - DECEMBER 22, 2018).



SCALE: 1" = 200'



PROJECT NO.	25218201.00	DRAWN BY:	BSS
DRAWN:	07/03/19	CHECKED BY:	MDB
REVISED:	07/15/19	APPROVED BY:	TJK 09/10/19

SCS ENGINEERS
 2830 DAIRY DRIVE MADISON, WI 53718-6751
 PHONE: (608) 224-2830

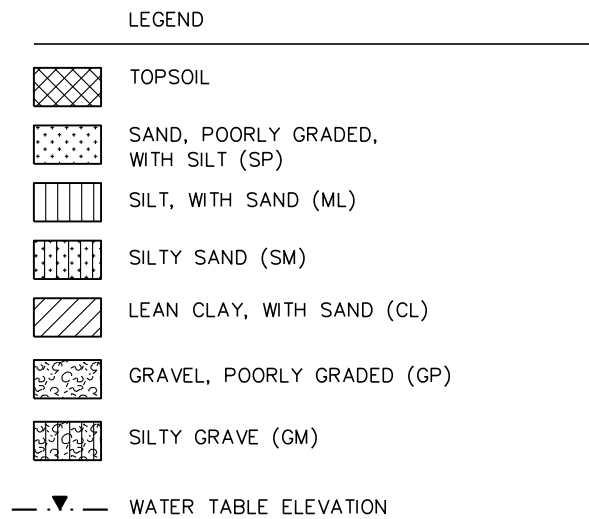
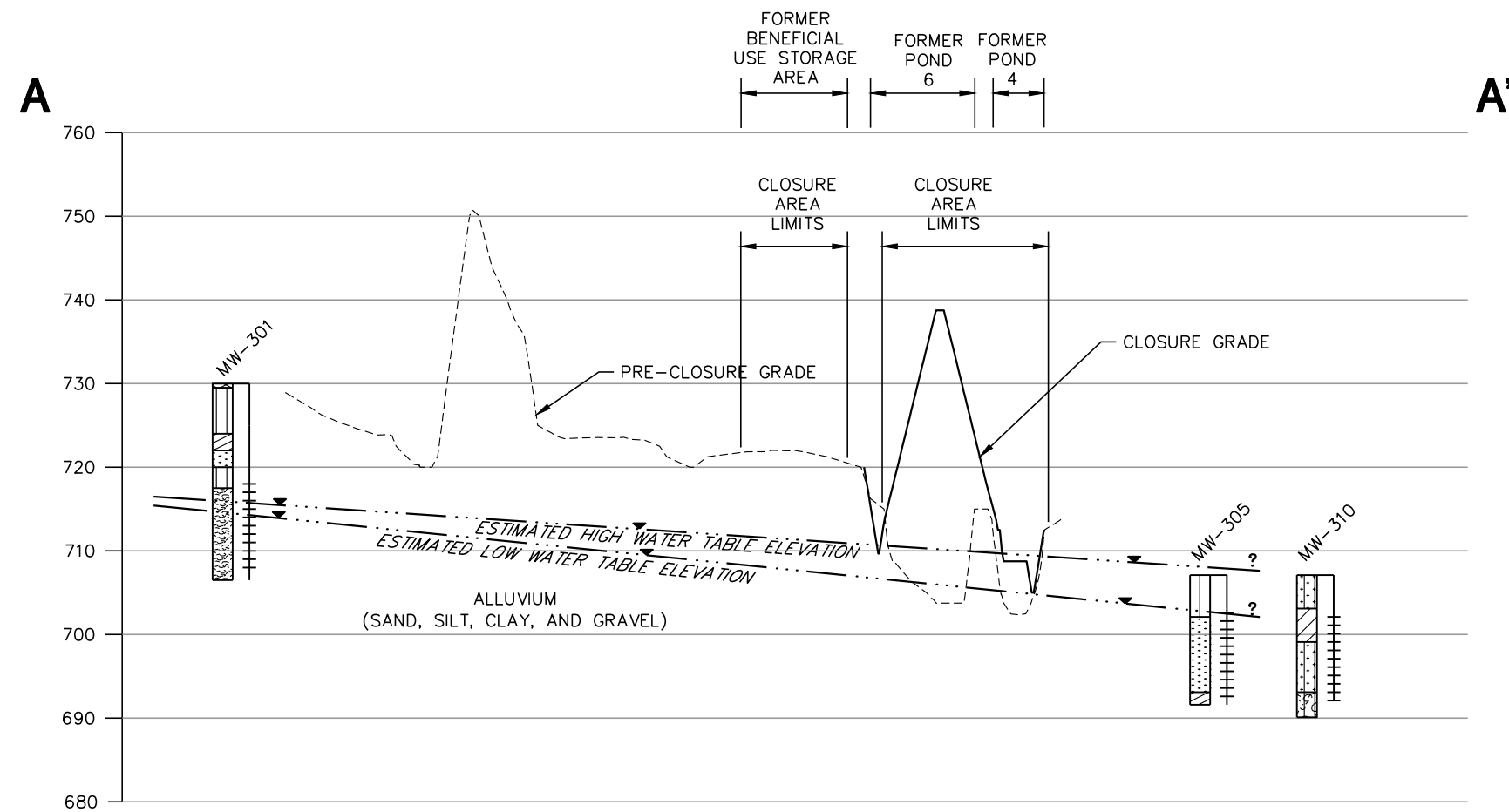
ALLIANT ENERGY
 4902 N. BILTMORE LANE
 MADISON, WI 53718

IPL-PRAIRIE CREEK GENERATING STATION
 3300 C ST. SW
 CEDAR RAPIDS, IA 52404

WATER TABLE MAP - APRIL 2019

FIGURE
3

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NOTES:

1. PRE-CLOSURE GRADE IS A COMPOSITE OF A SURVEY OF THE CCR IMPOUNDMENTS AND FLY ASH STOCKPILES, DATED 09-26-2016 BY FRENCH-RENEKER ASSOCIATES, AND A SURVEY OF THE REMAINDER OF THE PLANT PROPERTY BY ANDERSON BOGERT DATED 06-05-2017
2. PROPOSED CLOSURE GRADE FROM PRAIRE CREEK GENERATION STATION INTERSTATE POWER & LIGHT CO. (A SUBSIDIARY OF ALLIANT ENERGY) CCR SURFACE IMPOUNDMENT CLOSURE PLAN AND SITE STORM WATER MANAGEMENT PREPARED BY SARGENT & LUNDY AND DATED 08/01/2018.
3. HIGH WATER TABLE ELEVATION MEASURED IN OCTOBER 2018 AND LOW WATER TABLE ELEVATION MEASURED IN AUGUST 2018.



HORIZONTAL SCALE: 1" = 200'
 VERTICAL SCALE: 1" = 20'
 VERTICAL EXAGGERATION = 10X

PROJECT NO. 25218201.00	DRAWN BY: BSS	ENGINEER	 2830 DAIRY DRIVE MADISON, WI 53718-6751 PHONE: (608) 224-2830	CLIENT	 ALLIANT ENERGY 4902 N. BILTMORE LANE MADISON, WI 53718	SITE	IPL-PRAIRIE CREEK GENERATING STATION 3300 C ST. SW CEDAR RAPIDS, IA 52404	CROSS SECTION A-A'	FIGURE
DRAWN: 07/03/19	CHECKED BY: MDB						4		
REVISED: 08/27/19	APPROVED BY: TJK 09/10/19								



Appendix A
Regional Geological and Hydrogeological Information

**Table PC-2. Regional Hydrogeologic Stratigraphy
Prairie Creek Generating Station / SCS Engineers Project #25215053.01**

Age of Rocks	Hydrogeologic Unit	General Thickness (feet)	Name of Rock Unit*	Type of Rock
Quaternary (0-1 million years old)	Surficial Aquifers • Alluvial • Buried-Channel • Drift	0 to 400	Undifferentiated	<ul style="list-style-type: none"> • Sand, gravel, silt, and clay • Sand, gravel, silt, and clay • Till (sandy, pebbly clay), sand, and silt
Pennsylvanian (280 to 310 million years old)	Aquiclude, locally contains waterbearing sandstone	0 to 70	Undifferentiated	<ul style="list-style-type: none"> • Shale, sandstone, limestone, and coal
Mississippian (310 to 345 million years old)	Mississippian Aquifer	0 to 220	Meramecian Series Osagean Series Kinderhookian Series	<ul style="list-style-type: none"> • Limestone and sandstone • Dolomite, limestone, and shale • Limestone, dolomite, and siltstone
Devonian (345 to 400 million years old)	Devonian Aquiclude	0 to 350	Yellow Spring Group Lime Creek Group	<ul style="list-style-type: none"> • Shale, dolomite, and siltstone • Dolomite and shale
	Devonian Aquifer	0 to 400	Cedar Valley Limestone Wapsipinicon Limestone	<ul style="list-style-type: none"> • Limestone and dolomite • Dolomite, limestone, and shale
Silurian (400 to 425 million years old)	Silurian Aquifer	0 to 450	Gower Dolomite Hopkinton Dolomite Kankakee Limestone Edgewood Dolomite	<ul style="list-style-type: none"> • Dolomite, with some chert and limestone
Ordovician (425 to 500 million years old)	Aquiclude	300 to 600	Maquoketa Shale Galena Dolomite Decorah Formation Platteville Formation	<ul style="list-style-type: none"> • Dolomite and shale • Dolomite and chert • Limestone and shale • Limestone and shale
	Cambrian-Ordovician aquifer	400 to 650	St. Peter sandstone Prairie du Chien Formation Jordan Sandstone St. Lawrence Dolomite	<ul style="list-style-type: none"> • Sandstone • Dolomite, sandstone, and shale • Sandstone • Dolomite
Cambrian (500 to 600 million years old)	Cambrian confining beds	90 to 290	Franconia Sandstone	<ul style="list-style-type: none"> • Shale, siltstone, and sandstone
	Dresbach Aquifer	157 to 1644	Dresbach Group Galesville Sandstone Eau Claire Sandstone Mt. Simon Sandstone	<ul style="list-style-type: none"> • Sandstone • Sandstone, shale, and dolomite • Sandstone
Precambrian (600 million to more than 2 billion years old)	Precambrian rocks	Unknown	Crystalline rocks, undifferentiated	<ul style="list-style-type: none"> • Sandstone, igneous and metamorphic rocks

*This nomenclature and classification of rock units in this report are those of the Iowa Geological Survey and do not necessarily coincide with those accepted by the U.S. Geological Survey.

Source: "Water Resources of East-Central Iowa," Iowa Geologic Survey Water Atlas No. 6.

I:\25215053\Reports\Report 8 - OGS\Tables\Regional_Hydrogeologic_Stratigraphy.doc

GO

Things to See & Do Resident Resources Doing Business City Council Government City News CR Talks

Resident Resources

Parks & Recreation

Utilities

- Energy Management
- Garbage & Recycling
- Utility Bills

Water

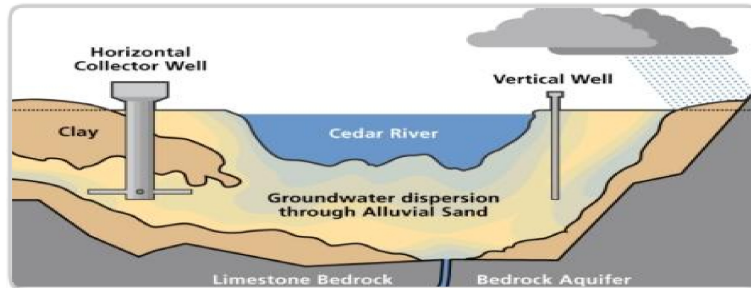
- About Us
- Backflow Prevention
- Outages/Main Breaks
- Our Treatment Process

Water Quality

Our Watershed

- Water Quality Report
- Best Tasting Water
- Water Engineering
- In the Home
- Drought
- Water Conservation
- Utility Bills
- 5 in 1 Dam
- Sewer Maintenance
- Water Pollution Control
- Sewer
- Storm Water
- City Buses
- Rental Services
- Neighborhood Services
- Streets Services
- Housing Services
- CleanUpCR
- iGreenCR
- Library
- Public Safety
- City Services
- Get Involved
- Americans with Disabilities Act

Our Watershed



SHARE

Where Does Our Water Come From?

The City of Cedar Rapids obtains its drinking water supplies from shallow vertical and collector wells constructed in the sand and gravel deposits along the Cedar River. Those deposits form an underground water-bearing layer called an alluvial aquifer. Because of continuous pumping of the City's wells, most of the water in the aquifer is pulled from the river. The rest of the water is supplied as water percolates up from a deeper bedrock aquifer or down from the top of the ground.

Our drinking water from those wells benefits from natural filtration through the riverbank. This natural sand filtration has proven beneficial, pre-treating the water before it ever reaches the City's two treatment plants (both conventional lime-softening facilities).

Watershed Monitoring

In order to most effectively manage our water resources, the Cedar Rapids Water Division has worked with state and federal agencies to complete a source water assessment, identifying potential contamination sources in the Cedar River watershed. The results of that assessment, paired with a continuous monitoring program, help us better understand our watershed. We have confirmed that some contaminants, including nitrate, herbicides and bacteria, enter the Cedar River watershed upstream from our wells. The watershed of the Cedar River upstream from Cedar Rapids is over 6,500 square miles and extends into southern Minnesota. Monitoring of these contaminants will continue to ensure a strong watershed protection program.

If you are interested in reviewing our source water assessment or any monitoring results, please contact the CRWD at 319-286-5910.

- | | | | |
|-----------------------------|------------------------|---------------------------|--------------------|
| How do I...? | Building Permit Viewer | Flood Recovery Progress | Parks & Recreation |
| Contact Us | City Buses | Garbage Pickup | Public Safety |
| Subscribe | City Departments | Licenses, Permits & Taxes | Utility Bills |
| Bid Opportunities & Results | Report a Problem | Maps | FAQ |

Select Language ▼

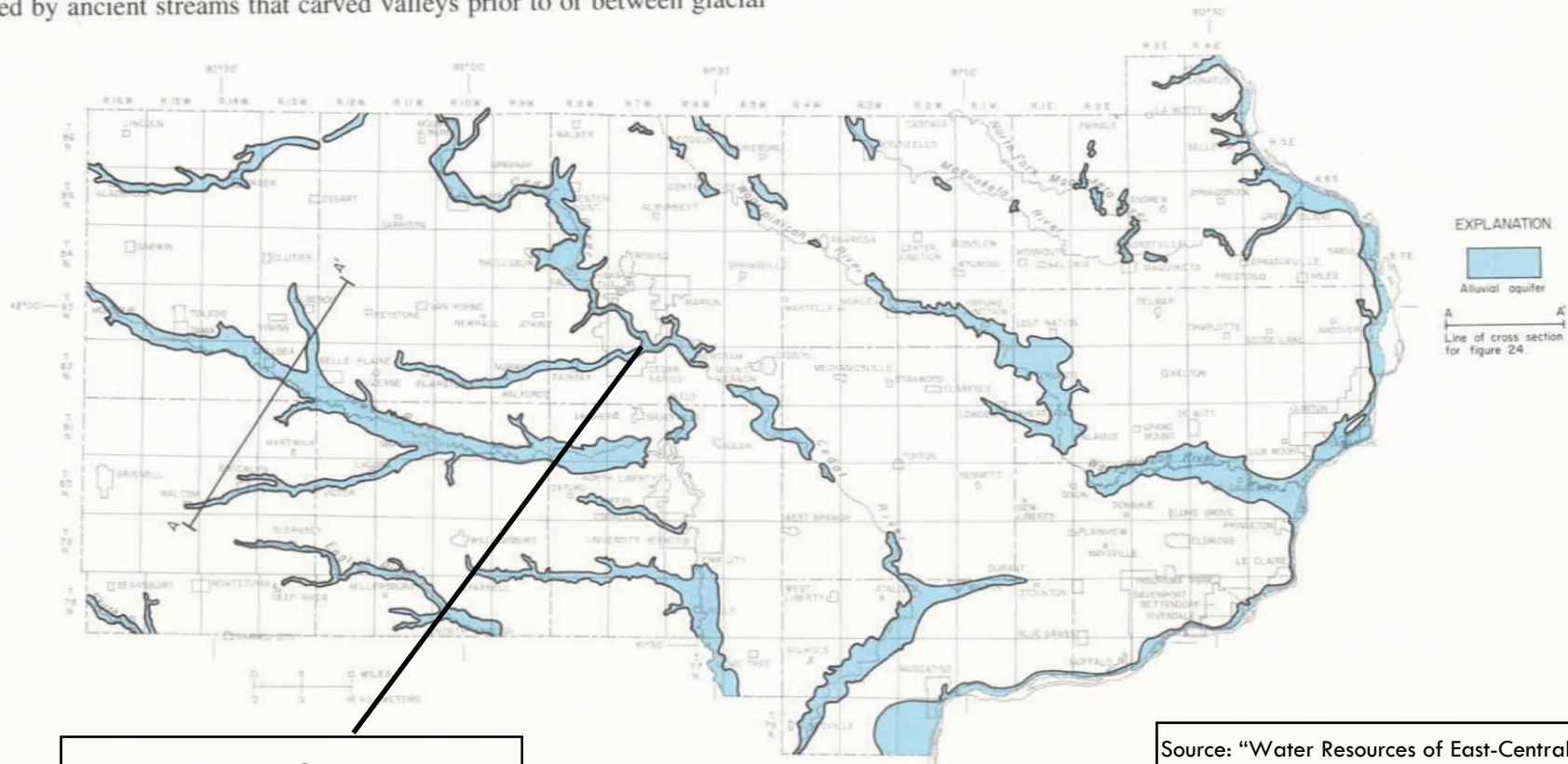
Surficial Aquifers

The surficial aquifers are located within the unconsolidated materials above the bedrock surface. They are subdivided into alluvial, buried-channel, and drift aquifers.

The alluvial aquifers are deposits located along present-day watercourses. They consist of sands and gravels interbedded with less-permeable silts and clays and lie beneath the flood plains of larger rivers and creeks. In the eastern half of the report area, the Iowa, Cedar, Wapsipinicon, and Maquoketa Rivers as well as Buffalo Creek alternately flow through narrow bedrock gorges and wide flood plains (fig. 22). Thus the alluvial aquifers occur irregularly in the valleys of these rivers.

The buried-channel aquifers (fig. 23) are the unconsolidated material deposited by ancient streams that carved valleys prior to or between glacial

advances. Many of these ancient valleys were scoured deeply into the bedrock and are much wider than the valleys of present streams (fig. 24). Buried channels may be easily recognized on the bedrock topography map (fig. 25), but are only poorly expressed in the modern landscape. While they are not generally expressed as primary features of present topography, they exert noticeable influences on modern drainage. Prairie Creek near Cedar Rapids, Deep Creek near Preston, and the lower stretches of the Cedar, Wapsipinicon, and Maquoketa Rivers follow the courses of buried channels. See figures 22 and 23. In addition, most of the irregularly occurring alluvial aquifers in the eastern half of the report area are located where modern stream valleys intersect buried bedrock channels.



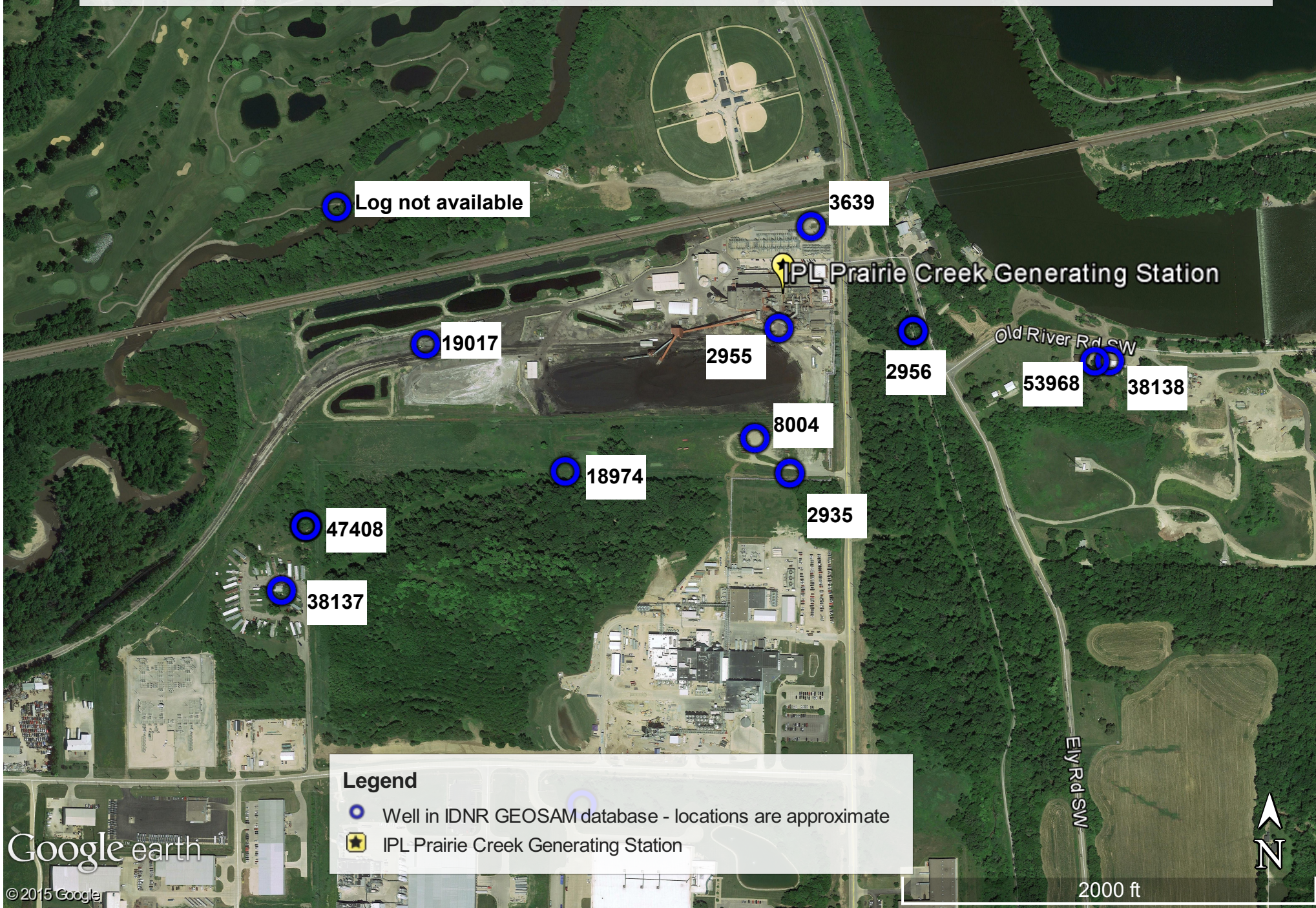
Approximate Site Location

Source: "Water Resources of East-Central Iowa,"
Iowa Geologic Survey Water Atlas No. 6.

Figure 22.—Areal distribution of alluvial aquifers in east-central Iowa

Historical Well Logs Near Prairie Creek Generating Station

Labeled well locations are included in IDNR's GEOSAM database. Logs are not available for all well borings. Well locations are approximate.



Legend

- Well in IDNR GEOSAM database - locations are approximate
- IPL Prairie Creek Generating Station

Google earth

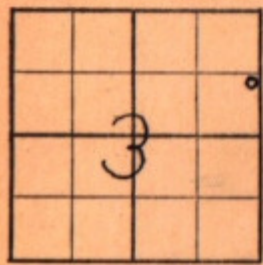
© 2015 Google

2000 ft



FORM NO. 79 -- In stock and for sale by Mid-West Prtg. Co., Tulsa W-2935

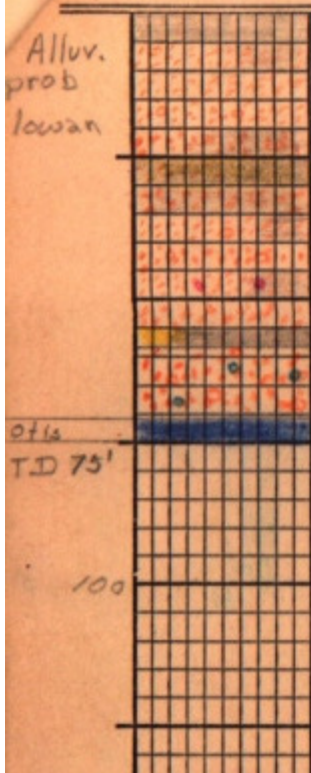
STATE IOWA CEDAR RAPIDS (LINN)
 NE/SE NE CENTRAL IOWA POWER CO-OP
 SEC. 3 Test hole No. 1
 TWP. 82N RGE. 7W COMMENCED COMPLETED



Art Bruinekool
 CASING RECORD
 LOGGED BY
 Aug 11, 1947 S.E.T. + G.

REMARKS
 Elev. 722 ± S.W.L. 19.6' below L.S. - 8-11-47
 T.D. 75'

CB7-3



soil reddish brn, silty
 sd med to crse, dirty, brn to red
 yel crser this is clean
 Gray clay masses sdy
 silt sdy, calc, gr. Aluv.
 sd crs pbls
 some pbls
 cht pbls
 sd med poorly sorted, rd, bright
 silt clay bl gr. v. fn; silt lam, wh, qtz
 sd, crse to v. crsw. some grav.
 yel bedrock reported
 71
 Bertram

22 1/2
77 1/2
100

General	Construction	Logs	Stratigraphy	Water	Storage
---------	--------------	------	--------------	-------	---------

Identification

Date Received
Owner Name Hide-A-Way Manor
Alt Name
WNumber 38137
PWTS ID
Storet ID
SDWIS ID 2411834
USGS ID
Project SOURCE WATER PROTECTION
Operator Unknown

Location

State Iowa
County Linn
Quadrangle Cedar Rapids South, Iowa
Township T82N
Range R7W
Section 3
Quarter SW NE NE
Latitude 41.9401300000
Longitude -91.6478370000
Accuracy GPS +/- 20 m.
UTM X 612089
UTM Y 4644013

Site

Site Type Drilled hole
Well Status Active
Field Located
Elevation 741 ft
Elevation Accuracy Digital Elevation Model
 Accurate to 5 ft
Landscape Position Valley

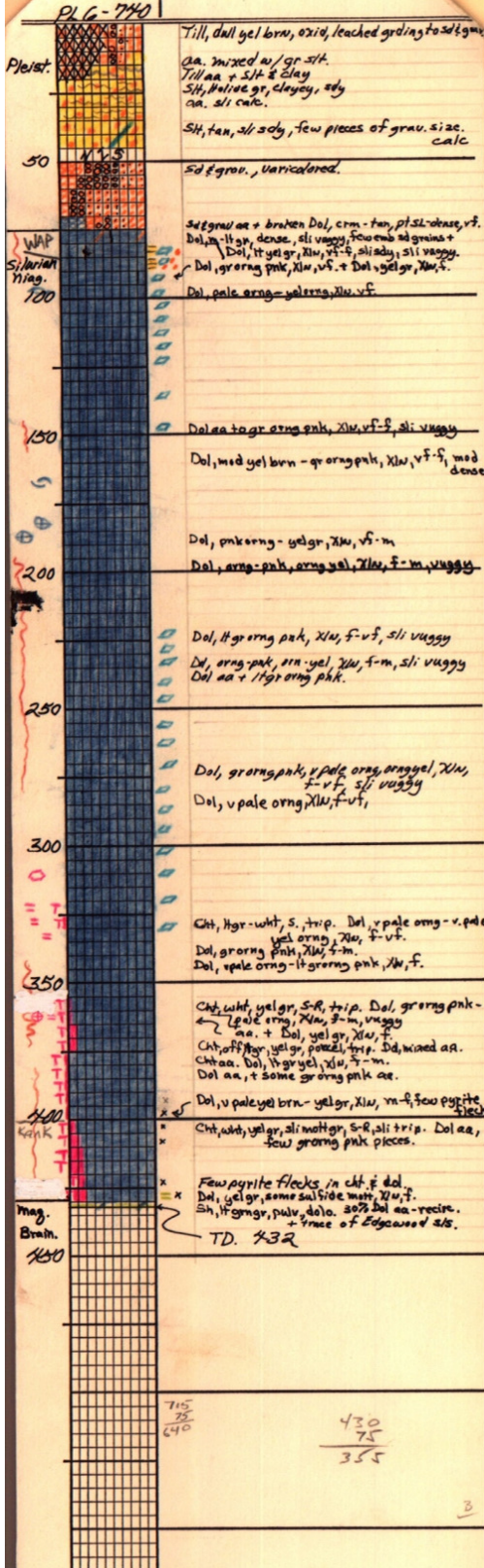
Drilling

Drilling Company Unknown
Drilling Date
Drill Method Unknown
Bedrock Depth
Well Depth 142 ft
Total Depth 142 ft
Well Types Public Access
Aquifers Silurian

STATE Iowa Cedar Rapids (Linna)
 SW NW SW NE Iowa Elec. L & P #5
 SEC. 3
 TWP. 82 RGE. 7W COMMENCED _____ COMPLETED 10/66
 THORPE
 CASING RECORD

LOGGED July 1974 BY Gilmore
 REMARKS

El. 715' Top.
 TD. 432'



715
 32
 640

430
 75
 355

STATE Iowa Cedar Rapids (Linn)

SENE SWNE Central Iowa Power #4

SEC. 3

TWP. 82 RGE. 7W COMMENCED 8-22-66 COMPLETED 9-17-66

Thorpe well co.

CASING RECORD
42" csg 0-5', 32" csg +1'-23', 24" csg

+17'-69'7", 16" csg +2'10"-90'

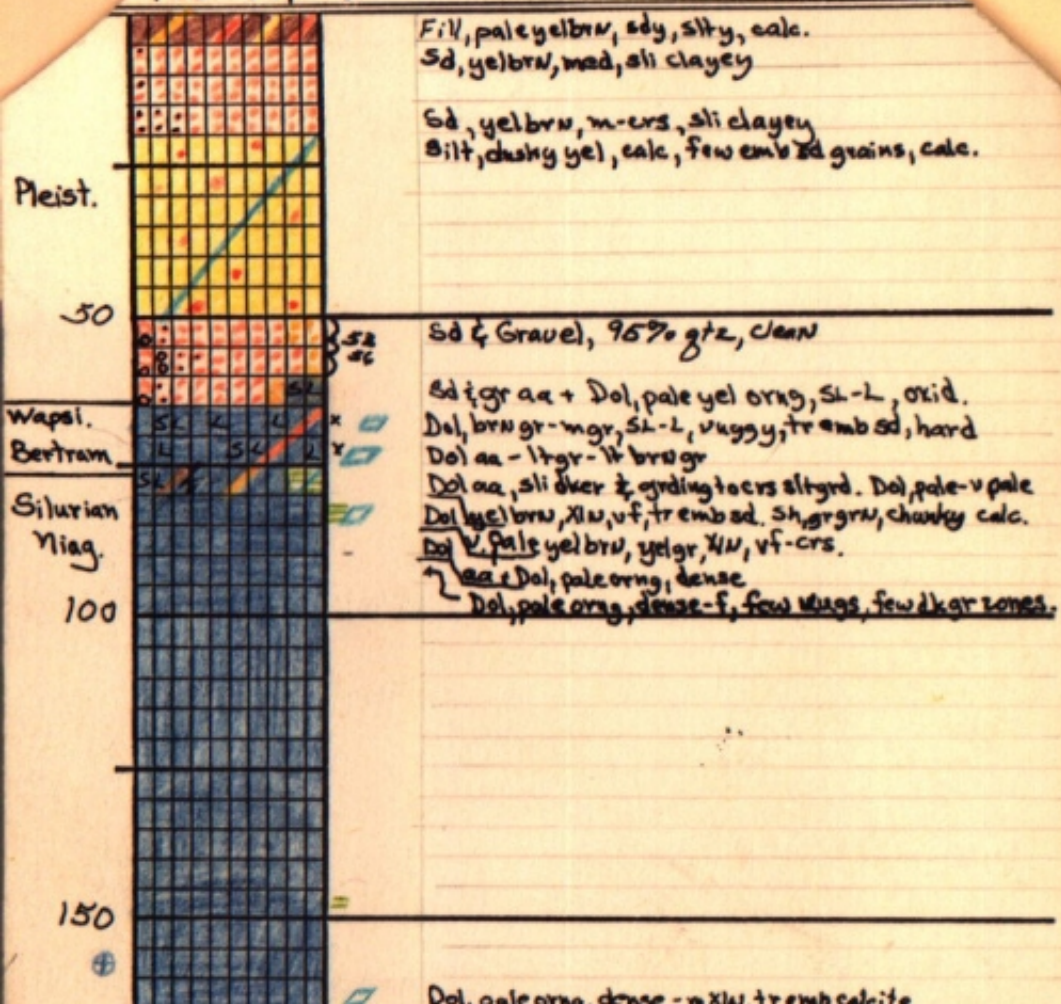
LOGGED 10-22-71 BY Gilmore

REMARKS
Cable tools

EL. 722' TD. 439' SWL-40-58', PL-113.9'

Yield-600 gpm

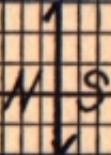
PL6-717



Dol aa, more XW, some pin point por.
Dol, pale org - pink org, XW, f, pt dense, few gr zones

200

Dol, org pink - pale org, XW, v.f., pin point por.



Dol, mod org pink - pale org, XW, v.f., pt dense, sh por, vuggy, calcite - clear - yel.

250



Dol, gro org, org pink, dense, f, emb calcite

300

Dol aa few gr zones
Dol, v. pale org, dense - f, emb calcite - yel - clear
Dol aa + some org pink

Dol, pale org, tr pink, XW, f, emb calcite, pin point por
cht, yel gr, wht, trip. Dol aa.
cht aa foss.

cht, lt gr, wht, trip, foss. Dol, v. pale org, XW, f,
sh vuggy - por, trace org pink,
cht aa. Dol, v. pale org, trace org pink, XW, f - v.f.
Dol, pale org, gro org pink, dense, f, sh vuggy & por.

350

cht, v. lt gr, wht, slt trip. S. Dol, pale - v. pale org, XW, f-m.
Dol aa, sh vuggy

cht aa. Dol, v. pale org, XW, f - v.f.
cht, lt gr, wht, slt trip. Dol, v. pale yel brn, pale org, XW, f - m.
cht, lt - v. lt gr, S. Dol aa.
cht, lt gr, wht, pale yel brn, S, slt trip. Dol aa sh vuggy
cht aa. Dol, pale gro org, XW, f - m.
cht, lt - v. lt gr, S, sh mett. Dol aa.

400

cht, off wht, lt gr, S-R, slt trip. Dol aa, some dissem. pyrite.
cht aa. Dol, v. pale yel brn, XW, f - m.
cht, off wht, yel brn, lt gr, S-R, slt trip. Dol aa w/ dk gr mett.,
pt sh mett & arg.

Sh, gr gr, chunky, dolo.

TD. 439'

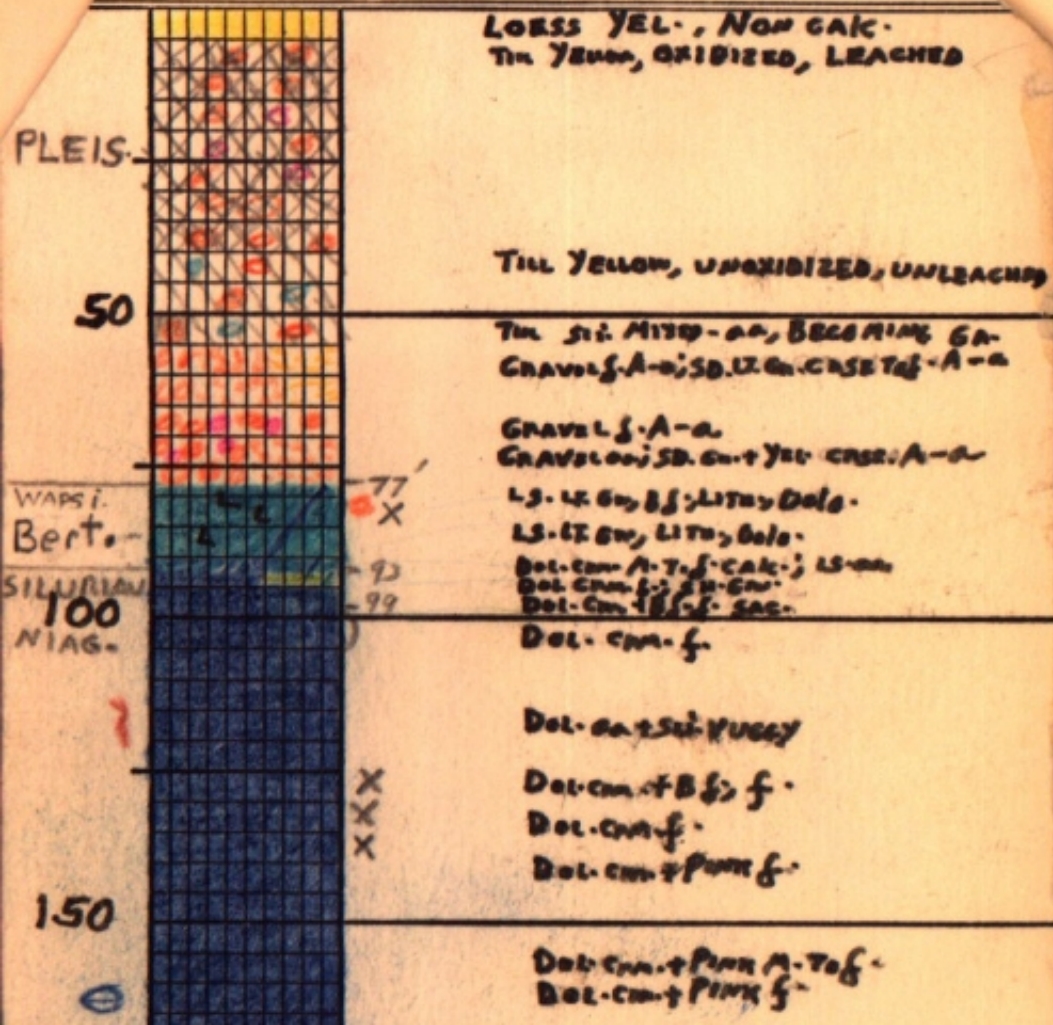
Kank.

Mag. 450

$$\begin{array}{r} 720 \\ 60 \\ \hline 660 \end{array}$$

$$\begin{array}{r} 722 \\ 436 \\ \hline 286 \end{array}$$

STATE		IOWA		CEDAR RAPIDS (LINN)													
NW NE SE NE		APP. C NE SE		CENTRAL IOWA POWER COOP #3													
SEC. 3		DAWN SE NE		(REA)													
TWP.	RGE.	COMMENCED	COMPLETED														
82N	7W	AUG. 21 - SEPT. 14, 1956															
<table border="1"> <tr><td></td><td></td><td></td></tr> <tr><td></td><td></td><td></td></tr> <tr><td></td><td></td><td></td></tr> <tr><td></td><td></td><td></td></tr> </table>														HORG & AMES			
CASING RECORD																	
77' OF 20" CASING																	
99' OF 12" CASING (CEMENT)																	
LOGGED		FEB. 25, 1957		BY NORTROP													
REMARKS		EL 722'															
TD		SWL 38.67'															
E		PL 144.9' @															
SWL 39.12'																	
SWL 145' @ 476 gpm																	
EK8-1																	



Dol. Bl. + P. f.

Dol. Bl. f.; sil. porous - some P. f.

Dol. con + P. f. + porous
Dol. P. f., Vuggy
Dol. con + P. f., Vuggy
Dol. con + P. f., sil. porous

Dol. con f.

Dol. con + P. f.
Dol. mostly con. f. - some P. f.
Dol. con. f., sil. vuggy

Dol. con. + P. f. > sil. porous

CHZ. W. - Room, Tap; Dol. con + P. f.
sil. porous
CHZ. con; Dol. mostly con. f. sil. porous
Dol. con + P. f. some P. f.

CHZ. W. - Room, Tap; Dol. con. A. T. f.
CHZ. W. - Room, Tap, P. f.; Dol. con
CHZ. W. - Room + S. m. Dol. con. A. T. f.
CHZ. W. - Room, Tap; Dol. con. A. T. f.
CHZ. W. - Room, S. m.; Dol. con.

CHZ. con + Room, Tap; Dol. con. A. T. f.

X Dol. con. A. T. f.

CHZ. W. - Room, Tap + S. m.; Dol. con. A. T. f.
CHZ. con; Dol. con. f.

CHZ. con; Dol. con. + sil. vuggy, chunky
Dol. con. f.; sil. chunky con. Dol. lumpy

Vertical column of blue scribbles on the left side of the page.

200

250

300

350

400

450

500

722 722
95 77
627 645

Note: The location of this

well should be checked. The map provided by the Company indicates the plant is in the

NE 1/4 sec. 3-82-7W

Elev. should be checked also.

A set of geophysical logs was run 3-23-76. Caliper and radiation logs gave indications of major cavities from 200-220' and 300-320'. These

logs are on file with the Carbonate Hydrology Project data.

3-24-76

Bunker.

LB

722
+30

292

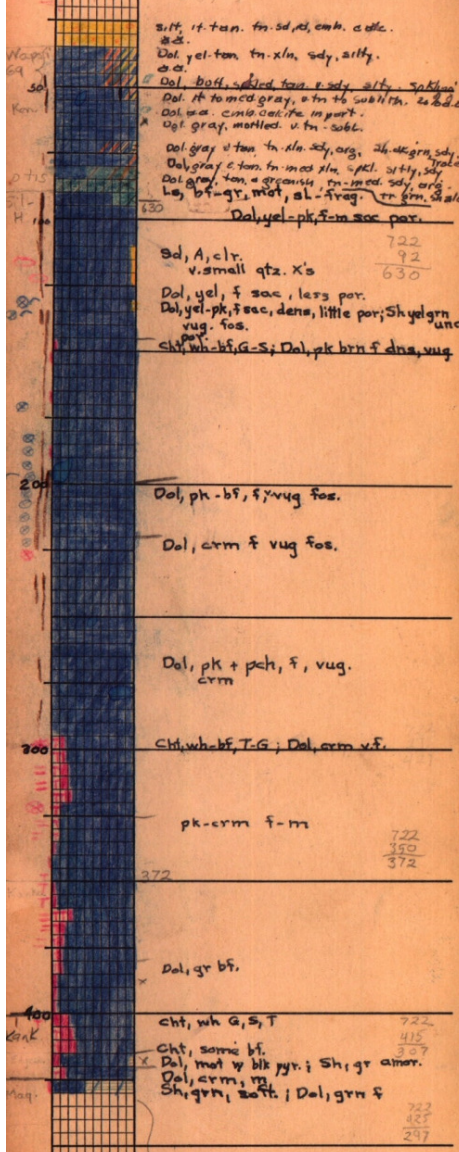
STATE
IOWA
Cedar Rapids Polk (Linw) #1

SESE-NE-NE
SEC. 3
TWP. 82N RGE. 7W
COMENCED
MAY 5-1999
R.E.A.
COMPLETED
JUNE 1, 1999

Hoes & Gmes - Ed Martin
CASING RECORD
110' of 12" casing cemented in
20" hole - (open 12" hole balance)
LOGGED BY
M. Parker

REMARKS
Pump setting 290'
2nd Prod. Test after 1st acid.
SWL. 24.50'
PWL 250±' @ 248 gpm

CE10-6
for 1/2 hrs. when rate
was increased to 250 gpm
well started pumping air



Driller reports shale at 432' - TD 439'. When measured hole was found to be 5' deeper than shown on samples.

722
425
297

STATE Iowa CEDAR RAPIDS (LINN)

NW-SW-NW Central Iowa Power Co-op #3(47)
 SEC. 2

TWP. 82N RGE. 7W COMMENCED August 13, 1947 COMPLETED

		2	

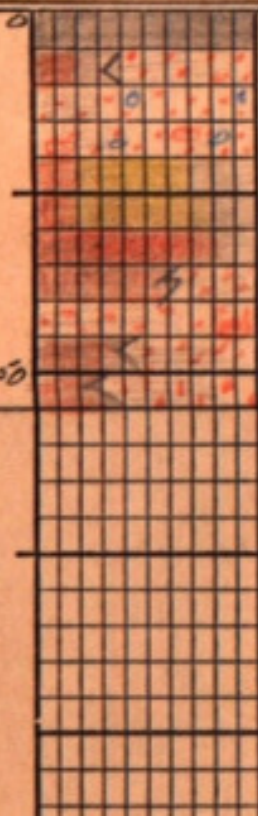
Pella Tank & Pipe Co. Brunner-Kool
 CASING RECORD
cased with 5 3/16" casing (retained)

LOGGED Aug. 25, 1947 BY M. Parker

REMARKS El. 715.5
No water level data

T.O. 55'
Test hole abandoned

CB8-1



Top soil dk. brn. silty sdy.
 sd. fn-med. r.-a dirty clay tan v. sdy.
 so med-crse r.-a. dirty.
 sd. a.a. some gravel
 clay H. gray silty sdy v. silty calc
 a.a.
 Clay H. gray-tan v. sdy.
 clay a.a. r' sd. fn-med a.-r.
 sd. med-crse a.-r. dirty some gravel

715
 55

 660

FORM NO. 79 - In stock and for sale by Mid-West Prtg. Co., Tulsa W-2955

STATE <u>Iowa</u>	<u>CEDAR RAPIDS (LIVAK)</u>
<u>NE-SE-NE</u> SEC. <u>3</u>	<u>Central Iowa Power Coop. Test hole #</u>
TWP. <u>82N</u>	RGE. <u>7W</u>
COMMENCED	COMPLETED

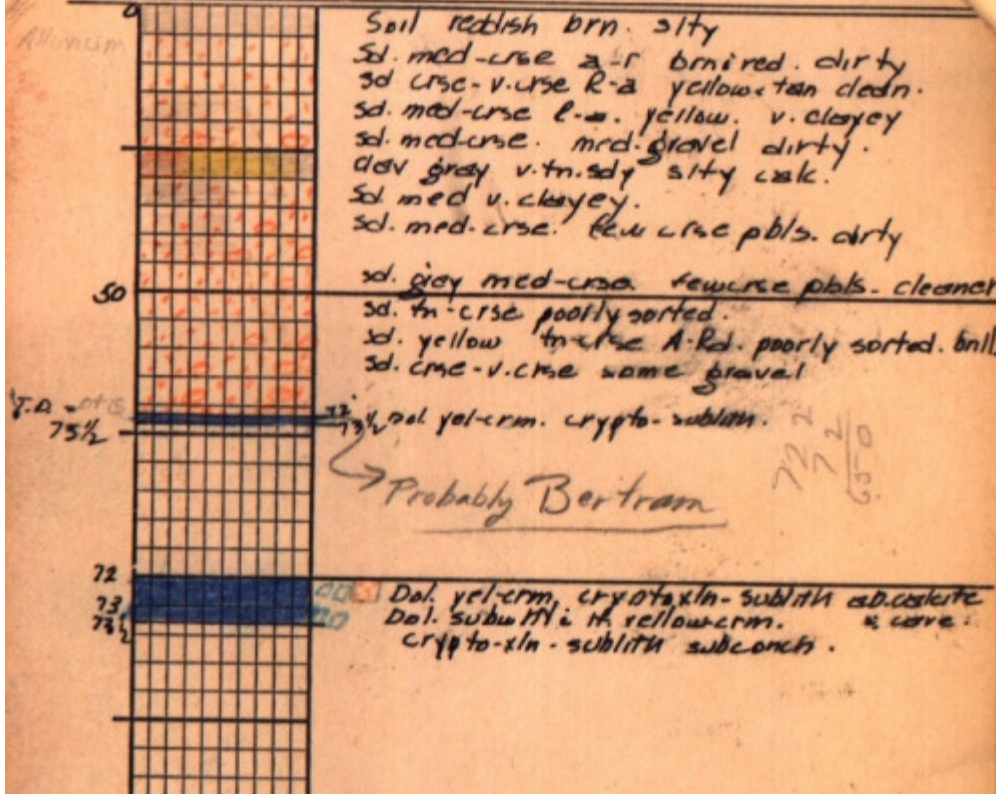


Art Bruinekool
CASING RECORD
5 3/4" casing tubed rock

LOGGED Aug 13, 1947 BY M. Parker

EL. 722[±]
T.D. 73 1/2

CB7-9



General	Construction	Logs	Stratigraphy	Water	Storage
---------	--------------	------	--------------	-------	---------

Identification

Date Received
Owner Name New Shack Tavern, The
Alt Name
WNumber 38138
PWTS ID
Storet ID
SDWIS ID 2409013
USGS ID
Project SOURCE WATER PROTECTION
Operator Unknown

Location

State Iowa
County Linn
Quadrangle Cedar Rapids South, Iowa
Township T82N
Range R7W
Section 2
Quarter NW SW NE
Latitude 41.9431790000
Longitude -91.6330300000
Accuracy GPS
UTM X 613311
UTM Y 4644371

Site

Site Type Drilled hole
Well Status Not Used
Field Located
Elevation 728 ft
Elevation Accuracy Digital Elevation Model Accurate to 5 ft
Landscape Position Valley

Drilling

Drilling Company Unknown
Drilling Date
Drill Method Unknown
Bedrock Depth
Well Depth 120 ft
Total Depth 120 ft
Well Types Public Access
Aquifers Silurian

Identification

Date Received
Owner Name New Shack Tavern, The
Alt Name
WNumber 53968
PWTS ID
Storet ID
SDWIS ID 2413414
USGS ID
Project SOURCE WATER PROTECTION
Operator Unknown

Site

Site Type Drilled hole
Well Status Not Used
Field Located
Elevation 731 ft
Elevation Accuracy Digital Elevation Model
 Accurate to 5 ft
Landscape Position Valley

Location

State Iowa
County Linn
Quadrangle Cedar Rapids South, Iowa
Township T82N
Range R7W
Section 2
Quarter NW SW NE
Latitude 41.9431730000
Longitude -91.6332960000
Accuracy GPS +/- 20 m.
UTM X 613289
UTM Y 4644370

Drilling

Drilling Company Unknown
Drilling Date
Drill Method Unknown
Bedrock Depth
Well Depth 40 ft
Total Depth 40 ft
Well Types Public Access
Aquifers Alluvium

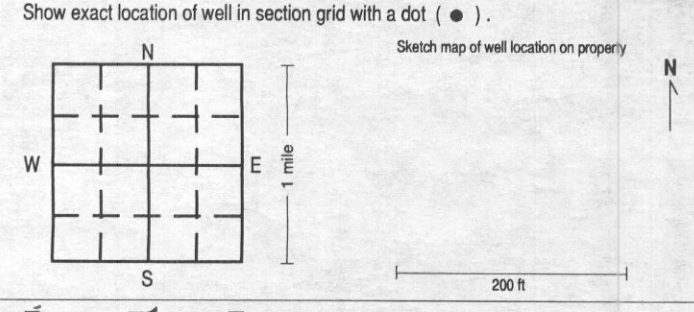
Site identification
 Property Owner Kloubec Aquaculture Well Number _____
 Address 3800 cst SW C.R.
 Tenant _____
 Well Depth 335 ft Date Completed 7 / 25 / 96

Drill method rotary auger cable other _____
Hole size
18 inch from 0 ft to 20 ft hole size continued 6 inch from 100 ft to 335 ft
8 inch from 20 ft to 100 ft _____ inch from _____ ft to _____ ft
 Record all depth measurements from ground level (GL). Use (+) for above GL measurements.

Location County Linn
 _____ mi. N and _____ mi. E of intersection of _____ and _____
 _____ mi. S and _____ mi. W of intersection of _____ and _____
 1/4 of the _____ 1/4 of the _____ 1/4 of Sec 3 TWP 82 RNG 7 W

Casing Drive shoe (yes/no) Pitless adaptor (yes/no)

Size (ID/OD)	Type / Wt	Depth top	Depth bottom	Amount (length)
<u>6 SDR 21</u>	<u>PVC</u>	<u>+1</u>	<u>100</u>	<u>101</u>
5 1/2 SDR 21				
<u>4 1/2 SCH 40</u>	<u>PVC</u>	<u>95</u>	<u>215</u>	<u>120</u>



Perforated or slotted casing? (yes/no)
 Perforated / slotted from 175 ft to 215 ft
 Perforated / slotted from _____ ft to _____ ft

upland hillside valley Elevation (if known) _____

Casing grouted? (yes/no)

Type	Depth Top	Depth Bottom	Amount
<u>Bensaul</u>	<u>0</u>	<u>20</u>	<u>2 SACKS</u>
<u>Bentonite + DeLanth</u>	<u>20</u>	<u>100</u>	

Formation log

From	To	Color	Hardness	Formation description
<u>0</u>	<u>38</u>	<u>Yellow</u>		<u>Clay</u>
<u>38</u>	<u>78</u>			<u>Limestone</u>
<u>78</u>	<u>170</u>			<u>Devonian</u>
<u>170</u>	<u>335</u>			<u>Silurian</u>

Well screen? (yes/no)

Diameter	Slot size	Depth Top	Depth Bottom	Length	Material

Bottom capped (yes/no) with _____
 Seals / Packers (yes/no) kind _____ depth _____ ft
 Gravel packed (yes/no) from _____ ft to _____ ft
 type _____ amount _____

Well developed? (yes/no)
 Explain A.R.

Pump installed? (yes/no) Date _____ / _____ / _____
 Installer's name SAVE
 Type of pump sub Depth to intake 200 ft
 Pump diameter 4 Rated capacity 70 GPM

Water information Aquifer: sand/gravel limestone sandstone
 Main water-supply zone from 175 ft to 335 ft
 Final water level (static water level) 110 ft below / above GL.
 Pumping water level 170 ft below GL; tape airline E-line EST
 At yield of 100 GPM; orifice volumetric estimate Date 7/25

Remarks (including depth of lost drilling fluids, materials, or tools)

Water quality test? (yes/no) Date tested _____ / _____ / _____
 Tested by _____
 Test results _____

Well use
 Domestic Municipal Industrial
 Livestock Public Supply Monitoring
 Test Well Irrigation Other _____ (explain)

Contractor Gingerich Well & Pump
Address 13210 Locust Ave, Kalona
Driller Kel Gingerich Certification no. 40046

Bedrock Aquifers

The bedrock hydrogeologic map (fig. 26) shows the aquifers and confining beds that make up the bedrock surface in east-central Iowa. Pennsylvanian confining beds are the bedrock in the extreme southwest corner of the area, in southeast Muscatine County and southwest Scott County, and in other small outlying localities. The Mississippian aquifer is found beneath the surficial deposits in most of the southwest part of the region. The Devonian confining beds comprise the bedrock surface in an area about 25 miles wide extending from the northwest corner to the south-central part of the report area. They have been partly or completely removed in parts of the Belle Plaine and Poweshiek buried bedrock channels.

The Devonian aquifer is the bedrock in a broad belt that parallels the northeast side of the Devonian confining beds. This belt is from 12 to 25 miles wide and extends from northern Benton and Linn Counties to the southern border of Muscatine County. The Devonian and Silurian aquifers are separated by an irregular zone of relatively thin shale occurring near the base of the Devonian and represented by a single line on figure 26.

The Silurian aquifer comprises the bedrock surface over most of the eastern half of the area. In the extreme northeastern border area the Ordovician confining beds are found at the bedrock surface. They also appear in several buried bedrock channels where the Silurian aquifer has been removed locally by erosion.

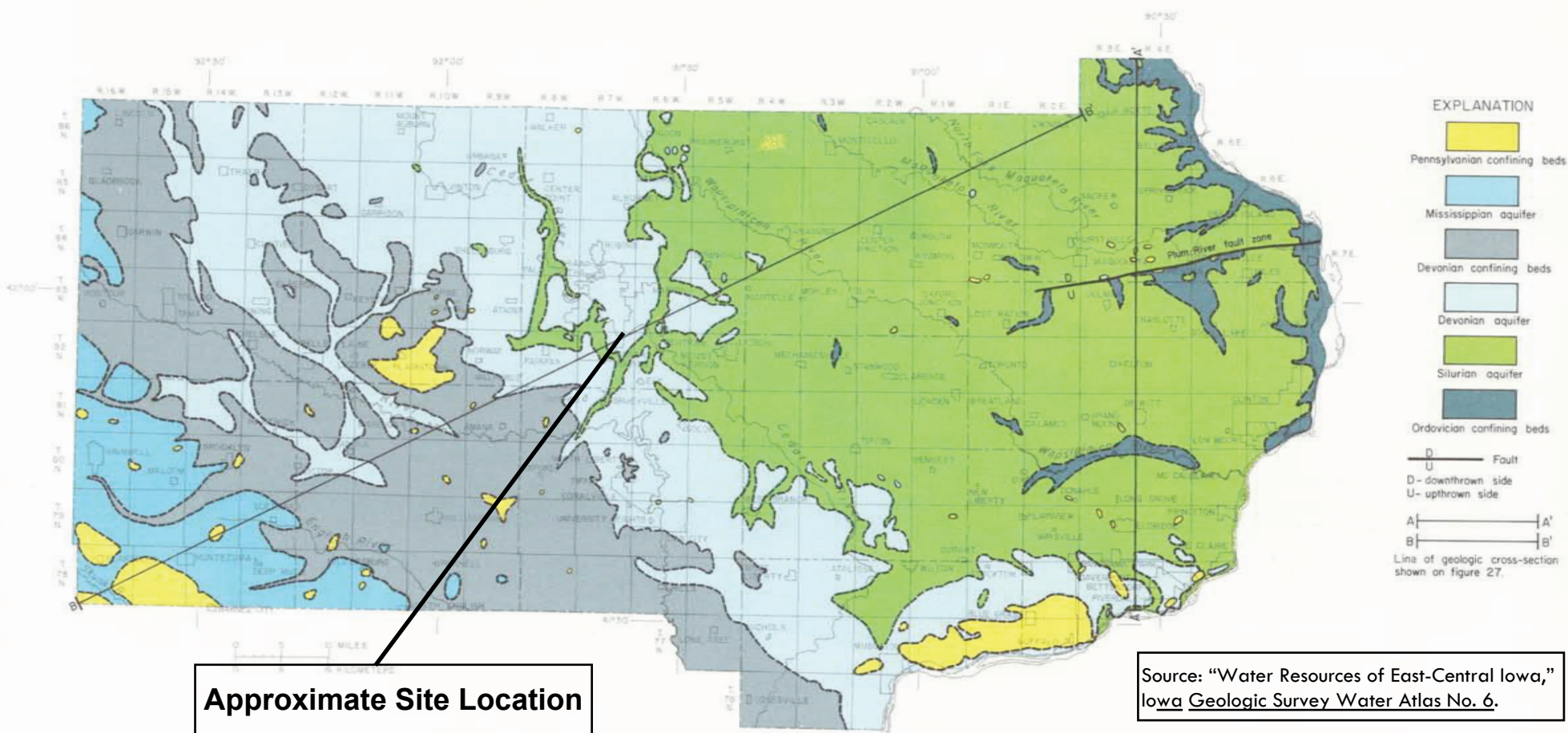


Figure 26.—Bedrock hydrogeologic map

The Cambrian-Ordovician aquifer and the underlying Dresbach aquifer are not at the bedrock surface in east-central Iowa. These aquifers are shallowest in the northeastern part of the area; they slope southwest and become progressively deeper in the subsurface. Figure 27 shows that all the rock units are approximately parallel to each other and dip (slope) toward the southwest.

A major structural feature, the Plum River fault zone, extends approximately 30 miles through southern Jackson County and northwest Clinton County. This structure continues eastward approximately 40 miles into northwest Illinois, where it was originally recognized and mapped (Kolata and Buschbach, 1976). As much as 400 feet of vertical displacement has been inferred by the Illinois State Geological Survey in the vicinity of Savannah, Illinois, and similar displacements may occur in Iowa between Preston and Maquoketa. In the vicinity of Preston, an uplifted area south of the fault zone

is indicated by the anomalous presence of the Ordovician confining beds at the land surface. Preliminary results from an ongoing research drilling program in the Devonian and Silurian aquifers have indicated a possible extension of the structure as far west as southern Linn County, Iowa. The Plum River fault zone is probably quiescent, as no evidence of geologically recent movement along the fault has been found.

The fault zone has cut the various bedrock aquifers and confining beds, and faulting has placed them adjacent to rock units of dissimilar hydrologic characteristics (fig. 27). Depending on the local displacement or associated fracturing, the fault may serve either as a barrier to or a conduit for ground water movement. Where an aquifer is placed against a confining bed the fault may serve as an impediment to ground-water movement. Where two different aquifers are placed against one another by the fault there may be continuity between the two aquifers.

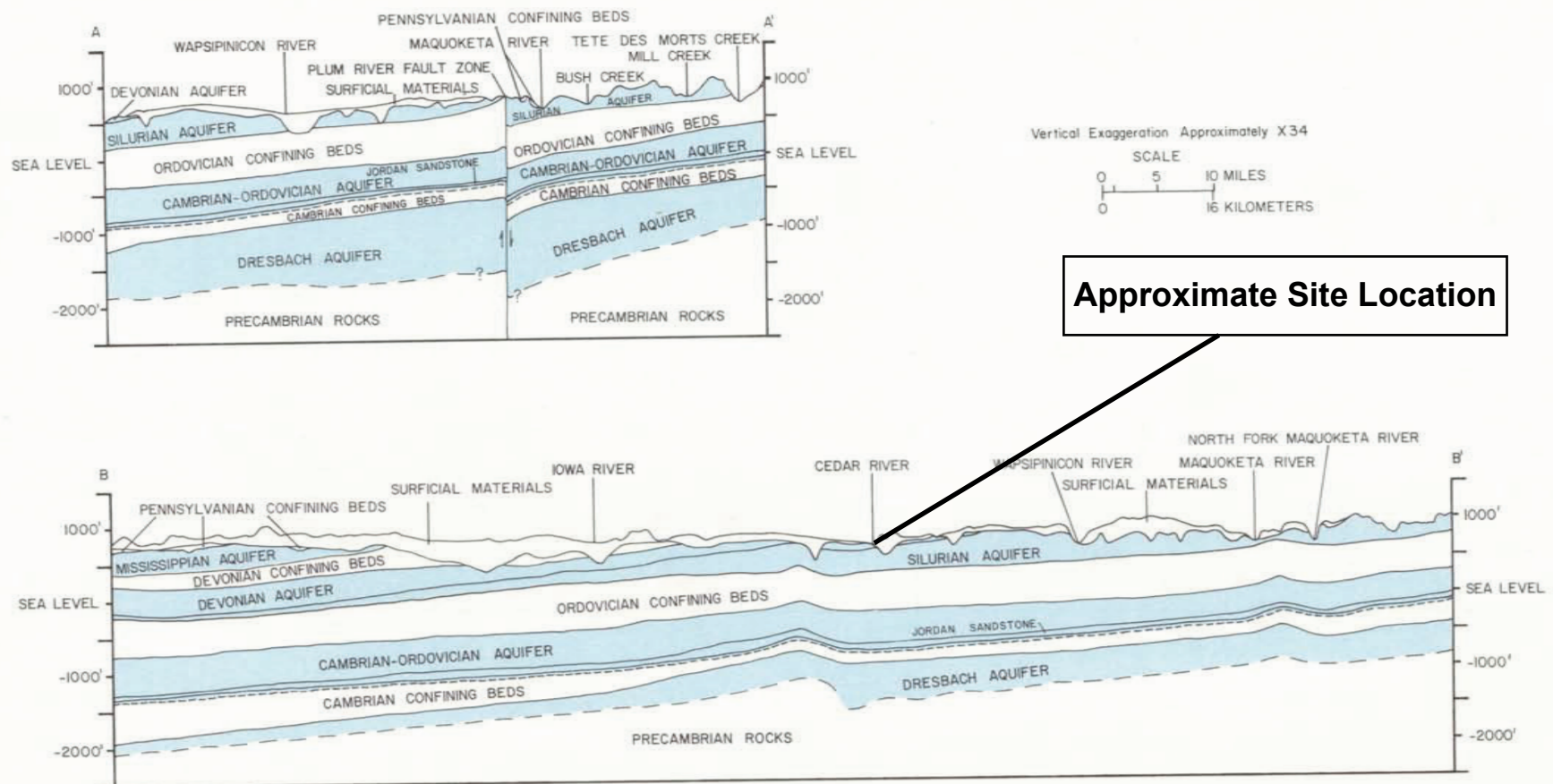


Figure 27.—Hydrogeologic cross sections

Source: "Water Resources of East-Central Iowa," Iowa Geologic Survey Water Atlas No. 6.

Appendix B

Boring Logs

SCS ENGINEERS

Environmental Consultants and Contractors

SOIL BORING LOG INFORMATION

Route To: Watershed/Wastewater Waste Management
 Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-301	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 10/31/2016		Date Drilling Completed 10/31/2016	
Unique Well No.		DNR Well ID No.		Common Well Name MW-301	
Final Static Water Level Feet		Surface Elevation 730.0 Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		State Plane 3,447,401 N, 5,426,409 E S/C/N		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W	
SW 1/4 of NE 1/4 of Section 3, T 82 N, R 7 W		Lat _____"		Long _____"	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments	
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200		
			1	TOPSOIL.											
S1	19	3 4 4 6	3-4	SILT WITH SAND, very dark grayish brown (10YR 3/2).	ML			0.5		M					
S2	24	2 7 6 9	6-7	LEAN CLAY WITH SAND, dark grayish brown (10YR 4/2).	CL			0.3		M					
S3	22	3 3 4 6	8-9	POORLY GRADED SAND WITH SILT, dark yellowish brown (10YR 3/4), medium grained.	SP			0.4		M					
S4	23	3 4 4 5	10-11	SANDY SILT, dark yellowish brown (10YR 3/4).	ML			0.3		M					
S5	12	4 9 11 12	13-14	POORLY GRADED GRAVEL, dark yellowish brown (10YR 3/4), coarse grained.	GP			0.3		W					water at 12.5 ft bgs.

I hereby certify that the information on this form is true and correct to the best of my knowledge.


Signature <i>Mike Mueller</i>	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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Route To: Watershed/Wastewater Waste Management
 Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-302	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 10/31/2016		Date Drilling Completed 10/31/2016	
Unique Well No.		DNR Well ID No.		Common Well Name MW-302	
Final Static Water Level Feet		Surface Elevation 720.3 Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		State Plane 3,447,399 N, 5,426,146 E S/C/N		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W	
SW 1/4 of NE 1/4 of Section 3, T 82 N, R 7 W		Lat _____ ' _____ "		Long _____ ' _____ "	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments	
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200		
			1	TOPSOIL.											
			2	SILT WITH SAND, very dark grayish brown (10YR 3/2).											
S1	5	14 89	3		ML			0.5		M					
			4												
			5	SILTY SAND, greenish gray (5GY6/1).	SM										
S2	14	23 37	6	POORLY GRADED SAND, greenish gray (5GY 6/1), coarse grained.				1.0		W					
			7												
			8	Same as above except, dark yellowish brown (10YR 3/4).											
S3	12	12 22	9					0.7		W					
			10												
S4	24	23 46	11		SP			0.5		W					
			12												
			13												
S5	14	12 22	14					0.5		W					
			15												
			16												

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature 	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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Route To: Watershed/Wastewater Waste Management
Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-303	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 12/6/2016		Date Drilling Completed 12/6/2016	
Unique Well No.		DNR Well ID No.		Common Well Name MW-303	
Final Static Water Level Feet		Surface Elevation 707.0 Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		State Plane 3,448,275 N, 5,425,166 E S/C/N		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W	
NW 1/4 of NE 1/4 of Section 3, T 82 N, R 7 W		Lat _____"		Long _____"	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
S1	20	20 20 27 34	1	SILT, very dark grayish brown (10YR 3/2).	ML			0.2	M					
			2											
S2	12	2 17 20 21	3	POORLY GRADED SAND, very dark grayish brown (10YR 3/2), coarse grained.	SP			0.2	W					saturation @ 5ft.
			4											
			5											
S3	16	7 8 8 6	6	Same as above except, brown (10YR 5/3), trace fine gravel.	SP			0.2	W					
			7											
S4	17	4 3 3 3	8	End of boring at 15.5 ft bgs.				0.2	W					
			9											
S5	17	1 1 2 3	10											
			11											

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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Route To: Watershed/Wastewater Waste Management
Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-304	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 12/6/2016		Date Drilling Completed 12/6/2016	
Drilling Method HSA		Unique Well No. MW-304		Borehole Diameter 8.5 in	
DNR Well ID No.		Final Static Water Level Feet		Surface Elevation 707.1 Feet	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		Local Grid Location			
State Plane 3,448,415 N, 5,425,664 E S/C/N		Lat _____ ' _____ "		<input type="checkbox"/> N <input type="checkbox"/> E	
NW 1/4 of NE 1/4 of Section 3, T 82 N, R 7 W		Long _____ ' _____ "		Feet <input type="checkbox"/> S Feet <input type="checkbox"/> W	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
S1	6	50/0.2	1-3	SILT, very dark grayish brown (10YR 3/2),	ML			0.2		M				water in borehole at 3 ft bgs.
S2	5	65/77	4-6					0.3		W				saturation @ 5ft.
S3	5	34/69	7-9	POORLY GRADED SAND, very dark grayish brown, medium to coarse grained.						W				
S4	12	12/22	10-12		SP					W				
S5	23	46/68	13-15	SILTY CLAY, gray.	CL					W				
				End of boring at 15.5 ft bgs.										

I hereby certify that the information on this form is true and correct to the best of my knowledge.

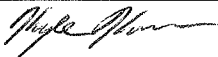
Signature <i>Mike Mueller</i>	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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Route To: Watershed/Wastewater Waste Management
Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-305	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 12/5/2016		Date Drilling Completed 12/5/2016	
Unique Well No.		DNR Well ID No.		Common Well Name MW-305	
Final Static Water Level Feet		Surface Elevation 707.1 Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		State Plane 3,448,467 N, 5,425,930 E S/C/N		Local Grid Location	
NW 1/4 of NE 1/4 of Section 3, T 82 N, R 7 W		Lat _____"		_____ E	
		Long _____"		_____ S _____ W	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
S1	17	13 5 6	1	SILT, very dark grayish brown (10YR 3/2), trace sand.	ML			0.2	M					water in borehole at 3 ft bgs.
			2											
S2	12	13 4 5	3	POORLY GRADED SAND, dark brown (10YR 3/3), coarse sand.	SP			0.1	W					saturation @ 5ft.
			4											
S3	18	11 3 4	5					0.9	W					
			6											
S4	14	9 13 21 19	7					0.4	W					
			8											
S5	16	14 15 23	9	LEAN CLAY, very dark gray (10YR 3/1).	CL				W					
			10											
			11											
			12											
			13											
			14											
			15											
				End of boring at 15.5 ft bgs.										

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature 	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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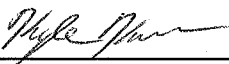
Route To: Watershed/Wastewater Waste Management
Remediation/Redevelopment Other

Facility/Project Name IPL - Prairie Creek Generating Station SCS#: 25215135.60		License/Permit/Monitoring Number		Boring Number MW-306	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling		Date Drilling Started 11/2/2016		Date Drilling Completed 11/2/2016	
Unique Well No.		DNR Well ID No.		Common Well Name MW-306	
Final Static Water Level Feet		Surface Elevation 710.1 Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		State Plane 3,448,572 N, 5,426,326 E S/C/N		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W	
NW 1/4 of NE 1/4 of Section 3 , T 82 N, R 7 W		Lat _____"		Long _____"	

Facility ID	County Linn	Civil Town/City/ or Village Cedar Rapids
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Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
S1	9.5	4 5 5 5	1	SILT, dark yellowish brown (10YR 3/4).	ML			0.7		W				Plastic debris- water at 4 ft bgs
			4											
S2	14	1 1 1 1	6	SILT, very dark grayish brown (10YR 3/2).				0.5		W				
S3	NR	3 2 1 1	9		ML			-		-				plastic debris
S4	NR	1 1 2 3	11					-		-				
S5	10	1 2 3 3	14	POORLY GRADED SAND, very dark gray (10YR 3/1), coarse grained.	SP			0.1		W				plastic and glass debris

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature 	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53711	Tel: (608) 224-2830 Fax:
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Boring Number MW-306

Page 2 of 2

Sample		Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
Number and Type	Length Att. & Recovered (in)								Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
S6	22	21 11	17	POORLY GRADED SAND, very dark gray (10YR 3/1), coarse grained. (continued)				0.4	W				plastic debris	
			18											
S7	19	21 11	19					0.3	W					
			20											
S8	6	21 12	21					0.2	W					
			22											
S9	14	8 4 4 12	23	Same as above except, dark gray (5Y 4/1).	SP			0.6	W					
			24											
			25											
S10	20	4 4 15 22	26					0.3	W					
			27											
			28											
S11	12	8 8 20 31	29					0.2	W					
			30											
				End of boring at 30.5 ft bgs.										

Route To: Watershed/Wastewater Waste Management
 Remediation/Redevelopment Other

Facility/Project Name Prairie Creek Generating Station SCS#: 25218184		License/Permit/Monitoring Number	Boring Number MW-307	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling, LP		Date Drilling Started 11/27/2018	Date Drilling Completed 11/27/2018	Drilling Method sonic
	Common Well Name MW-307	Final Static Water Level 708.5 Feet	Surface Elevation 718.9 Feet	Borehole Diameter 6.5 in

Local Grid Origin (estimated:) or Boring Location
 State Plane **3,448,497 N, 5,426,934 E** S/C/N Lat _____ " N E
NE 1/4 of NE 1/4 of Section 3, T 83 N, R 7 W Long _____ " Feet S Feet W

Facility ID _____ County **Linn** Civil Town/City/ or Village **Cedar Rapids**

Sample	Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments		
										Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200			
	S1			1-5	Topsoil and clay, black, (10YR 2/1), (Fill).												
				5-6	Black ash? (Fill).												
	S2			6-7	LEAN CLAY, black (10YR 2/1), (Fill).	CL											
				7-8	SILT, dark gray/black, (5YR 3/1).	ML											
	S3			8-9	LEAN CLAY, dark gray, (5YR 2.5/2).												
	S4			9-11		CL											
	S5			11-14	SILTY SAND, coarse sand, light brown, (2.5YR 3/1).	SM											

I hereby certify that the information on this form is true and correct to the best of my knowledge.


Signature  Firm **SCS Engineers** 3900 Kilroy Airport Way Long Beach, CA 90806 Tel: _____ Fax: _____

Route To: Watershed/Wastewater Waste Management
 Remediation/Redevelopment Other

Facility/Project Name Prairie Creek Generating Station		License/Permit/Monitoring Number SCS#: 25218184		Boring Number MW-308	
Boring Drilled By: Name of crew chief (first, last) and Firm Mike Mueller Cascade Drilling, LP		Date Drilling Started 11/27/2018		Date Drilling Completed 11/27/2018	
Common Well Name MW-308		Final Static Water Level 711.5 Feet		Surface Elevation 717.5 Feet	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>		Final Static Water Level		Borehole Diameter 6.5 in	
State Plane 3,448,434 N, 5,426,646 E		S/C/N S/C/N		Local Grid Location	
NE 1/4 of NE 1/4 of Section 3, T 83 N, R 7 W		Lat _____"		<input type="checkbox"/> N <input type="checkbox"/> E	
		Long _____"		<input type="checkbox"/> S <input type="checkbox"/> W	
Facility ID		County Linn		Civil Town/City/ or Village Cedar Rapids	

Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
			1	Topsoil, black.										
S1			2	LEAN CLAY, black, (2.5YR 2.5/1), (Fill).	CL									
S2			4	LEAN CLAY, brown, (2.5YR 4/4), (Fill).	CL				1.5		M			
S3			6	Ash, black, (2.5YR 3/1), (Fill).							M			
S4			8	LEAN CLAY with silt, gray, (5YR 5/1).							M			
S5			9		CL						M			
S6			11	SANDY SILT, dark gray, (5YR 2.5/1).							W			
S7			14	Same as above but (5YR 2.5/2).	ML						W			

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature 	Firm SCS Engineers 3900 kilroy Airport Way Long Beach, CA 90806	Tel: Fax:
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Route To: Watershed/Wastewater Waste Management
 Remediation/Redevelopment Other

Facility/Project Name Prairie Creek Generating Station		License/Permit/Monitoring Number SCS#:		Boring Number MW-309	
Boring Drilled By: Name of crew chief (first, last) and Firm Jeff Crank Roberts Environmental Drilling, Inc.			Date Drilling Started 8/5/2019		Date Drilling Completed 8/5/2019
Unique Well No.	DNR Well ID No.	Common Well Name MW-309	Final Static Water Level Feet		Surface Elevation Feet
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/>	State Plane N, E S/C/N		Lat ° ' "		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W
1/4 of	1/4 of Section	T	N, R	Long ° ' "	
Facility ID		County		Civil Town/City/ or Village	

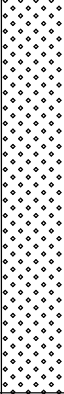
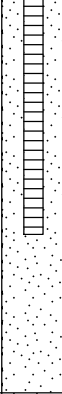
Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments	
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200		
1	8	13 34	1	SILT, silt dark brown (10YR 2/1), trace gravel, moist.	ML			1.5							
			2	coarsening sand with depth. SILTY SAND, moist.											
2	18	33 23	3		SM			0.5							
			4												
3	12	11 12	5	SILT, with sand, brown (10YR 3/2), wet, soft.	ML										
			6												
4	12	22 12	7	SILTY SAND, grey, tan brown, mottled wet sand.											
			8	very wet, varying colors observed including grey, rust, and tan.	SM										Water table observed during drilling
5	20	01 21	9												
			10	transitions into coarser material.											
6	12	00 11	11	WELL GRADED SAND, wet, mostly coarse sand, some fine and medium sand.	SW										Water table measured at depth of 9.84' after well development.
			12												

I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature	DRAFT	Firm	SCS Engineers 2830 Dairy Drive Madison, WI 53718	Tel: 608-224-2830	Fax:
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Boring Number MW-309

Page 2 of 2

Sample		Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
Number and Type	Length Att. & Recovered (in)								Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
7	12	11 33	13	WELL GRADED SAND, wet, mostly coarse sand, some fine and medium sand. <i>(continued)</i> Organic material.	SW									
8	12	12 45	15											
			17	End of Boring									Blind Drilled from 16' to 17'	

Route To: Watershed/Wastewater Waste Management
Remediation/Redevelopment Other

Facility/Project Name Prairie Creek Generating Station		License/Permit/Monitoring Number		Boring Number MW-310	
Boring Drilled By: Name of crew chief (first, last) and Firm Jeff Crank Roberts Environmental Drilling, Inc.		Date Drilling Started 8/6/2019		Date Drilling Completed 8/6/2019	
Unique Well No.		DNR Well ID No.		Common Well Name MW-310	
Final Static Water Level Feet		Surface Elevation Feet		Borehole Diameter 8.5 in	
Local Grid Origin <input type="checkbox"/> (estimated: <input type="checkbox"/>) or Boring Location <input checked="" type="checkbox"/> State Plane N, E S/C/N		Lat ° ' "		Local Grid Location <input type="checkbox"/> N <input type="checkbox"/> E <input type="checkbox"/> S <input type="checkbox"/> W	
1/4 of		1/4 of Section		T N, R	
Facility ID		County		Civil Town/City/ or Village	


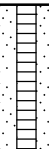


Sample Number and Type	Length Att. & Recovered (in)	Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	USCS	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments	
									Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200		
1	12	12 24	1	TOPSOIL, Brown (10YR2/1), with silty sand, moist											
			2	Poor recovery.	SM										
2	2	66 44	3												
3	10	44 23	5	LEAN CLAY, with lenses of silty sand and organic material, brown (10YR 2/1), moist.	CL										
4	6	31 12	7												
5	20	32 11	9	SILTY SAND, wet.											
			10	coarse sand, wet.	SM										Water table observed during drilling
6	18	32 11	11												Water table measured at depth of 10.21' after well
			12												


I hereby certify that the information on this form is true and correct to the best of my knowledge.

Signature DRAFT	Firm SCS Engineers 2830 Dairy Drive Madison, WI 53718	Tel: 608-224-2830 Fax:
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Boring Number MW-310

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Sample		Blow Counts	Depth In Feet	Soil/Rock Description And Geologic Origin For Each Major Unit	U S C S	Graphic Log	Well Diagram	PID/FID	Soil Properties					RQD/ Comments
Number and Type	Length Att. & Recovered (in)								Standard Penetration	Moisture Content	Liquid Limit	Plasticity Index	P 200	
7	12	11 22	13	SILTY SAND, wet. (continued) trace gravel, wet.	SM									development.
8	12	15 43	15	SILTY GRAVEL, with sand, wet.	GM									
			17	End of Boring										blind drilled to from 16' to 17'



Appendix C

Information on Arsenic and Molybdenum

This fact sheet answers the most frequently asked health questions (FAQs) about arsenic. For more information, call the CDC Information Center at 1-800-232-4636. This fact sheet is one in a series of summaries about hazardous substances and their health effects. It is important you understand this information because this substance may harm you. The effects of exposure to any hazardous substance depend on the dose, the duration, how you are exposed, personal traits and habits, and whether other chemicals are present.

HIGHLIGHTS: Exposure to higher than average levels of arsenic occur mostly in the workplace, near hazardous waste sites, or in areas with high natural levels. At high levels, inorganic arsenic can cause death. Exposure to lower levels for a long time can cause a discoloration of the skin and the appearance of small corns or warts. Arsenic has been found in at least 1,149 of the 1,684 National Priority List (NPL) sites identified by the Environmental Protection Agency (EPA).

What is arsenic?

Arsenic is a naturally occurring element widely distributed in the earth's crust. In the environment, arsenic is combined with oxygen, chlorine, and sulfur to form inorganic arsenic compounds. Arsenic in animals and plants combines with carbon and hydrogen to form organic arsenic compounds.

Inorganic arsenic compounds are mainly used to preserve wood. Copper chromated arsenate (CCA) is used to make "pressure-treated" lumber. CCA is no longer used in the U.S. for residential uses; it is still used in industrial applications. Organic arsenic compounds are used as pesticides, primarily on cotton fields and orchards.

What happens to arsenic when it enters the environment?

- Arsenic occurs naturally in soil and minerals and may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching.
- Arsenic cannot be destroyed in the environment. It can only change its form.
- Rain and snow remove arsenic dust particles from the air.
- Many common arsenic compounds can dissolve in water. Most of the arsenic in water will ultimately end up in soil or sediment.
- Fish and shellfish can accumulate arsenic; most of this arsenic is in an organic form called arsenobetaine that is much less harmful.

How might I be exposed to arsenic?

- Ingesting small amounts present in your food and water or breathing air containing arsenic.
- Breathing sawdust or burning smoke from wood treated with arsenic.
- Living in areas with unusually high natural levels of arsenic in rock.
- Working in a job that involves arsenic production or use, such as copper or lead smelting, wood treating, or pesticide application.

How can arsenic affect my health?

Breathing high levels of inorganic arsenic can give you a sore throat or irritated lungs.

Ingesting very high levels of arsenic can result in death. Exposure to lower levels can cause nausea and vomiting, decreased production of red and white blood cells, abnormal heart rhythm, damage to blood vessels, and a sensation of "pins and needles" in hands and feet.

Ingesting or breathing low levels of inorganic arsenic for a long time can cause a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso.

Skin contact with inorganic arsenic may cause redness and swelling.

Almost nothing is known regarding health effects of organic arsenic compounds in humans. Studies in animals show that some simple organic arsenic

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compounds are less toxic than inorganic forms. Ingestion of methyl and dimethyl compounds can cause diarrhea and damage to the kidneys.

How likely is arsenic to cause cancer?

Several studies have shown that ingestion of inorganic arsenic can increase the risk of skin cancer and cancer in the liver, bladder, and lungs. Inhalation of inorganic arsenic can cause increased risk of lung cancer. The Department of Health and Human Services (DHHS) and the EPA have determined that inorganic arsenic is a known human carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans.

How can arsenic affect children?

There is some evidence that long-term exposure to arsenic in children may result in lower IQ scores. There is also some evidence that exposure to arsenic in the womb and early childhood may increase mortality in young adults.

There is some evidence that inhaled or ingested arsenic can injure pregnant women or their unborn babies, although the studies are not definitive. Studies in animals show that large doses of arsenic that cause illness in pregnant females, can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

How can families reduce the risks of exposure to arsenic?

- If you use arsenic-treated wood in home projects, you should wear dust masks, gloves, and protective clothing to decrease exposure to sawdust.
- If you live in an area with high levels of arsenic in water or soil, you should use cleaner sources of water and limit contact with soil.

- If you work in a job that may expose you to arsenic, be aware that you may carry arsenic home on your clothing, skin, hair, or tools. Be sure to shower and change clothes before going home.

Is there a medical test to determine whether I've been exposed to arsenic?

There are tests available to measure arsenic in your blood, urine, hair, and fingernails. The urine test is the most reliable test for arsenic exposure within the last few days. Tests on hair and fingernails can measure exposure to high levels of arsenic over the past 6-12 months. These tests can determine if you have been exposed to above-average levels of arsenic. They cannot predict whether the arsenic levels in your body will affect your health.

Has the federal government made recommendations to protect human health?

The EPA has set limits on the amount of arsenic that industrial sources can release to the environment and has restricted or cancelled many of the uses of arsenic in pesticides. EPA has set a limit of 0.01 parts per million (ppm) for arsenic in drinking water.

The Occupational Safety and Health Administration (OSHA) has set a permissible exposure limit (PEL) of 10 micrograms of arsenic per cubic meter of workplace air ($10 \mu\text{g}/\text{m}^3$) for 8 hour shifts and 40 hour work weeks.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological Profile for Arsenic (Update). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Where can I get more information?

For more information, contact the 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.

Phone: 1-800-232-4636

ToxFAQs™ Internet address via WWW is <http://www.atsdr.cdc.gov/toxfaqs/index.asp>.

ATSDR can tell you where to find occupational and environmental health clinics. Their specialists can recognize, evaluate, and treat illnesses resulting from exposure to hazardous substances. You can also contact your community or state health or environmental quality department if you have any more questions or concerns.



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Division of Toxicology and Environmental Medicine

August 2007

This Public Health Statement is the summary chapter from the Toxicological Profile for Arsenic. It is one in a series of Public Health Statements about hazardous substances and their health effects. A shorter version, the ToxFAQs™, is also available. This information is important because this substance may harm you. The effects of exposure to any hazardous substance depend on the dose, the duration, how you are exposed, personal traits and habits, and whether other chemicals are present. For more information, call the ATSDR Information Center at 1-800-232-4636.

This public health statement tells you about arsenic and the effects of exposure to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Arsenic has been found in at least 1,149 of the 1,684 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which arsenic is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to arsenic, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS ARSENIC?

Arsenic is a naturally occurring element that is widely distributed in the Earth's crust. Arsenic is classified chemically as a metalloid, having both properties of a metal and a nonmetal; however, it is frequently referred to as a metal. Elemental arsenic (sometimes referred to as metallic arsenic) is a steel grey solid material. However, arsenic is usually found in the environment combined with other elements such as oxygen, chlorine, and sulfur. Arsenic combined with these elements is called inorganic arsenic. Arsenic combined with carbon and hydrogen is referred to as organic arsenic.

Most inorganic and organic arsenic compounds are white or colorless powders that do not evaporate. They have no smell, and most have no special taste. Thus, you usually cannot tell if arsenic is present in your food, water, or air.

Inorganic arsenic occurs naturally in soil and in many kinds of rock, especially in minerals and ores that contain copper or lead. When these ores are heated in smelters, most of the arsenic goes up the stack and enters the air as a fine dust. Smelters may collect this dust and take out the arsenic as a compound called arsenic trioxide (As₂O₃).

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Fax: 770-488-4178

E-Mail: cdcinfo@cdc.gov



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However, arsenic is no longer produced in the United States; all of the arsenic used in the United States is imported.

Presently, about 90% of all arsenic produced is used as a preservative for wood to make it resistant to rotting and decay. The preservative is copper chromated arsenate (CCA) and the treated wood is referred to as "pressure-treated." In 2003, U.S. manufacturers of wood preservatives containing arsenic began a voluntary transition from CCA to other wood preservatives that do not contain arsenic in wood products for certain residential uses, such as play structures, picnic tables, decks, fencing, and boardwalks. This phase out was completed on December 31, 2003; however, wood treated prior to this date could still be used and existing structures made with CCA-treated wood would not be affected. CCA-treated wood products continue to be used in industrial applications. It is not known whether, or to what extent, CCA-treated wood products may contribute to exposure of people to arsenic.

In the past, inorganic arsenic compounds were predominantly used as pesticides, primarily on cotton fields and in orchards. Inorganic arsenic compounds can no longer be used in agriculture. However, organic arsenic compounds, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA), are still used as pesticides, principally on cotton. Some organic arsenic compounds are used as additives in animal feed. Small quantities of elemental arsenic are added to other metals to form metal mixtures or alloys with improved properties. The greatest use of arsenic in alloys is in lead-acid batteries for automobiles. Another important use of arsenic

compounds is in semiconductors and light-emitting diodes.

1.2 WHAT HAPPENS TO ARSENIC WHEN IT ENTERS THE ENVIRONMENT?

Arsenic occurs naturally in soil and minerals and it therefore may enter the air, water, and land from wind-blown dust and may get into water from runoff and leaching. Volcanic eruptions are another source of arsenic. Arsenic is associated with ores containing metals, such as copper and lead. Arsenic may enter the environment during the mining and smelting of these ores. Small amounts of arsenic also may be released into the atmosphere from coal-fired power plants and incinerators because coal and waste products often contain some arsenic.

Arsenic cannot be destroyed in the environment. It can only change its form, or become attached to or separated from particles. It may change its form by reacting with oxygen or other molecules present in air, water, or soil, or by the action of bacteria that live in soil or sediment. Arsenic released from power plants and other combustion processes is usually attached to very small particles. Arsenic contained in wind-borne soil is generally found in larger particles. These particles settle to the ground or are washed out of the air by rain. Arsenic that is attached to very small particles may stay in the air for many days and travel long distances. Many common arsenic compounds can dissolve in water. Thus, arsenic can get into lakes, rivers, or underground water by dissolving in rain or snow or through the discharge of industrial wastes. Some of the arsenic will stick to particles in the water or sediment on the bottom of lakes or rivers, and some

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will be carried along by the water. Ultimately, most arsenic ends up in the soil or sediment. Although some fish and shellfish take in arsenic, which may build up in tissues, most of this arsenic is in an organic form called arsenobetaine (commonly called "fish arsenic") that is much less harmful.

1.3 HOW MIGHT I BE EXPOSED TO ARSENIC?

Since arsenic is found naturally in the environment, you will be exposed to some arsenic by eating food, drinking water, or breathing air. Children may also be exposed to arsenic by eating soil. Analytical methods used by scientists to determine the levels of arsenic in the environment generally do not determine the specific form of arsenic present. Therefore, we do not always know the form of arsenic a person may be exposed to. Similarly, we often do not know what forms of arsenic are present at hazardous waste sites. Some forms of arsenic may be so tightly attached to particles or embedded in minerals that they are not taken up by plants and animals.

The concentration of arsenic in soil varies widely, generally ranging from about 1 to 40 parts of arsenic to a million parts of soil (ppm) with an average level of 3–4 ppm. However, soils in the vicinity of arsenic-rich geological deposits, some mining and smelting sites, or agricultural areas where arsenic pesticides had been applied in the past may contain much higher levels of arsenic. The concentration of arsenic in natural surface and groundwater is generally about 1 part in a billion parts of water (1 ppb), but may exceed 1,000 ppb in contaminated areas or where arsenic levels in soil

are high. Groundwater is far more likely to contain high levels of arsenic than surface water. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic. Levels of arsenic in food range from about 20 to 140 ppb. However, levels of inorganic arsenic, the form of most concern, are far lower. Levels of arsenic in the air generally range from less than 1 to about 2,000 nanograms (1 nanogram equals a billionth of a gram) of arsenic per cubic meter of air (less than 1–2,000 ng/m³), depending on location, weather conditions, and the level of industrial activity in the area. However, urban areas generally have mean arsenic levels in air ranging from 20 to 30 ng/m³.

You normally take in small amounts of arsenic in the air you breathe, the water you drink, and the food you eat. Of these, food is usually the largest source of arsenic. The predominant dietary source of arsenic is seafood, followed by rice/rice cereal, mushrooms, and poultry. While seafood contains the greatest amounts of arsenic, for fish and shellfish, this is mostly in an organic form of arsenic called arsenobetaine that is much less harmful. Some seaweeds may contain arsenic in inorganic forms that may be more harmful. Children are likely to eat small amounts of dust or soil each day, so this is another way they may be exposed to arsenic. The total amount of arsenic you take in from these sources is generally about 50 micrograms (1 microgram equals one-millionth of a gram) each day. The level of inorganic arsenic (the form of most concern) you take in from these sources is generally about 3.5 microgram/day. Children may be exposed to small amounts of arsenic from hand-to-mouth activities from playing on play structures or decks constructed out of CCA-treated wood. The potential exposure that children

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may receive from playing in play structures constructed from CCA-treated wood is generally smaller than that they would receive from food and water.

In addition to the normal levels of arsenic in air, water, soil, and food, you could be exposed to higher levels in several ways, such as the following:

- Some areas of the United States contain unusually high natural levels of arsenic in rock, and this can lead to unusually high levels of arsenic in soil or water. If you live in an area like this, you could take in elevated amounts of arsenic in drinking water. Children may be taking in higher amounts of arsenic because of hand-to-mouth contact or eating soil in areas with higher than usual arsenic concentrations.
- Some hazardous waste sites contain large quantities of arsenic. If the material is not properly disposed of, it can get into surrounding water, air, or soil. If you live near such a site, you could be exposed to elevated levels of arsenic from these media.
- If you work in an occupation that involves arsenic production or use (for example, copper or lead smelting, wood treating, or pesticide application), you could be exposed to elevated levels of arsenic during your work.

- If you saw or sand arsenic-treated wood, you could inhale some of the sawdust into your nose or throat. Similarly, if you burn arsenic-treated wood, you could inhale arsenic in the smoke.
- If you live in a former agricultural area where arsenic was used on crops, the soil could contain high levels of arsenic.
- In the past, several kinds of products used in the home (rat poison, ant poison, weed killer, some types of medicines) had arsenic in them. However, most of these uses of arsenic have ended, so you are not likely to be exposed from home products any longer.

1.4 HOW CAN ARSENIC ENTER AND LEAVE MY BODY?

If you swallow arsenic in water, soil, or food, most of the arsenic may quickly enter into your body. The amount that enters your body will depend on how much you swallow and the kind of arsenic that you swallow. This is the most likely way for you to be exposed near a waste site. If you breathe air that contains arsenic dusts, many of the dust particles settle onto the lining of the lungs. Most of the arsenic in these particles is then taken up from the lungs into the body. You might be exposed in this way near waste sites where arsenic-contaminated soils are allowed to blow into the air, or if you work with arsenic-containing soil or products. If you get arsenic-contaminated soil or water on your skin, only a small amount will go through your skin into your body, so this is usually not of concern.

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Both inorganic and organic forms leave your body in your urine. Most of the inorganic arsenic will be gone within several days, although some will remain in your body for several months or even longer. If you are exposed to organic arsenic, most of it will leave your body within several days.

1.5 HOW CAN ARSENIC AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Inorganic arsenic has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in water which is 10,000 times higher than 80% of U.S. drinking water arsenic levels) can result in death. If you swallow lower levels of inorganic arsenic (ranging from about 300 to 30,000 ppb in water; 100–10,000 times higher than most U.S. drinking water levels), you may experience irritation of your stomach and

intestines, with symptoms such as stomachache, nausea, vomiting, and diarrhea. Other effects you might experience from swallowing inorganic arsenic include decreased production of red and white blood cells, which may cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in your hands and feet.

Perhaps the single-most characteristic effect of long-term oral exposure to inorganic arsenic is a pattern of skin changes. These include patches of darkened skin and the appearance of small "corns" or "warts" on the palms, soles, and torso, and are often associated with changes in the blood vessels of the skin. Skin cancer may also develop. Swallowing arsenic has also been reported to increase the risk of cancer in the liver, bladder, and lungs. The Department of Health and Human Services (DHHS) has determined that inorganic arsenic is known to be a human carcinogen (a chemical that causes cancer). The International Agency for Research on Cancer (IARC) has determined that inorganic arsenic is carcinogenic to humans. EPA also has classified inorganic arsenic as a known human carcinogen.

If you breathe high levels of inorganic arsenic, then you are likely to experience a sore throat and irritated lungs. You may also develop some of the skin effects mentioned above. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of arsenic per cubic meter ($\mu\text{g}/\text{m}^3$) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic arsenic may also

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interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic arsenic to increase the risk of lung cancer. This has been seen mostly in workers exposed to arsenic at smelters, mines, and chemical factories, but also in residents living near smelters and arsenical chemical factories. People who live near waste sites with arsenic may have an increased risk of lung cancer as well.

If you have direct skin contact with high concentrations of inorganic arsenic compounds, your skin may become irritated, with some redness and swelling. However, it does not appear that skin contact is likely to lead to any serious internal effects.

Almost no information is available on the effects of organic arsenic compounds in humans. Studies in animals show that most simple organic arsenic compounds (such as methyl and dimethyl compounds) are less toxic than the inorganic forms. In animals, ingestion of methyl compounds can result in diarrhea, and lifetime exposure can damage the kidneys. Lifetime exposure to dimethyl compounds can damage the urinary bladder and the kidneys.

1.6 HOW CAN ARSENIC AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Children are exposed to arsenic in many of the same ways that adults are. Since arsenic is found in the

soil, water, food, and air, children may take in arsenic in the air they breathe, the water they drink, and the food they eat. Since children tend to eat or drink less of a variety of foods and beverages than do adults, ingestion of contaminated food or juice or infant formula made with arsenic-contaminated water may represent a significant source of exposure. In addition, since children often play in the soil and put their hands in their mouths and sometimes intentionally eat soil, ingestion of contaminated soil may be a more important source of arsenic exposure for children than for adults. In areas of the United States where natural levels of arsenic in the soil and water are high, or in areas in and around contaminated waste sites, exposure of children to arsenic through ingestion of soil and water may be significant. In addition, contact with adults who are wearing clothes contaminated with arsenic (e.g., with dust from copper- or lead-smelting factories, from wood-treating or pesticide application, or from arsenic-treated wood) could be a source of exposure. Because of the tendency of children to taste things that they find, accidental poisoning from ingestion of pesticides is also a possibility. Thus, although most of the exposure pathways for children are the same as those for adults, children may be at a higher risk of exposure because of normal hand-to-mouth activity.

Children who are exposed to inorganic arsenic may have many of the same effects as adults, including irritation of the stomach and intestines, blood vessel damage, skin changes, and reduced nerve function. Thus, all health effects observed in adults are of potential concern in children. There is also some evidence that suggests that long-term exposure to inorganic arsenic in children may result in lower IQ scores. We do not know if absorption of inorganic arsenic from the gut in children differs from adults.

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There is some evidence that exposure to arsenic in early life (including gestation and early childhood) may increase mortality in young adults.

There is some evidence that inhaled or ingested inorganic arsenic can injure pregnant women or their unborn babies, although the studies are not definitive. Studies in animals show that large doses of inorganic arsenic that cause illness in pregnant females can also cause low birth weight, fetal malformations, and even fetal death. Arsenic can cross the placenta and has been found in fetal tissues. Arsenic is found at low levels in breast milk.

In animals, exposure to organic arsenic compounds can cause low birth weight, fetal malformations, and fetal deaths. The dose levels that cause these effects also result in effects in the mothers.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ARSENIC?

If your doctor finds that you have been exposed to substantial amounts of arsenic, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Many communities may have high levels of arsenic in their drinking water, particularly from private wells, because of contamination or as a result of the geology of the area. The north central region and the western region of the United States have the highest arsenic levels in surface water and groundwater sources, respectively. Wells used to provide water for drinking and cooking should be

tested for arsenic. As of January 2006, EPA's Maximum Contaminant Level (MCL) for arsenic in drinking water is 10 ppb. If you have arsenic in your drinking water at levels higher than the EPA's MCL, an alternative source of water should be used for drinking and cooking should be considered.

If you use arsenic-treated wood in home projects, personal protection from exposure to arsenic-containing sawdust may be helpful in limiting exposure of family members. These measures may include dust masks, gloves, and protective clothing. Arsenic-treated wood should never be burned in open fires, or in stoves, residential boilers, or fire places, and should not be composted or used as mulch. EPA's Consumer Awareness Program (CAP) for CCA is a voluntary program established by the manufacturers of CCA products to inform consumers about the proper handling, use, and disposal of CCA-treated wood. You can find more information about this program in Section 6.5. Hand washing can reduce the potential exposure of children to arsenic after playing on play structures constructed with CCA-treated wood, since most of the arsenic on the children's hands was removed with water.

If you live in an area with a high level of arsenic in the water or soil, substituting cleaner sources of water and limiting contact with soil (for example, through use of a dense groundcover or thick lawn) would reduce family exposure to arsenic. By paying careful attention to dust and soil control in the home (air filters, frequent cleaning), you can reduce family exposure to contaminated soil. Some children eat a lot of soil. You should prevent your children from eating soil. You should discourage your children from putting objects in their mouths. Make sure they wash their hands frequently and

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before eating. Discourage your children from putting their hands in their mouths or engaging in other hand-to-mouth activities. Since arsenic may be found in the home as a pesticide, household chemicals containing arsenic should be stored out of reach of young children to prevent accidental poisonings. Always store household chemicals in their original labeled containers; never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center's number by the phone.

It is sometimes possible to carry arsenic from work on your clothing, skin, hair, tools, or other objects removed from the workplace. This is particularly likely if you work in the fertilizer, pesticide, glass, or copper/lead smelting industries. You may contaminate your car, home, or other locations outside work where children might be exposed to arsenic. You should know about this possibility if you work with arsenic.

Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes. Material safety data sheets (MSDS) for many chemicals used should be found at your place of work, as required by the Occupational Safety and Health Administration (OSHA) in the U.S. Department of Labor. MSDS information should include chemical names and hazardous ingredients, and important properties, such as fire and explosion data, potential health effects, how you get the

chemical(s) in your body, how to properly handle the materials, and what to do in the case of emergencies. Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your state OSHA-approved occupational safety and health program or OSHA can answer any further questions and help your employer identify and correct problems with hazardous substances. Your state OSHA-approved occupational safety and health program or OSHA will listen to your formal complaints about workplace health hazards and inspect your workplace when necessary. Employees have a right to seek safety and health on the job without fear of punishment.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ARSENIC?

Several sensitive and specific tests can measure arsenic in your blood, urine, hair, or fingernails, and these tests are often helpful in determining if you have been exposed to above-average levels of arsenic in the past. These tests are not usually performed in a doctor's office. They require sending the sample to a testing laboratory.

Measurement of arsenic in your urine is the most reliable means of detecting arsenic exposures that you experienced within the last several days. Most tests measure the total amount of arsenic present in your urine. This can sometimes be misleading, because the nonharmful forms of arsenic in fish and shellfish can give a high reading even if you have not been exposed to a toxic form of arsenic. For this reason, laboratories sometimes use a more

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complicated test to separate “fish arsenic” from other forms. Because most arsenic leaves your body within a few days, analysis of your urine cannot detect if you were exposed to arsenic in the past. Tests of your hair or fingernails can tell if you were exposed to high levels over the past 6–12 months, but these tests are not very useful in detecting low-level exposures. If high levels of arsenic are detected, this shows that you have been exposed, but unless more is known about when you were exposed and for how long, it is usually not possible to predict whether you will have any harmful health effects.

1.9 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

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 that is usually based on levels that affect animals; they are then adjusted to

levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it. Some regulations and recommendations for ARSENIC include the following:

The federal government has taken several steps to protect humans from arsenic. First, EPA has set limits on the amount of arsenic that industrial sources can release into the environment. Second, EPA has restricted or canceled many of the uses of arsenic in pesticides and is considering further restrictions. Third, in January 2001, the EPA lowered the limit for arsenic in drinking water from 50 to 10 ppb. Finally, OSHA has established a permissible exposure limit (PEL), 8-hour time-weighted average, of 10 $\mu\text{g}/\text{m}^3$ for airborne arsenic in various workplaces that use inorganic arsenic.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating,

DEPARTMENT of HEALTH AND HUMAN SERVICES, Public Health Service
Agency for Toxic Substances and Disease Registry



PUBLIC HEALTH STATEMENT

Arsenic
CAS#: 7440-38-2

Division of Toxicology and Environmental Medicine

August 2007

and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental
Medicine
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: <http://www.ntis.gov/>

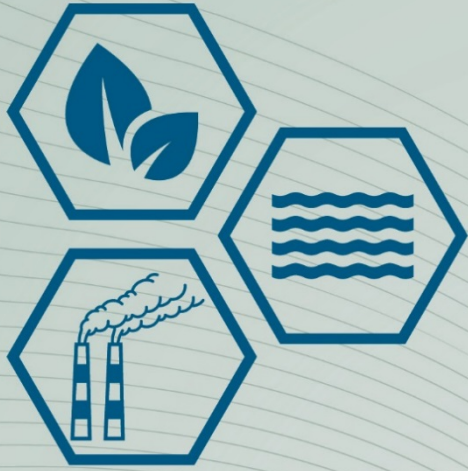
DEPARTMENT of HEALTH AND HUMAN SERVICES, Public Health Service
Agency for Toxic Substances and Disease Registry

www.atsdr.cdc.gov/

Telephone: 1-800-232-4636

Fax: 770-488-4178

E-Mail: cdcinfo@cdc.gov



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

DISCLAIMER

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This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

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. Breyse, 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.

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

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>).

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/>.

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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CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

G. Daniel Todd, Ph.D.
Sam Keith, M.S., CHP
Obaid Faroon, D.V.M., Ph.D.
Melanie Buser, M.P.H.
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Lisa Ingerman, Ph.D., DABT
Courtney Hard, B.A.
Mario Citra, Ph.D.
Amy Nguyen, Ph.D.
Julie Klotzbach, Ph.D.
Gary Diamond, Ph.D.
SRC, Inc., North Syracuse, NY

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.

1. PUBLIC HEALTH STATEMENT

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.

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HOW CAN MOLYBDENUM AFFECT MY HEALTH?

Molybdenum is essential for good health. An intake of 45 micrograms of molybdenum per day ($\mu\text{g}/\text{day}$) 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.

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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

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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/m³) for soluble molybdenum compounds and 15 mg/m³ 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/m³ for insoluble molybdenum compounds and 1,000 mg/m³ for soluble molybdenum

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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 ilsemanite.

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/m³. Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 µg/m³, are higher than those found in rural areas, 0.001–0.0032 µg/m³. 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,

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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

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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

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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-

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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.

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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				

^aThe 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

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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/m³ for 14 days (NTP 1997) or ≤ 67 mg molybdenum/m³ 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

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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 5M, 5F (F344/N)	6 hours/day; 5 days/week; 14 days 0, 2, 6.7, 20, 67, 200 mg Mo/m ³	CS, BW, HP	Resp 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 5M, 5F (B6C3F1)	6 hours/day; 5 days/week; 14 days 0, 2, 6.7, 20, 67, 200 mg Mo/m ³	CS, BW, HP	Resp 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 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	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Bd Wt	67 67 67 67 67 67 67 67 67			No alterations in organ weights, hematology or clinical chemistry parameters, or histological alterations were found.	NTP 1997 (molybdenum trioxide)
4	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	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Bd Wt	67 67 67 67 67 67 67 67 67			No alterations in organ weights, hematology or clinical chemistry parameters, or histological alterations were found.	NTP 1997 (molybdenum trioxide)

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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 Cardio Gastro Musc/skel Hepatic Renal Endocr Bd Wt	67 67 67 67 67 67 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 Cardio Gastro Musc/skel Hepatic Renal Endocr Bd Wt	67 67 67 67 67 67 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 suppurative 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)

3. HEALTH EFFECTS

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

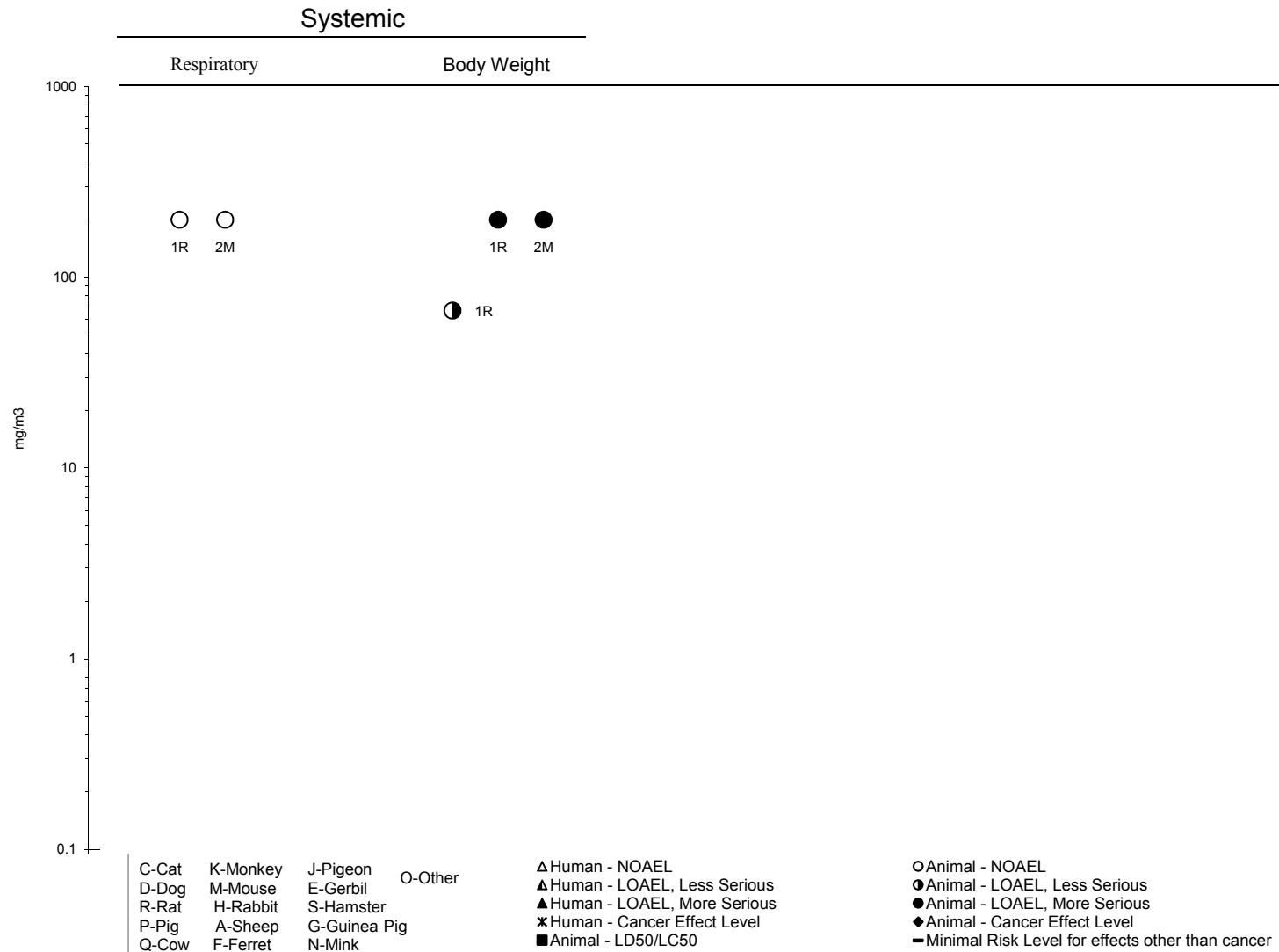
Figure key ^a	Species (strain) No./group	Exposure duration/concentrations	Parameters monitored	System	NOAEL (mg/m ³)	Less serious LOAEL (mg/m ³)	Serious LOAEL (mg/m ³)	Results	Reference/comments
Cancer									
9	Mouse 50M, 50F (B6C3F1)	6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/m ³	CS, 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)

^aThe 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); LC₅₀ = lethal concentration, 50% kill; LE = lethality; M = male(s); min = minute(s); MRL = Minimal Risk Level; NS = not specified; OP = ophthalmology; OW = organ weight; RD₅₀ = concentration resulting in a 50% reduction in respiratory rate; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)

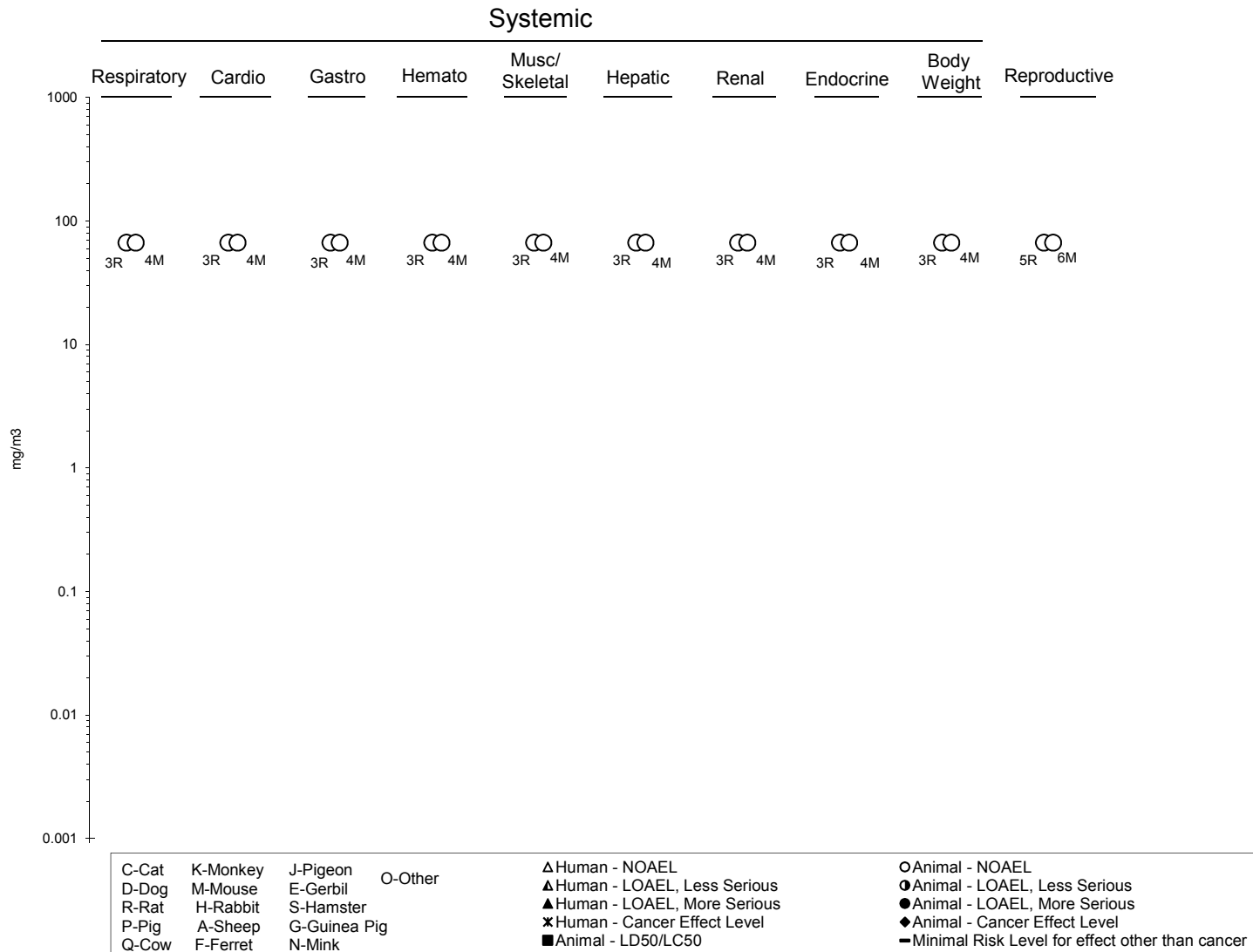
3. HEALTH EFFECTS

Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation
Acute (≤ 14 days)



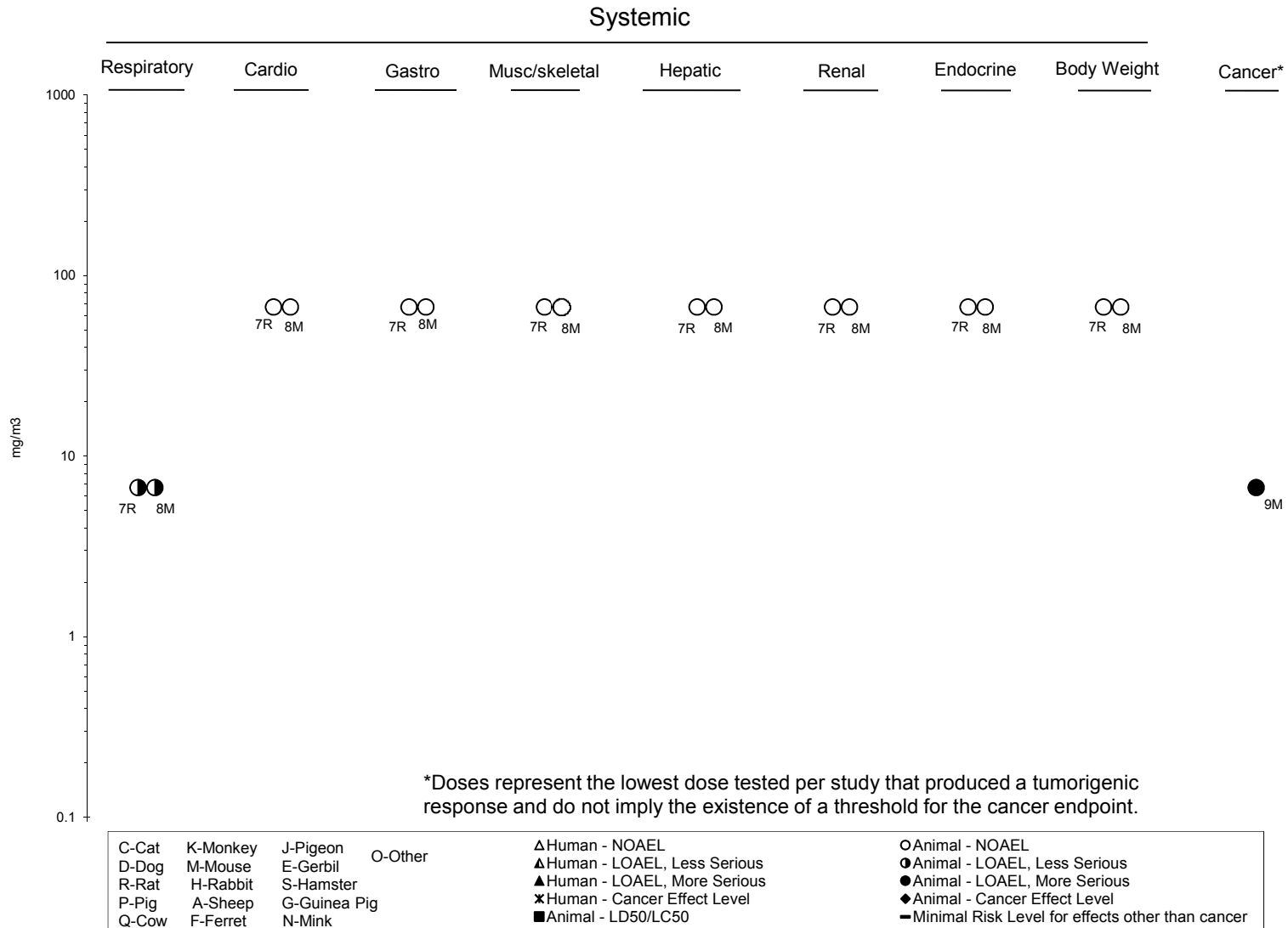
3. HEALTH EFFECTS

Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation (Continued)
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation (Continued)
 Chronic (≥365 days)



3. HEALTH EFFECTS

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, FEV₁) was observed in the remaining five workers; the decrease in FEV₁ 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/m³; the molybdenum content of the respirable dust ranged from 1.02 to 4.49 mg molybdenum/m³. 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 FEV₁ 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/m³ 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/m³ 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/m³ and in mice exposed to 67 mg molybdenum/m³; other nasal lesions observed in mice included suppurative inflammation at ≥20 mg molybdenum/m³ and olfactory epithelial atrophy at 67 mg molybdenum/m³. Squamous metaplasia of the epiglottis was observed in rats and mice exposed to ≥6.7 mg molybdenum/m³. In the lungs, chronic inflammation was observed in rats exposed to ≥20 mg molybdenum/m³ and alveolar epithelial metaplasia and histiocytic cellular infiltration were observed at ≥6.7 mg molybdenum/m³.

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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/m³ for 13 weeks or 2 years (NTP 1997).

Gastrointestinal Effects. Intermediate- or chronic-duration exposure to ≤67 mg molybdenum/m³ 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/m³ 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/m³ 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/m³ (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/m³ 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/m³) 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/m³ 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/m³ than in the controls, and weight loss was observed in male rats and mice exposed to 200 mg molybdenum/m³. In female rats and mice exposed to 200 mg molybdenum/m³, the terminal body weights were 13 and 10%, respectively, lower than the control

3. HEALTH EFFECTS

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/m³ 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/m³ 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/m³ (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/m³ 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/m³ (NTP 1997). No histological alterations were observed in male or female reproductive tissues following exposure to ≤67 mg molybdenum/m³ 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.

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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/m³; 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/m³, alveolar/bronchiolar adenoma or carcinoma in males at 6.7 and 20 mg molybdenum/m³, alveolar/bronchiolar adenoma in females at 20 and 67 mg molybdenum/m³, and alveolar/bronchiolar adenoma or carcinoma in females at 67 mg molybdenum/m³ (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

3. HEALTH EFFECTS

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 4 M	10 days (F); 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) 22 M	PND 4-17; 0 or 50 mg/kg/day	BW, HP	Musc/Skel Bd Wt	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) 5 F	14 day (F); 0, 1.2 mg/kg/day	BW, HP	Hepatic Renal Bd Wt	1.2 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) 5 M	14 day (F); 0, 0.58 mg/kg/day	BW, HP	Hepatic Renal Bd Wt	0.58 0.58 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) 25 F	14 days (W); 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) 10 M	14 days; 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) 5 F	14 days (F); 0, 1.2 mg/kg/day	BW, HP		1.2			No histological alterations were observed in the ovaries.	Bersenyi et al. 2008 (ammonium heptamolybdate)

3. HEALTH EFFECTS

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) 5 M	14 days (F); 0, 0.58 mg/kg/day	BW, HP			0.58		Reduction in germ cells and mature spermatocytes (incidence and statistical significance were not reported)	Bersenyi et al. 2008 (ammonium heptamolybdate)
INTERMEDIATE EXPOSURE									
Systemic									
9	Rat (Sprague Dawley) 7 M	8 weeks (GW); 0, 40, 80 mg/kg/day	BW, OW, UR	Renal Bd Wt	40 40	80 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 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) 25M, 25F	59-61 days (males) 22-35 days (females) (GW); 0, 0.4, 1.5, 4.4 mg/kg/day	BW, HE	Hemato Bd Wt	1.5 1.5	4.4 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) 4M	5 weeks; 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) 10M, 10F	90 days (F); 0, 5, 17, or 60 mg/kg/day	CS, BW, BC, HE, FI, GN, HP, OW	Resp Cardio Gastro Hemato Renal Endocr Ocular Bd Wt	60 60 60 60 17 60 60 17		60 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)

3. HEALTH EFFECTS

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, Bl, OW	Cardio Bd Wt Metab	100 100 100			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 (Wistar) 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)

3. HEALTH EFFECTS

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 Dermal Bd Wt	25 25 25	54 54	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)

3. HEALTH EFFECTS

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 testes at 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)

3. HEALTH EFFECTS

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)
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^aThe number corresponds to entries in Figure 3-2.

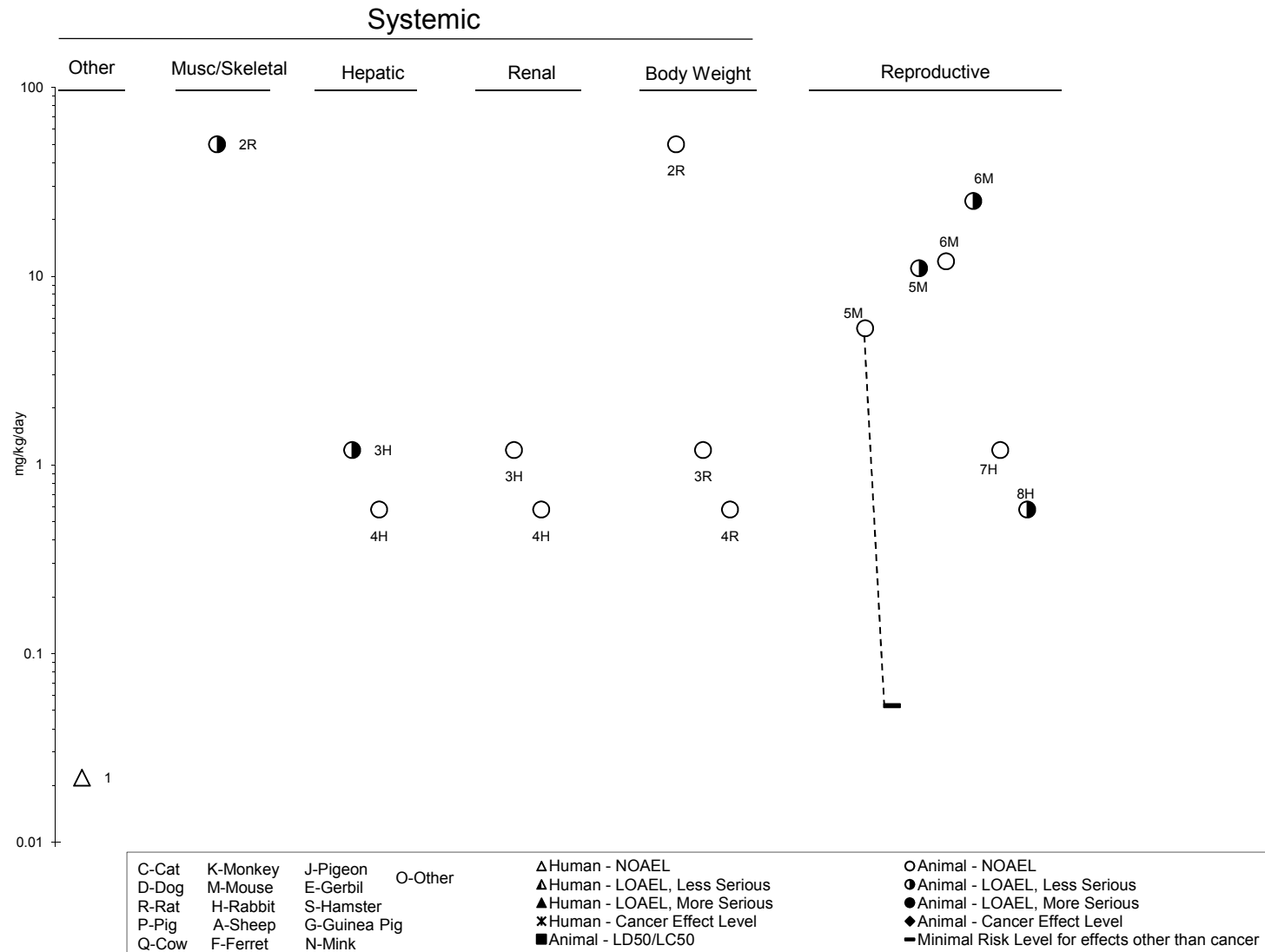
^bUsed to derive an acute-duration oral minimal risk level (MRL) of 0.053 m molybdenum/kg/day based on the NOAEL of 5.3 mg molybdenum/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

^cUsed 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 = musculoskeletal; OP = ophthalmology; OW = organ weight; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)

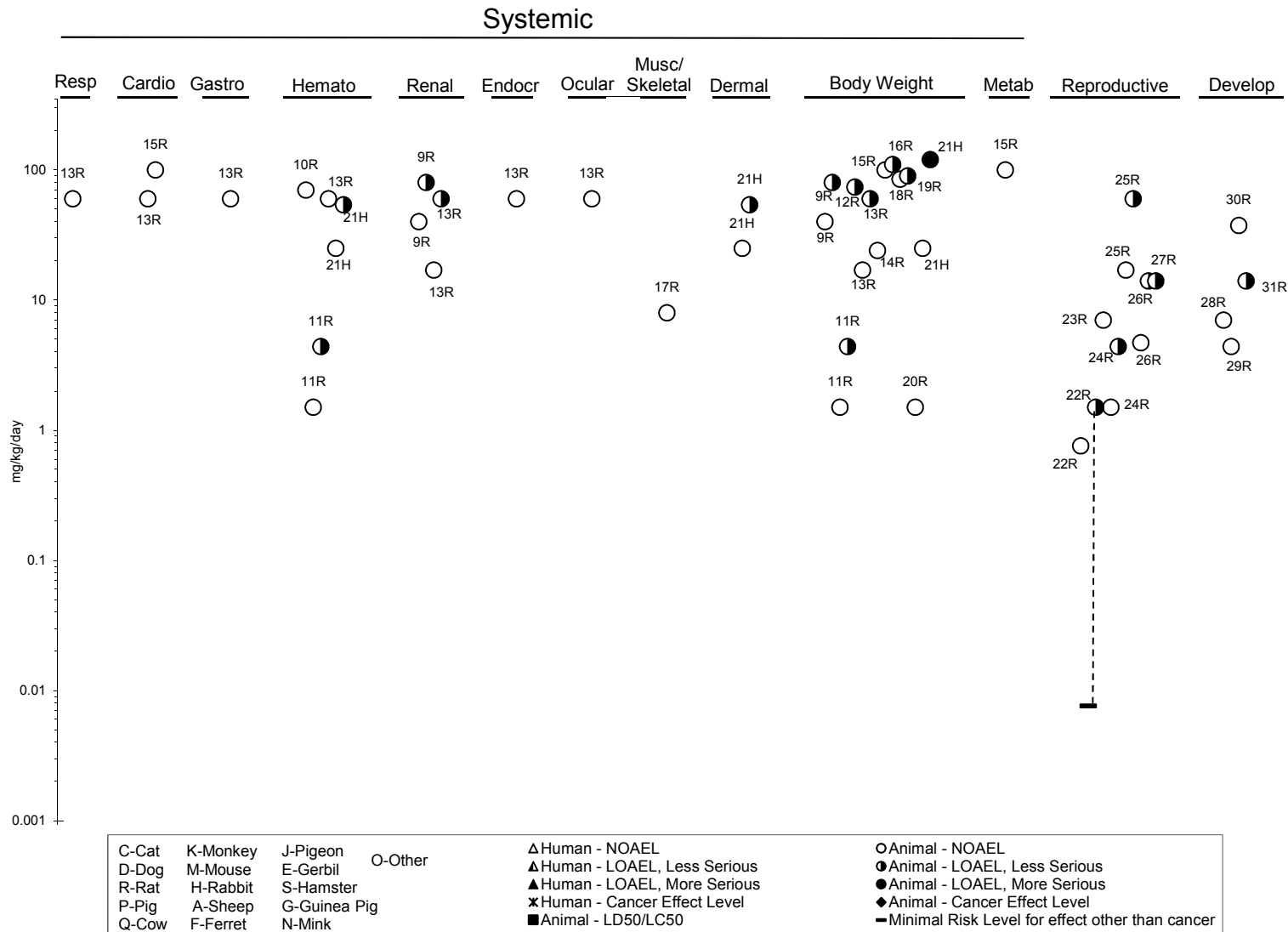
3. HEALTH EFFECTS

Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral
Acute (≤ 14 days)



3. HEALTH EFFECTS

Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral (Continued)
Intermediate (15-364 days)



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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).

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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 $\mu\text{g/L}$ (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 $\mu\text{g/L}$. 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

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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

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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

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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

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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

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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.

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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 triiodothyronine (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 (<70th percentile, 70th–85th percentile, and >85th 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

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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 molybdenum/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

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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

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(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.

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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 molybdenum; 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 (>85th 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 ($\geq 70^{\text{th}}$ 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.

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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

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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 $\mu\text{g/g}$ 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 $\mu\text{g/g}$ 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 $\mu\text{g/g}$ 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.

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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).

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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 $\geq 0.35\%$ 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).

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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

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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
<i>Drosophila melanogaster</i> wing spot test	Molybdenum chloride	Gene mutation	+	Ogawa et al. 1994

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

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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

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

Species (test system)	Compound	End point	Results		Reference
			With activation	Without activation	
Prokaryotic organisms:					
<i>Salmonella typhimurium</i> , TA98, TA100, TA1535, TA1537, 1538	Ammonium molybdate	Gene mutation	No data	–	Arlauskas et al. 1985
<i>S. typhimurium</i> , TA97, TA98, TA100, TA 1535, TA1537	Molybdenum trioxide	Gene mutation	–	–	NTP 1997; Zeiger et al. 1992
<i>Saccharmyces cerevistiae</i> D3	Sodium molybdate	Gene conversion and mutation	No data	–	Singh 1983
<i>Escherichia coli</i> , WP2uvrA ⁻	Ammonium molybdate	Reverse gene mutation	No data	–	Arlauskas et al. 1985
<i>E. coli</i> , 2 WP2 strains	Ammonium molybdate	Reverse gene mutation	No data	+	Nishioka 1975
<i>E. coli</i> , CM571	Ammonium molybdate	Reverse gene mutation	No data	–	Nishioka 1975
<i>E. coli</i> PQ37	Molybdenum chloride	DNA damage	No data	–	Olivier and Marzin 1987
<i>E. coli</i> WP2 _s (λ)	Sodium molybdate	DNA damage	No data	(+)	Rossmann et al. 1984
<i>E. coli</i> WP2 _s (λ)	Sodium molybdate	DNA damage	No data	(+)	Rossmann et al. 1991
<i>Bacillus subtilis</i> , H17 and M45	Molybdic acid	DNA repair assay	No data	–	Kanematsu et al. 1980
<i>B. subtilis</i> H17 and M45	Molybdenum disulfide	DNA repair assay	No data	–	Kanematsu et al. 1980
<i>B. subtilis</i> H17 and M45	Molybdenum chloride	DNA repair assay	No data	–	Nishioka 1975
<i>B. subtilis</i> H17 and M45	Potassium molybdate	DNA repair assay	No data	+	Nishioka 1975
<i>B. subtilis</i> H17 and M45	Ammonium molybdate	DNA repair assay	No data	+	Nishioka 1975
<i>Photobacterium fischeri</i>	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

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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

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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 $>5 \mu\text{m}$ 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 ($\leq 5 \mu\text{m}$) 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 (Bailey et al. 2007; ICRP 1994). More soluble forms of molybdenum, such as molybdenum trioxide ($\text{Mo}^{\text{VI}}\text{O}_3$), 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

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molybdenum/m³ 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 (⁹⁵Mo, ⁹⁶Mo), 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]O₄²⁻) 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

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(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 $\mu\text{g}/\text{day}$ (approximately 0.3 $\mu\text{g Mo}/\text{kg}/\text{day}$), compared to 94% when fed a diet containing 467 $\mu\text{g Mo}/\text{day}$ (approximately 7 $\mu\text{g Mo}/\text{kg}/\text{day}$) (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 (Giussani 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 ($\text{Mo}^{\text{VI}}\text{S}_4^{2-}$) 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).

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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/m³, 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).

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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 $\mu\text{g/L}$, mean \pm standard deviation [SD]; fetal: 1.44 ± 0.89 $\mu\text{g/L}$) (Bougle et al. 1989). Molybdenum concentrations in venous cord blood (flowing from the placenta to the fetus; 0.7 ± 0.2 $\mu\text{g/L}$, mean \pm SD) were slightly higher than in arterial cord blood (flowing from the fetus to the placenta; 0.6 ± 0.2 $\mu\text{g/L}$), 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 $\mu\text{g/L}$. 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 $\mu\text{g/L}$) and maternal molybdenum intake (mean intake of 132 $\mu\text{g/day}$).

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

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(Mo^[VI]O₂²⁻) (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 ¹⁰⁰Mo/day) and administered intravenous doses of stable isotope of molybdenum (33 µg ⁹⁷Mo). Six days after exposure to ¹⁰⁰Mo in the diet, 17.8% of the ¹⁰⁰Mo 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 ¹⁰⁰Mo was excreted in the urine. A similar pattern of urinary excretion was found when ⁹⁷Mo 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 ¹⁰⁰Mo dose was excreted in the feces; at the highest dose, 7.5% of the ¹⁰⁰Mo dose was excreted in the feces. In contrast, no consistent pattern of fecal ⁹⁷Mo 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

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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

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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.

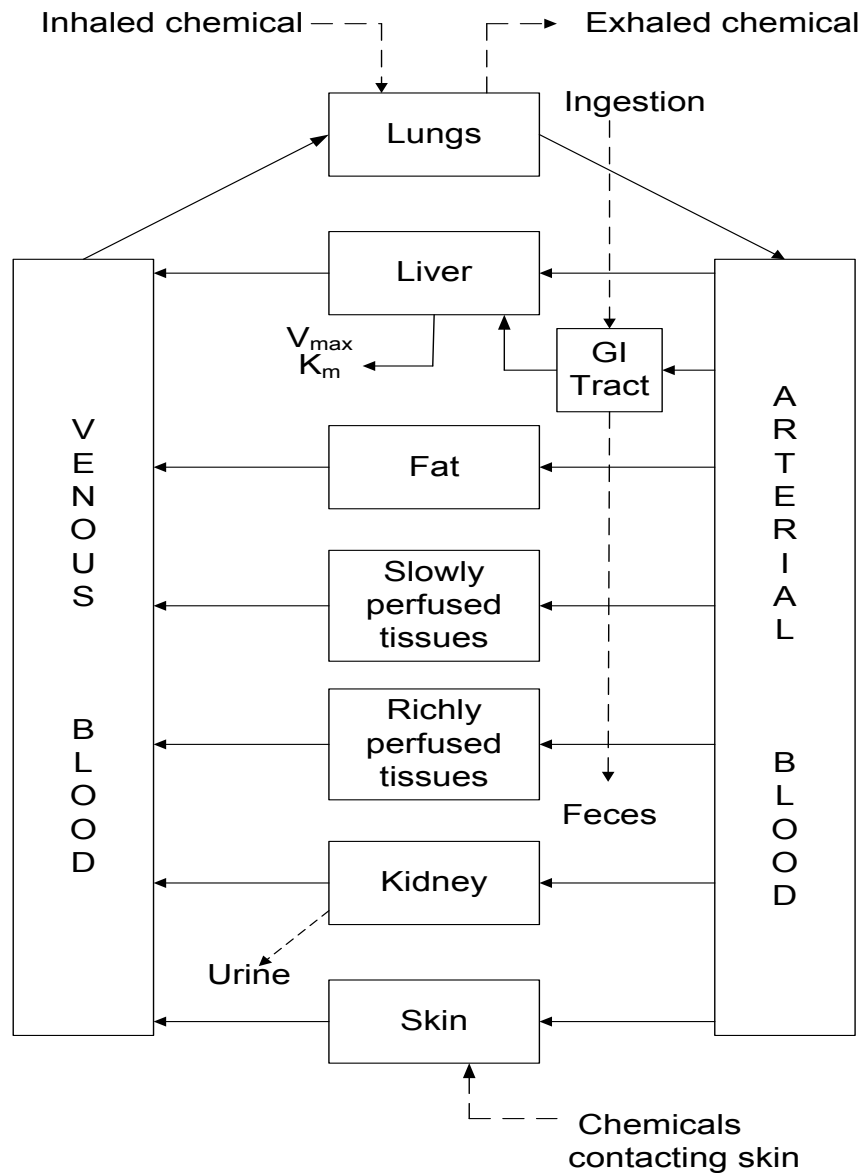
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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

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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

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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.

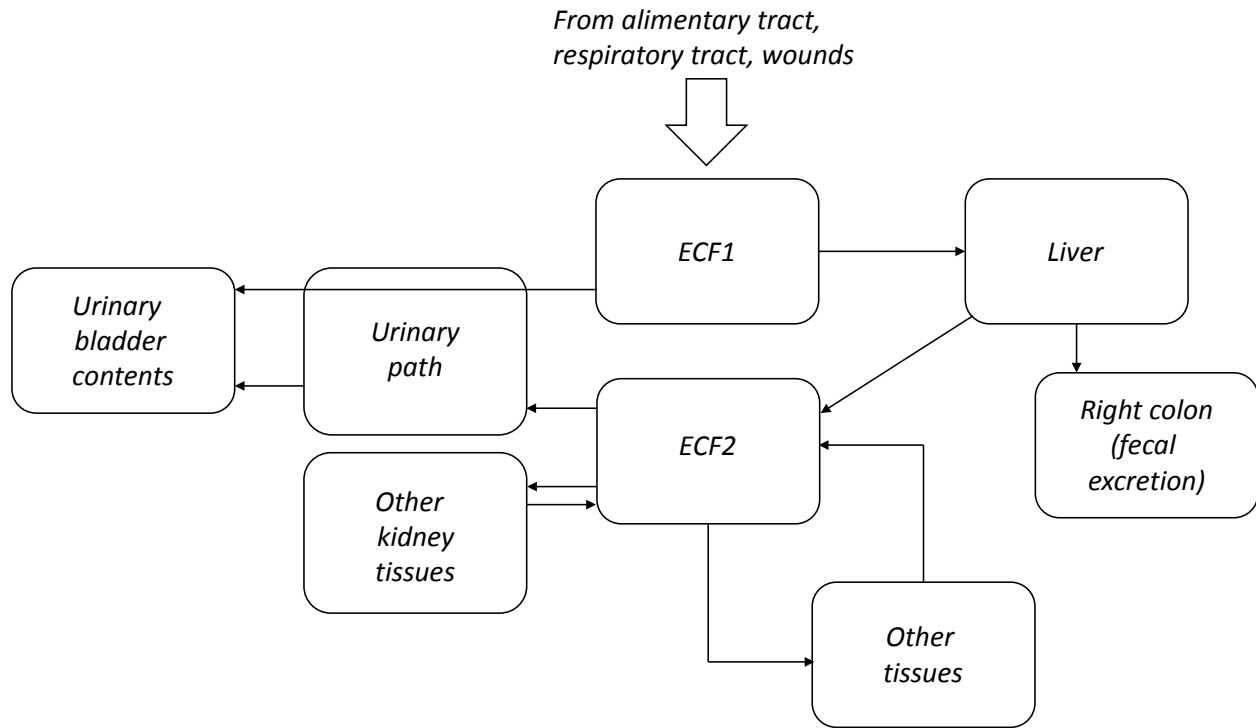
Giussani (2008) developed a model of molybdenum kinetics in humans. The structure of the model is shown in Figure 3-4 and parameter values are presented in Table 3-5. Data used to derive and evaluate the model are described in Giusanni (2008) and included human clinical studies in which subjects were 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

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



ECF = extracellular fluid

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

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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
<i>f_A</i> (liquid form) ^a	0.9
<i>f_A</i> (diet) ^a	0.6

^aDimensionless number.

ECF = extracellular fluid

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

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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 $\mu\text{g Mo/day}$) 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 $>121 \mu\text{g Mo/day}$ 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 ($>121 \mu\text{g Mo/day}$) 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 $\text{Na}^+/\text{SO}_4^{2-}$ symporter (NaS1 or SLC13A1) expressed in rodent small intestine and renal proximal tubule (Markovich

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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 et al. 2000).

Distribution. Bacteria and eukaryotes express cell membrane molybdate transporters, one of which (MoT₂) 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). MoT₂ 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⁻/HCO₃⁻ 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 (MoO₄²⁻) 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 (MoO₄²⁻) and sulfate (SO₄²⁻) exhibit mutual inhibition (Ryan et al. 1987). This is consistent with participation of the Na⁺/SO₄²⁻ 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

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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.

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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).

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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.

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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/m³); decreases in body weight gain were observed in male rats exposed to 67 mg molybdenum/m³ and in female rats and mice exposed to 200 mg/m³. 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/m³. 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/m³. 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).

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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/m³ and 95% lower confidence limits on the BMC (BMCL) ranging from 0.19 to 4.26 mg molybdenum/m³. 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/m³ 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/m³.

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,

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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

^aSignificantly different from controls; p≤0.01.

^bSignificantly different from controls; p≤0.05.

Source: NTP 1997

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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);

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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).

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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'skiy 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

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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 isoflavonoid 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.

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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

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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

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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

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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 ± 0.5 nmol/L; 25 days after the subjects were maintained on a low molybdenum diet (22 $\mu\text{g}/\text{day}$), 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 $\mu\text{g}/\text{day}$ (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 $\mu\text{g}/\text{L}$ and the creatinine-corrected value was 42.0 $\mu\text{g}/\text{g}$ creatinine (CDC 2015); see Section 6.5 for additional information.

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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-

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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.

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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.

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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

3. HEALTH EFFECTS

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

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation			●							●
Oral			●			●	●			
Dermal										

Human

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●	●	●	●	●				●
Oral	●	●	●			●	●	●	●	
Dermal				●						

Animal

● Existing Studies

3. HEALTH EFFECTS

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 LOELs for effects on oocytes and sperm and were used to derive an acute-duration oral MRL for molybdenum.

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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

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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

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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

3. HEALTH EFFECTS

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 (Turnlund 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 ($\text{Mo}^{\text{VI}}\text{O}_4^{2-}$) 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 ($\text{Mo}^{\text{VI}}\text{S}_4^{2-}$) 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.

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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, ferrimolybdate, 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.

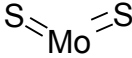
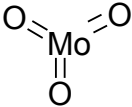
Under physiological conditions ($\text{pH} > 6.5$), molybdate anion, $[\text{MoO}_4]^{2-}$ is the sole molybdenum species in aqueous media (Cruywagen 2000; Cruywagen et al. 2002). Molybdenum compounds (e.g., molybdenum trioxide and polymolybdates) transform rapidly to the $[\text{MoO}_4]^{2-}$ ion under 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-99m or $^{99\text{m}}\text{Tc}$) 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.

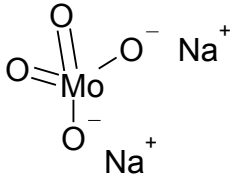
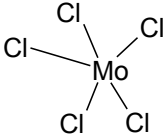
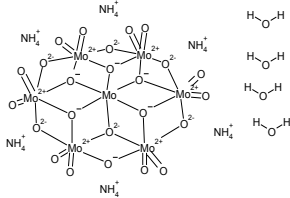
4. CHEMICAL AND PHYSICAL INFORMATION

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

4. CHEMICAL AND PHYSICAL INFORMATION

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	$(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$
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

4. CHEMICAL AND PHYSICAL INFORMATION

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) ₂ MoO ₄	(NH ₄) ₂ MoS 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

^aAll information obtained from HSDB (2009a, 2009b, 2009c, 2010) unless otherwise noted.

^bSigma-Aldrich 2015e

^cNOAA 2015

^dNIOSH 2015c

^eSigma-Aldrich 2015a

^fSigma-Aldrich 2015b

^gChemIDplus 2015

^hSigma-Aldrich 2015d

ⁱRTECS 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. CHEMICAL AND PHYSICAL INFORMATION

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.

4. CHEMICAL AND PHYSICAL INFORMATION

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

4. CHEMICAL AND PHYSICAL INFORMATION

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 ₂ O)
Boiling point	Not applicable	No data	190°C (decomposes)
Density	3.78 g/cm ^{3f}	2.928 g/cm ^{3g}	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

4. CHEMICAL AND PHYSICAL INFORMATION

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 ⁱ	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

^aAll information obtained from HSDB (2009a, 2009b, 2009c, 2010) unless otherwise noted.

^bSebenik et al. 2012

^cNOAA 2015

^dBIAC 2013

^eECHA 2015

^fNIOSH 2015c

^gSigma-Aldrich 2015a

^hNJDOH 2009

ⁱSigma-Aldrich 2015c

^jPatnaik 1999

^kAlfa 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 $\geq 90\%$ 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 $1,000\text{--}1,100^\circ\text{C}$ (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).

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

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.

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

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

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

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

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/Uses:

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

Source: TRI13 2015 (Data are from 2013)

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

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. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

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 MoS₂ and its selectivity to hydrogenation to be 3 times that of MoS₂ 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, ⁹⁹Mo, 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 MoS₂ 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. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

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.

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

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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.

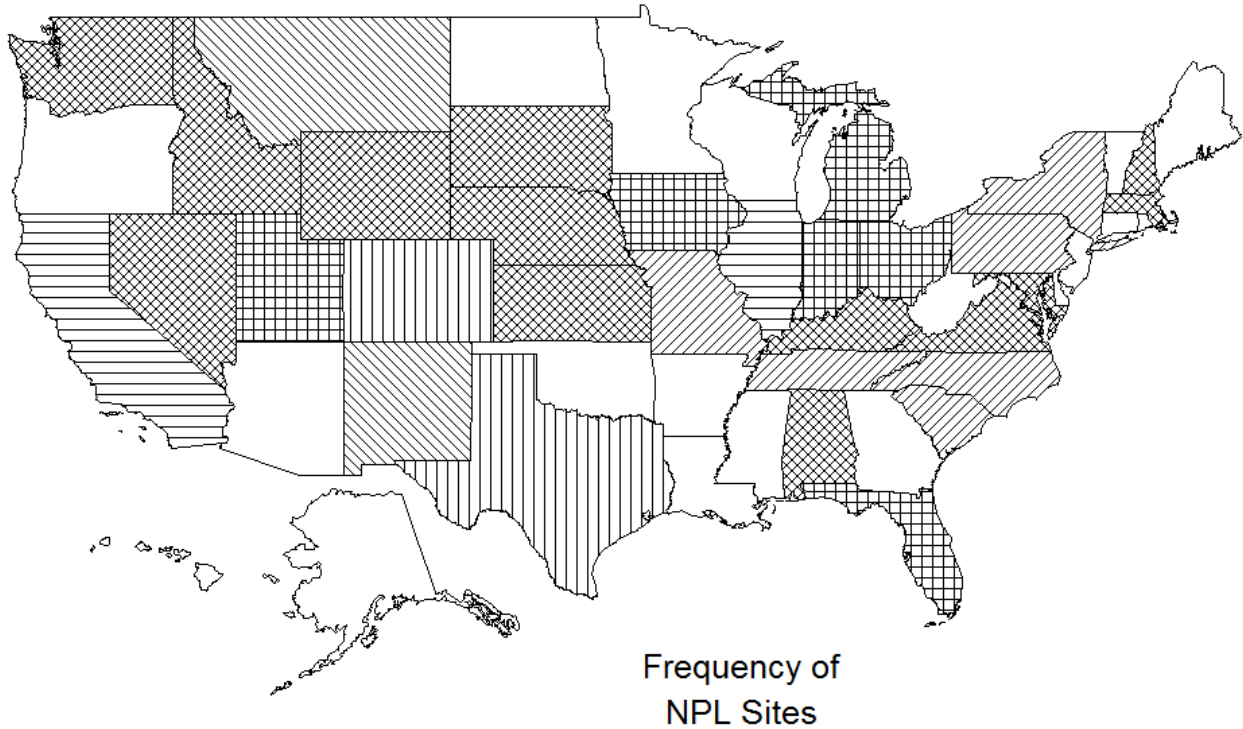
Molybdenum is a naturally occurring trace element that can be found extensively in nature. Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (EPA 1979). A radioactive isotope of molybdenum (^{99}Mo) is used as a source for producing metastable technetium-99 ($^{99\text{m}}\text{Tc}$), 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, ferrimolybdate, and ilsemanite. 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 oxidic 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.

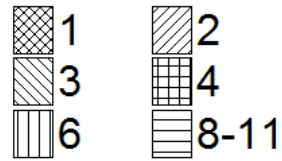
Molybdenum is infrequently detected in ambient air, but is a natural constituent of water and soils. The earth's crust contains an average of 0.0001% (1 ppm) of molybdenum, and surface waters usually have molybdenum concentrations of $<5 \mu\text{g/L}$ (EPA 1979). A decade-long study conducted by the 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 $1 \mu\text{g/L}$ (USGS 2011).

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with Molybdenum



Source: ATSDR 2015



6. POTENTIAL FOR HUMAN EXPOSURE

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/m³, 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/m³ during mining, crushing, milling, and open pit operations, respectively, at a Colorado mine (EPA 1979).

The extensive nationwide use of radioactive ⁹⁹Mo 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).

6. POTENTIAL FOR HUMAN EXPOSURE

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 3.6×10^{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

6. POTENTIAL FOR HUMAN EXPOSURE

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

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							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

6. POTENTIAL FOR HUMAN EXPOSURE

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

State ^c	RF ^d	Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							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

^aThe 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.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI13 2015 (Data are from 2013)

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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

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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 cm³/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 µg/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.

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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 $\text{pH} > 7$, whereas at $\text{pH} < 7$, polymeric species, such as a tetrahedral polyatomic anion or other isopolyanions, may form. At $\text{pH} < 5$, 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.

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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/m³ (EPA 1979). Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 µg/m³, are higher than those found in rural areas, 0.001–0.0032 µg/m³ (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

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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 (Kiryama 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

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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 $\mu\text{g/L}$, respectively, were reported (USGS 1964). Another study reported a mean molybdenum concentration of 8 $\mu\text{g/L}$ 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 $\mu\text{g/L}$) to 1.51 $\mu\text{g/L}$ 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 $\mu\text{g/L}$. 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 $\mu\text{g/L}$. However, after the mine closed in 1974, the mean concentration in drinking water samples decreased to 150 $\mu\text{g/L}$ by January 1975, 60 $\mu\text{g/L}$ by June 1975, and 30 $\mu\text{g/L}$ 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).

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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 foothills 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).

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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).

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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

^aTrace values were defined as results \geq LOD and $<$ LOQ. Results \geq LOD and $<$ LOQ (trace values) were used as reported when calculating the means.

LOD = limit of detection; LOQ = limit of quantification

Source: FDA 2014

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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 $\mu\text{g}/\text{day}$ 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 $<5 \mu\text{g}/\text{day}$ (EPA 1979). Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum ($>50 \mu\text{g}/\text{L}$) (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 $\mu\text{g}/\text{g}$ of creatinine, respectively. The 95th percentile mean concentrations of molybdenum in urine were 144, 130, 120, 132, 137, 143, and 130 $\mu\text{g}/\text{g}$ 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 $\mu\text{g}/\text{g}$ 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 $\mu\text{g}/\text{L}$ and the 25th, 50th, 75th, and 95th percentiles were 27.9, 56.5, 93.9, and 168.0, $\mu\text{g}/\text{L}$, respectively. The creatinine-adjusted 25th, 50th, 75th, and 95th percentiles were 30.9, 45.7, 64.3, and 133.8 $\mu\text{g}/\text{g}$, respectively, with a geometric mean of 39.6 $\mu\text{g}/\text{g}$. Urinary molybdenum levels were about 1–2 orders of magnitude greater than any of the other 12 metals analyzed.

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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/m³ 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/m³, 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/m³, while air samples collected in the breathing zone of workers had molybdenum concentrations ranging from 1.4 to 5.4 mg/m³ (EPA 1979). The air concentrations of molybdenum in two plants that produce molybdenum salts were 0.5–200 and 0.2–30 mg/m³ (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/m³, respectively. Stationary air samplers in the facility detected coarse (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/m³, 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

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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 $^{99\text{m}}\text{Tc}$ 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 $\mu\text{g/L}$ (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).

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

Lactation day	Molybdenum levels in breast milk ($\mu\text{g/L}$)		Reference
	Term infants	Preterm infants	
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	

^aSignificantly different from term infant levels ($p < 0.05$).

^bSignificantly different from molybdenum concentration at 2-6 days ($p < 0.01$).

^cSignificantly different from molybdenum concentration at 2-6 days ($p < 0.05$).

^dSignificantly different from molybdenum concentration for whole group at 3-5 days ($p < 0.01$).

^eSignificantly different from molybdenum concentration at for whole group at 3-5 days ($p < 0.05$).

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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 $\mu\text{g/g}$ of creatinine, respectively. The 95th percentile mean concentrations of molybdenum in urine were 214, 185, 160, 201, 274, 195, and 259 $\mu\text{g/g}$ 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).

⁹⁹Mo 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.

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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

6. POTENTIAL FOR HUMAN EXPOSURE

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- $\mu\text{g/L}$ 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 ($\mu\text{g/L}$). Electrothermal atomic absorption spectrometry (ETAAS) is a widely accepted technique that is less expensive than ICP instruments and capable of detecting $\mu\text{g/L}$ 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 $\mu\text{g}/100$ g blood and 0.2 $\mu\text{g/g}$ tissue, which is the average LOD for 20 elements, including molybdenum.

7. ANALYTICAL METHODS

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 ₄ OH.	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 ₂ O 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

7. ANALYTICAL METHODS

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 ₂ O 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

^aMolybdenum is the target analyte unless otherwise specified.

AES = atomic emission spectrometry; HPGe = high-purity germanium 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 = quadrupole 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

7. ANALYTICAL METHODS

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 germanium (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.

7. ANALYTICAL METHODS

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.	Spectrophotometry	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

7. ANALYTICAL METHODS

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

^aMolybdenum is the target analyte unless otherwise specified.

^bDetection 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; TiO₂ = titanium dioxide; USGS = U.S. Geological Survey

7. ANALYTICAL METHODS

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

7. ANALYTICAL METHODS

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/m³ was derived for molybdenum. The MRL is based on a BMCL_{HEC} of 0.013 mg molybdenum/m³ 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).

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
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
<u>NATIONAL</u>			
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 molybdate	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	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
DOE (<i>cont.</i>)	PACs (<i>cont.</i>)		
	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 molybdate	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 molybdate	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	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
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	

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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

Agency	Description	Information	Reference
NATIONAL (<i>cont.</i>)			
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 40 CFR 302.4
	Effective date of toxic chemical release reporting		EPA 2014b 40 CFR 372.65
	Molybdenum trioxide	01/01/1987	
	TSCA chemical lists and reporting periods	No data	EPA 2014c 40 CFR 712.30
DHHS	Carcinogenicity classification	No data	NTP 2014

^aReason for not establishing a guideline value: occurs in drinking-water at concentrations well below those of health concern.

^bRespirable fraction; deposited in the gas-exchange region.

^cInhalable fraction; deposited anywhere in the respiratory tract.

^dDefinitions of PAC terminology are available from U.S. Department of Energy (DOE 2012b).

^eA proposed PEL TWA of 5 mg/m³ 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/m³ for insoluble compounds as molybdenum (NIOSH 2015b).

^fThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

^gA3: 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

8. REGULATIONS, ADVISORIES, AND GUIDELINES

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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 (K_d)—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.

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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.

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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₎ (LC₅₀)—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₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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.

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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.

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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.

q₁*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q₁* 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/m³ 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/m³ 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.

10. GLOSSARY

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₎ (TD₅₀)—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

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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.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 8
Species: Mouse

Minimal Risk Level: 0.0004 mg/kg/day mg molybdenum/m³

Reference: NTP. 1997. Toxicology and carcinogenicity studies of molybdenum trioxide (CAS No. 1313-27-5) in F344/N rats and B6C3F₁ 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/m³ molybdenum trioxide (0, 6.7, 20, and 67 mg Mo/m³) 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/m³ 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/m³, adenoma or carcinoma (combined) in male mice at 6.7 and 20 mg/m³, adenoma in female mice at ≥20 and 67 mg/m³, and adenoma or carcinoma (combined) in female mice at 67 mg/m³. 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.

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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

^aSignificantly different from controls; p≤0.01.

^bSignificantly 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/m³ 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/m³ (squamous metaplasia of the epiglottis in male and female rats and mice, hyaline

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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)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC	Overall largest			
<i>Gamma</i>^{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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSelected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3 -fold). Therefore, the model with the lowest AIC was selected.

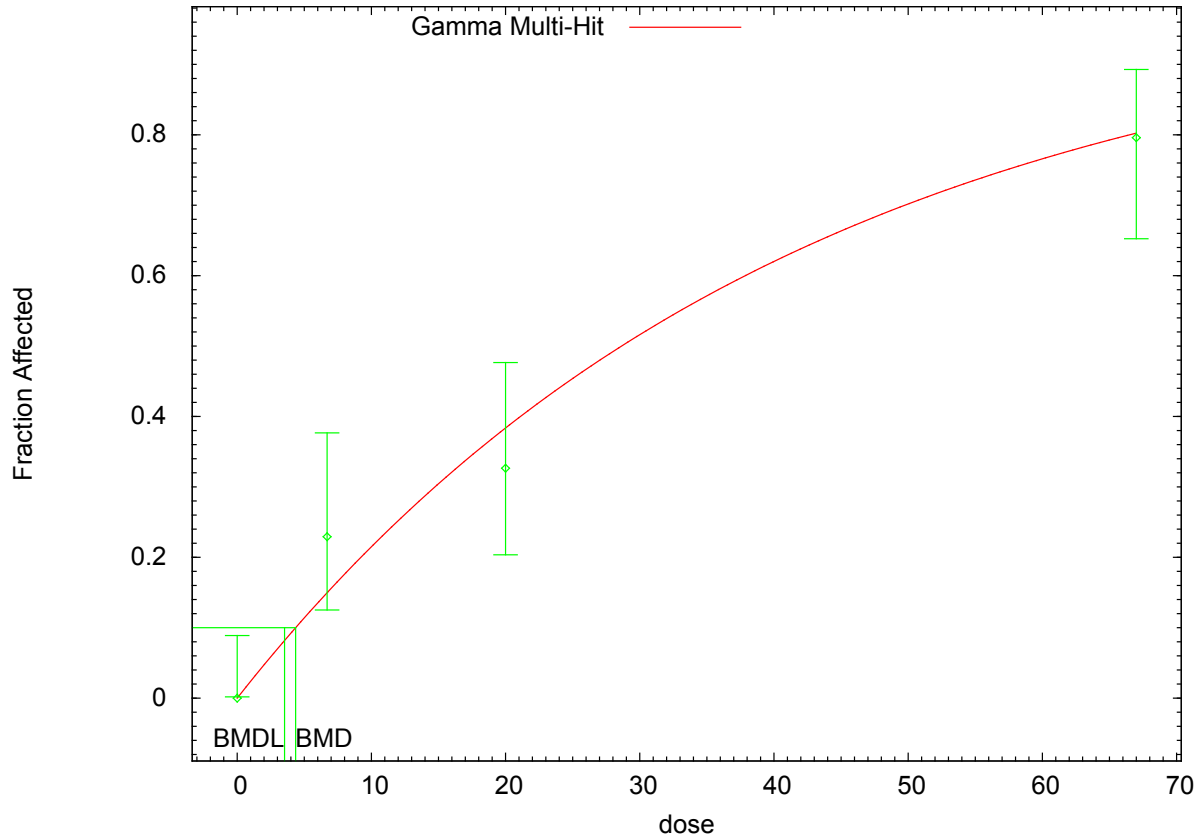
^eSlope restricted to ≥ 1 .

^fBetas 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/m³)

Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



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Table A-3. Model Predictions for Hyaline Degeneration of the Nasal Respiratory Epithelium in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			Overall largest AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC				
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSelected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

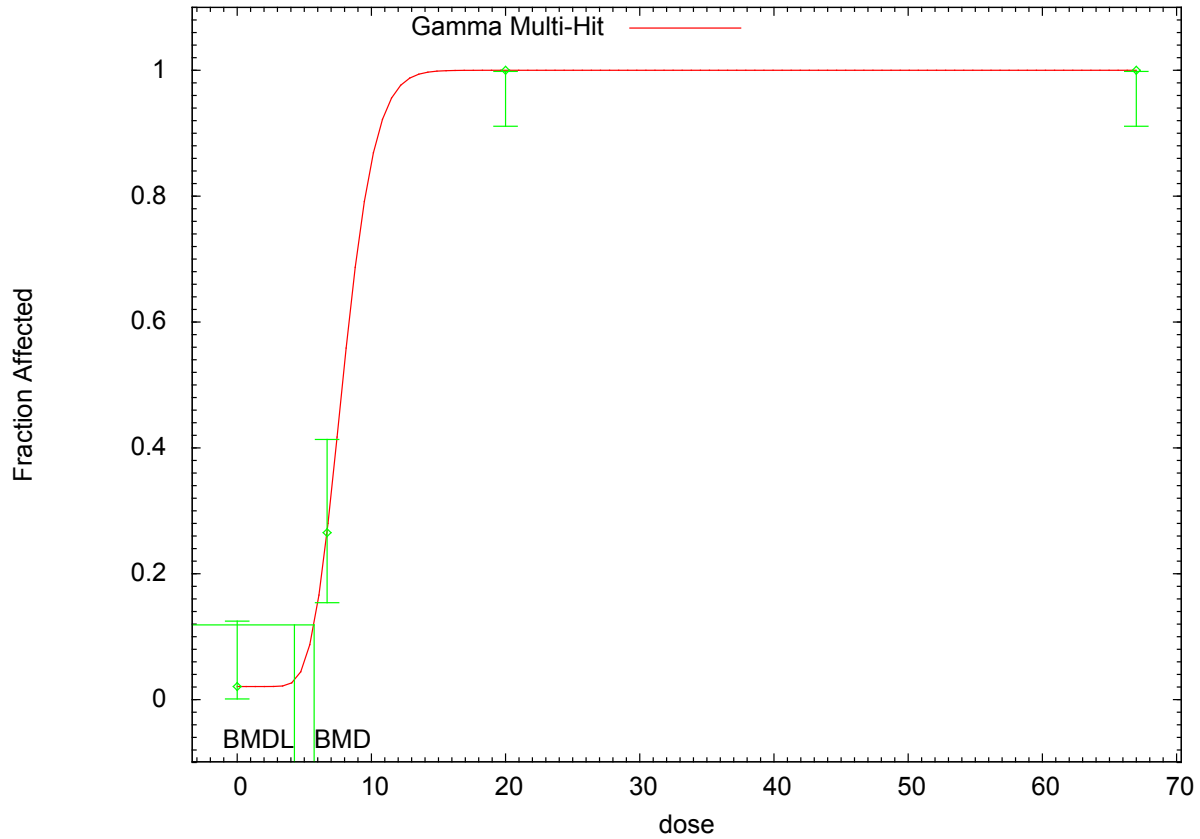
^eSlope restricted to ≥ 1 .

^fBetas 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/m³)

Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



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Table A-4. Model Predictions for Squamous Metaplasia of the Epiglottis in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			Overall AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC	largest			
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSelected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

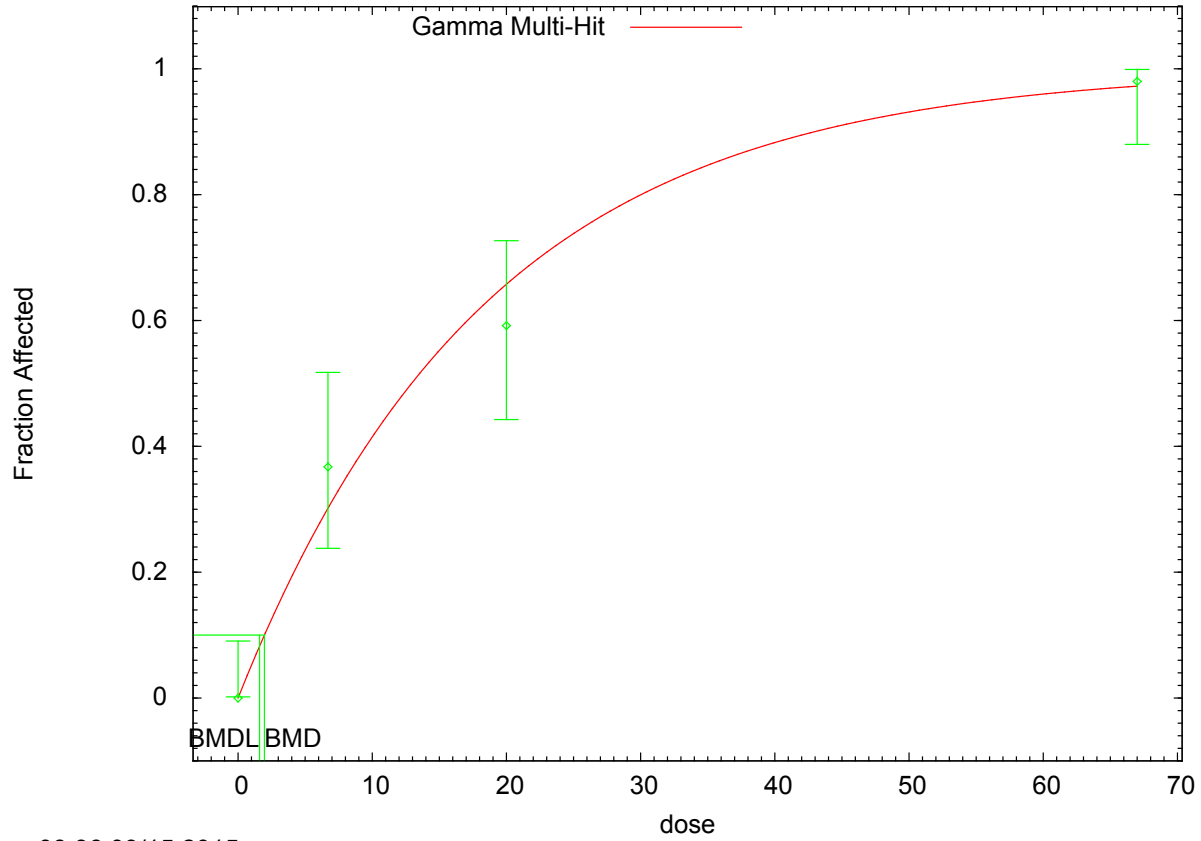
^eSlope restricted to ≥ 1 .

^fBetas 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/m³)

Gamma Multi-Hit Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the



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Table A-5. Model Predictions for Squamous Metaplasia of the Epiglottis in Male Mice Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b				BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC	Overall largest	AIC		
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

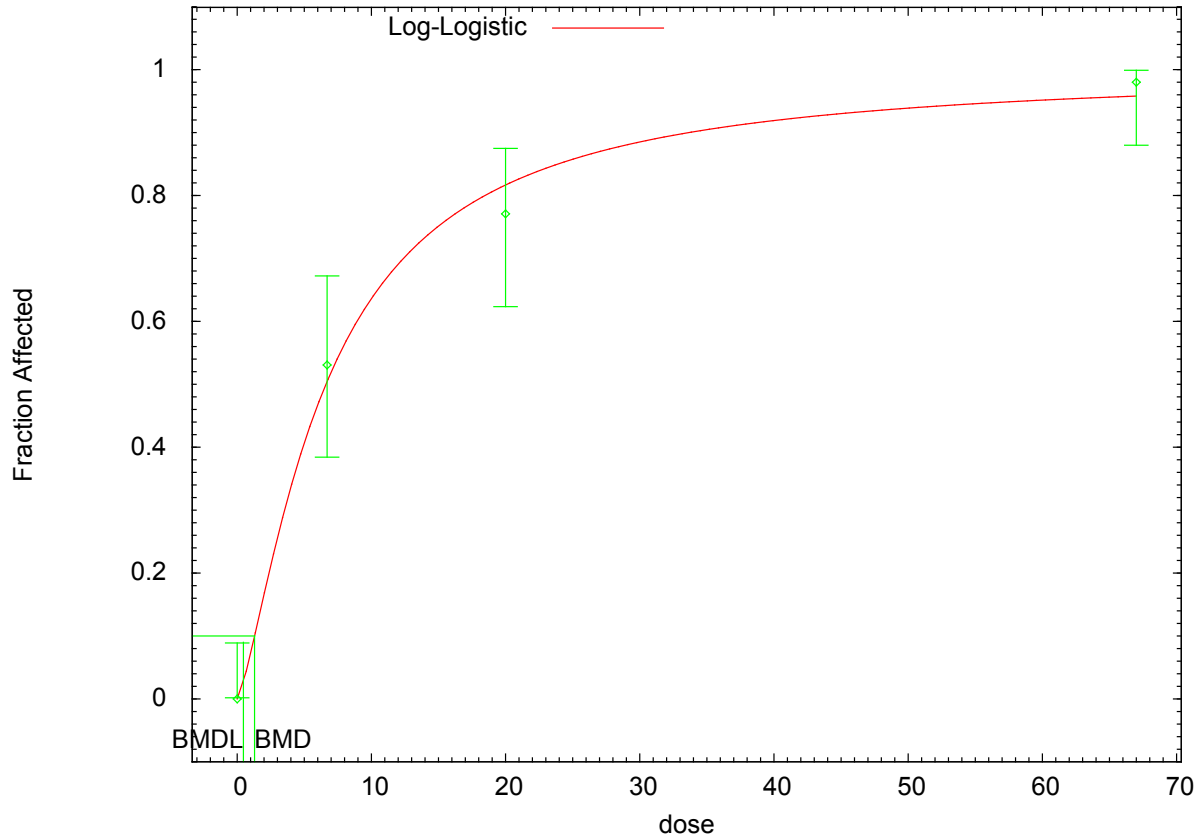
^eSelected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

^fBetas 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/m³)

Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



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Table A-6. Model Predictions for Alveolar Epithelial Metaplasia in Male Mice Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			Overall largest AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC				
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

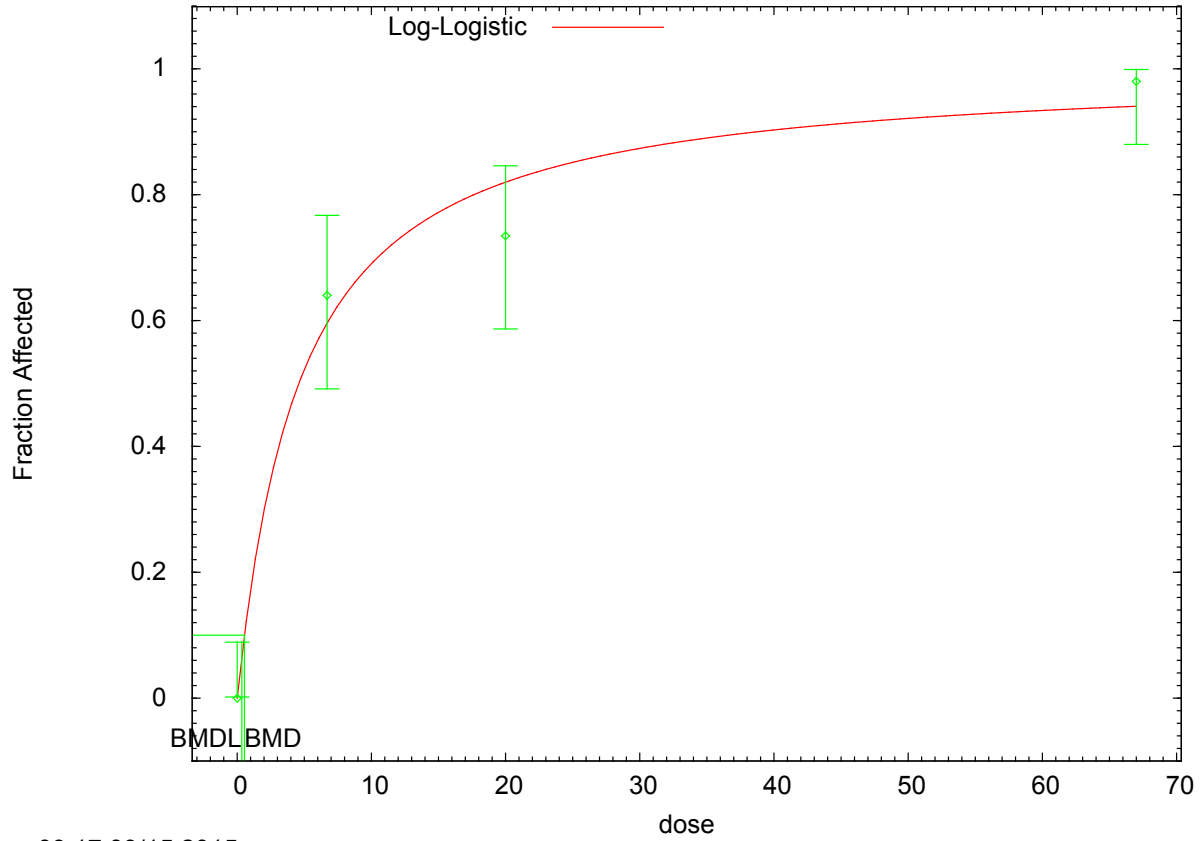
^eSelected model. The only model that provided adequate fit to the data was the Log-Logistic model.

^fBetas 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/m³)

Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



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Table A-7. Model Predictions for Squamous Metaplasia of the Epiglottis in Female Mice Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			Overall largest AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC				
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

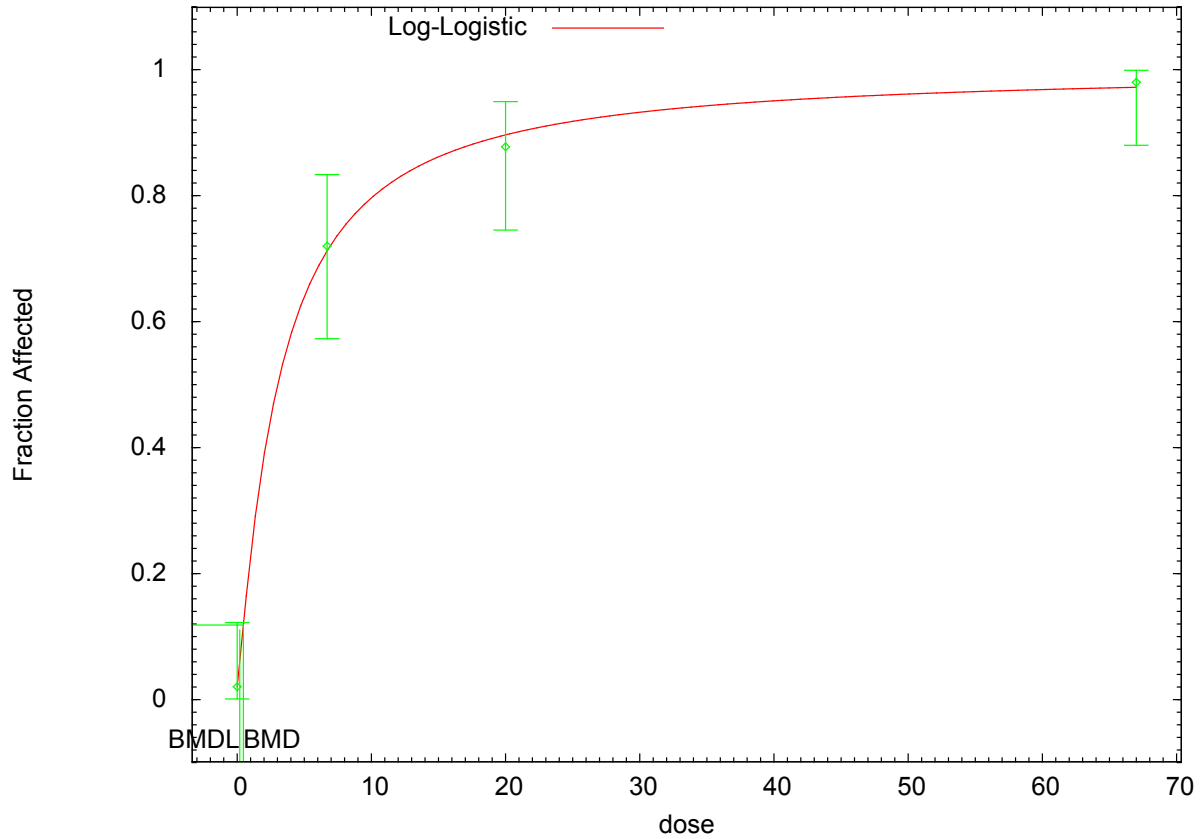
^eSelected model. The only model that provided adequate fit to the data was the Log-Logistic model.

^fBetas 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/m³)

Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



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Table A-8. Model Predictions for Alveolar Epithelial Metaplasia in Female Mice Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value ^a	Scaled residuals ^b			Overall largest AIC	BMC ₁₀ (mg/m ³)	BMCL ₁₀ (mg/m ³)
				Dose below BMC	Dose above BMC				
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

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eSelected model. The only model that provided adequate fit to the data was the Log-Logistic model.

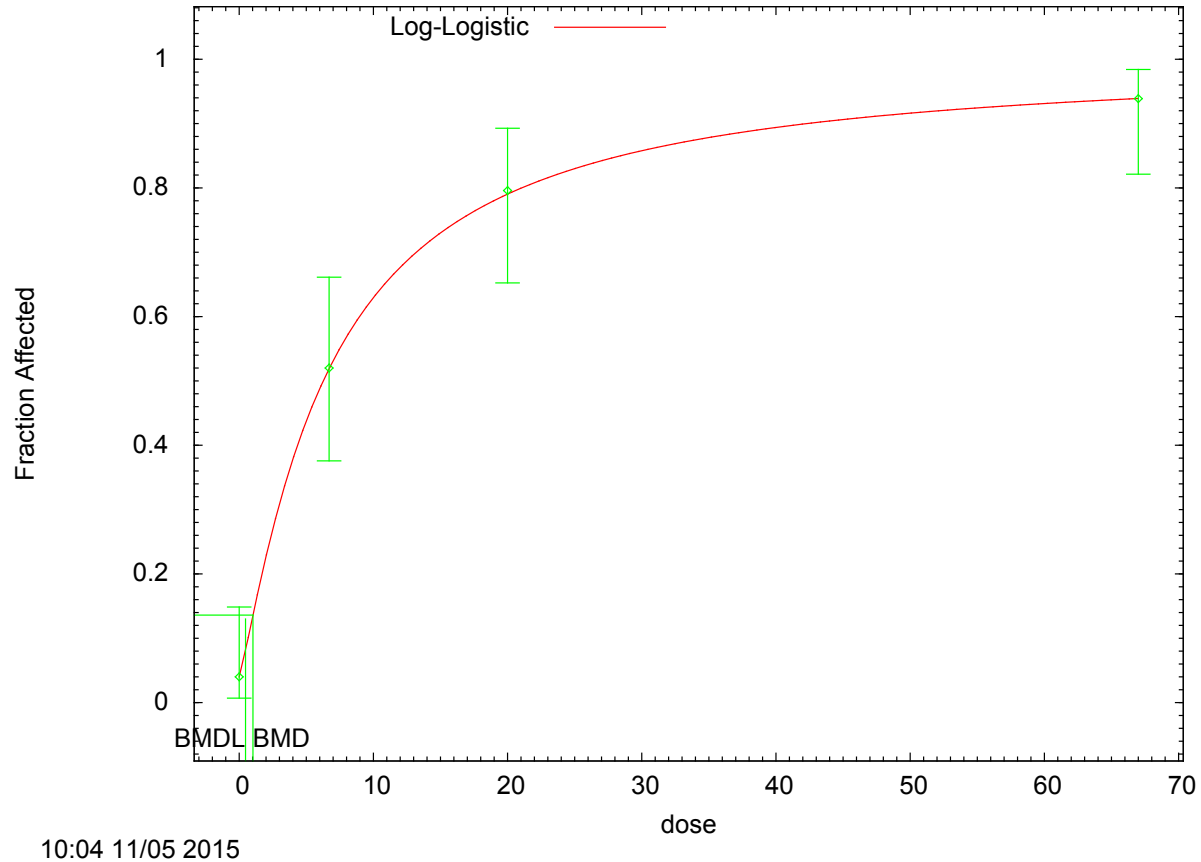
^fBetas restricted to ≥ 0 .

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, $p < 0.10$

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Figure A-7. Fit of LogLogistic Model to Data on Incidence of Alveolar Epithelial Metaplasia in Female Mice Exposed to Molybdenum Trioxide (mg/m³)

Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the E



Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans with dosimetric adjustments
- 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.

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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

^aHEC 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/m³. 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

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 5
Species: Mouse

Minimal Risk Level: 0.05 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.

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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

^aMean ± standard deviation; n = 25/group.

^bStatistically 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.

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
- 10 for extrapolation from animals to humans
- 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

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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

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Molybdenum
CAS Numbers: 7439-98-7
Date: April 2017
Profile Status: Final for Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 24
Species: Rat

Minimal Risk Level: 0.008 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.

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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

^aData extracted using GrabIt! Software from Figure 1 in the Fungwe et al. (1990) study.

^bMean ± standard error.

^cStatistically 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.

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
- 10 for extrapolation from animals to humans
- 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.

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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)

^aAdjusted 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.

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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

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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:

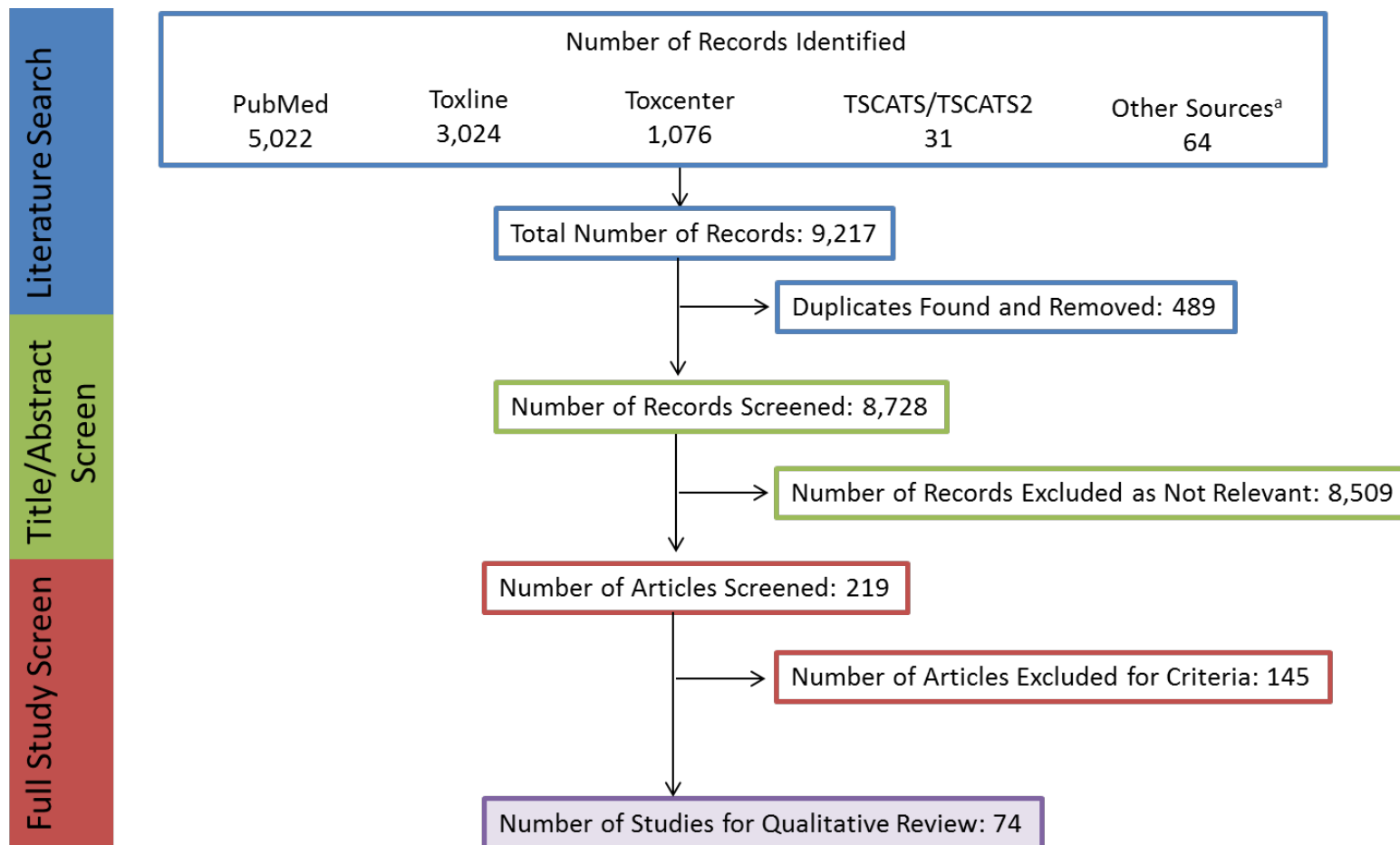
- Title and Abstract Screen
- Full Text Screen

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



^aRed 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).

APPENDIX B

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.

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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

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Table B-3. Overview of the Health Outcomes for Molybdenum Evaluated In Human Studies

	Systemic effects															Cancer	
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Metabolic	Other	Immunological effects	Neurological effects		Reproductive effects
Inhalation studies																	
Cohort	2 1												1 1				1 1
Case control																	
Population																	
Controlled exposure																	
Oral studies																	
Cohort											1 1	1 1			2 2	2 1	
Case control																	
Population					1 1		3 3										
Controlled exposure												1 0					
Dermal studies																	
Cohort																	
Case control																	
Population																	
Controlled Exposure																	
Number of studies examining end point				0	1	2	3	4	5-9	≥10							

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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													Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Metabolic	Other					
Inhalation studies																		
Acute-duration	2 0																	
Intermediate-duration	2 0																	
Chronic-duration	2 2																2 2	
Oral studies																		
Acute-duration					4 4	2 1	2 1				5 0						4 3	
Intermediate-duration	1 0	2 0	3 1	16 5	9 8	8 7	8 8	6 5	2 2	0 0	31 24	2 0	1 0		2 1	10 7	8 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								

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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?

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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.

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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					Risk of bias tier	
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias			Selective reporting bias
	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	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?	
Outcome: Respiratory effects							
<i>Cohort studies</i>							
Ott et al. 2004	-	-	+	na	+	++	Second
Walravens et al. 1979	-	-	+	+	-	+	Second
Outcome: Hepatic effects							
<i>Cross-sectional studies</i>							
Mendy et al. 2012	+	+	+	+	-	+	Second
Outcome: Alterations in Uric Acid Levels							
<i>Cross-sectional studies</i>							
Koval'sky et al. 1961	-	-	+	-	+	+	Second
<i>Cohort studies</i>							
Walravens et al. 1979	-	-	+	+	-	+	Second
Outcome: Reproductive Effects							
<i>Cross-sectional studies</i>							
Lewis and Meeker 2015	na	-	+	+	+	+	First
Meeker et al. 2008	+	+	+	++	++	++	First
Meeker et al. 2010	+	+	++	+	++	++	First

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Table B-8. Summary of Risk of Bias Assessment for Molybdenum—Observational Epidemiology Studies

	Risk of bias criteria and ratings					Risk of bias tier	
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias			Selective reporting bias
Reference	Were the comparison groups appropriate?	Did the study design or analysis account for important confounding and modifying variables?*	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?	
Outcome: Developmental Effects							
<i>Cross-sectional studies</i>							
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.

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Table B-9. Summary of Risk of Bias Assessment for Molybdenum—Human-Controlled Exposure Studies

	Risk of bias criteria and ratings							Risk of bias tier
	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?	
Outcome: Alterations in Uric Acid Levels <i>Oral acute exposure</i> 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.

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Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	Did the study design or analysis account for important confounding and modifying variables?	
Outcome: Respiratory effects										
<i>Inhalation acute exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
<i>Inhalation intermediate exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
<i>Inhalation chronic exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Outcome: Hepatic effects										
<i>Inhalation intermediate exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First

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Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	Did the study design or analysis account for important confounding and modifying variables?	
<i>Inhalation chronic exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
<i>Oral acute exposure</i>										
Bersenyi et al. 2008 (rabbit)	-	+	+	-	++	-	+	+	+	First
Bersenyi et al. 2008 (rabbit)	-	+	+	-	++	-	+	+	+	First
<i>Oral intermediate exposure</i>										
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		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	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											
<i>Inhalation intermediate exposure</i>											
NTP 1997 (rat)	++	+	++	+	++	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	++	+	First
<i>Inhalation chronic exposure</i>											
NTP 1997 (rat)	++	+	++	+	++	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	++	+	First
<i>Oral acute exposure</i>											
Bersenyi et al. 2008 (rabbit, males)	-	+	+	-	++	-	+	+	+	+	First
Bersenyi et al. 2008 (rabbit, females)	-	+	+	-	++	-	+	+	+	+	First

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Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	Did the study design or analysis account for important confounding and modifying variables?	
<i>Oral intermediate exposure</i>										
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										
<i>Oral intermediate exposure</i>										
Murray et al. 2013 (rat)	++	+	++	-	++	++	++	++	++	First
Outcome: Reproductive effects										
<i>Inhalation intermediate exposure</i>										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First

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Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	Did the study design or analysis account for important confounding and modifying variables?	
<i>Oral acute exposure</i>										
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
<i>Oral intermediate exposure</i>										
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

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Table B-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	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?	Did the study design or analysis account for important confounding and modifying variables?	
Pandey and Singh 2002 (rat fertility study)	-	+	++	-	++	+	+	++	-	First
Outcome: Developmental effects										
<i>Oral intermediate exposure</i>										
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.

APPENDIX B

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 molybdenum 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".

APPENDIX B

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.

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**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					
<i>Cohort studies</i>					
Ott et al. 2004	No	Yes	Yes	No	Low
Walravens et al. 1979	No	No	No	No	Very Low
Outcome: Hepatic effects					
<i>Cross-sectional studies</i>					
Mendy et al. 2012	No	No	Yes	Yes	Low
Outcome: Alterations in Uric Acid Levels					
<i>Cross-sectional studies</i>					
Koval'sky et al. 1961	No	Yes	Yes	No	Low
<i>Cohort studies</i>					
Walravens et al. 1979	No	No	No	No	Very Low
Outcome: Reproductive Effects					
<i>Cross-sectional studies</i>					
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					
<i>Cross-sectional studies</i>					
Vazquez-Salas et al. 2014	No	No	Yes	Yes	Low
Shirai et al. 2010	No	No	Yes	Yes	Low

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**Table B-15. Presence of Key Features of Study Design for Molybdenum—
Human-Controlled Exposure Studies**

Reference	Key feature				Initial study confidence
	Concurrent control group or self-control	Sufficient number of subjects tested	Appropriate methods to measure outcome	Adequate data for statistical analysis	
Outcome: Alterations in Uric Acid Levels					
<i>Oral acute exposure</i>					
Deosthale and Gopalan 1974	Yes	No	Yes	No	Low

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**Table B-16. Presence of Key Features of Study Design for Molybdenum—
Experimental Animal Studies**

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory effects					
<i>Inhalation acute exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Inhalation intermediate exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Inhalation chronic exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
<i>Inhalation intermediate exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Inhalation chronic exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Oral acute exposure</i>					
Bersenyi et al. 2008 (rabbit, males)	Yes	No	Yes	Yes	Moderate
Bersenyi et al. 2008 (rabbit, females)	Yes	No	Yes	Yes	Moderate
<i>Oral intermediate exposure</i>					
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					
<i>Inhalation intermediate exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High

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**Table B-16. Presence of Key Features of Study Design for Molybdenum—
Experimental Animal Studies**

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
<i>Inhalation chronic exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Oral acute exposure</i>					
Bersenyi et al. 2008 (rabbit, males)	Yes	No	Yes	Yes	Moderate
Bersenyi et al. 2008 (rabbit, females)	Yes	No	Yes	Yes	Moderate
<i>Oral intermediate exposure</i>					
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					
<i>Oral intermediate exposure</i>					
Murray et al. 2013 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Reproductive effects					
<i>Inhalation intermediate exposure</i>					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
<i>Oral acute exposure</i>					
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
<i>Oral intermediate exposure</i>					
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				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Developmental effects					
<i>Oral intermediate exposure</i>					
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

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Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
<i>Inhalation acute exposure</i>		
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	
<i>Inhalation intermediate exposure</i>		
Animal studies		
NTP 1997 (rat)	High	High
NTP 1997 (mouse)	High	
<i>Inhalation chronic exposure</i>		
Animal studies		
NTP 1997 (rat)	High	High
NTP 1997 (mouse)	High	
Outcome: Hepatic effects		
Human studies		
<i>Cross-sectional studies</i>		
Mendy et al. 2012	Low	Low
<i>Inhalation intermediate exposure</i>		
Animal studies		
NTP 1997 (rat)	High	High
NTP 1997 (mouse)	High	
<i>Inhalation chronic exposure</i>		
Animal studies		
NTP 1997 (rat)	High	High
NTP 1997 (mouse)	High	
<i>Oral acute exposure</i>		
Animal studies		
Bersenyi et al. 2008 (rabbit, males)	Moderate	Moderate
Bersenyi et al. 2008 (rabbit, females)	Moderate	
<i>Oral intermediate exposure</i>		
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	

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Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Renal effects		
<i>Inhalation intermediate exposure</i>		
Animal studies		
NTP 1997 (rat)	High	
NTP 1997 (mouse)	High	High
<i>Inhalation chronic exposure</i>		
Animal studies		
NTP 1997 (rat)	High	
NTP 1997 (mouse)	High	High
<i>Oral acute exposure</i>		
Animal studies		
Bersenyi et al. 2008 (rabbit, males)	Moderate	
Bersenyi et al. 2008 (rabbit, females)	Moderate	Moderate
<i>Oral intermediate exposure</i>		
Animal studies		
Bandyopadhyay et al. 1981 (rat)	Low	
Bompart et al. 1990 (rat)	Moderate	
Murray et al. 2013 (rat)	High	
Rana et al. 1980 (rat)	Low	High
Rana and Kumar 1980c	Moderate	
Rana and Kumar 1983 (rat)	Moderate	
Outcome: Alterations in Uric Acid Levels		
Human studies		
<i>Cross-sectional studies</i>		
Koval'sky et al. 1961	Low	Low
<i>Cohort studies</i>		
Walravens et al. 1979	Very Low	Very Low
<i>Oral acute exposure</i>		
Human studies		
<i>Controlled exposure</i>		
Deosthale and Gopalan 1974	Low	Low
<i>Oral intermediate exposure</i>		
Animal studies		
Murray et al. 2013 (rat)	High	High
Outcome: Reproductive Effects		
Human studies		
<i>Cross-sectional studies</i>		
Lewis and Meeker 2015	Low	
Meeker et al. 2008	Low	Low
Meeker et al. 2010	Low	

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Table B-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Initial study confidence	Initial confidence rating
<i>Inhalation intermediate exposure</i>		
Animal studies		
NTP 1997 (rat)	High	
NTP 1997 (mouse)	High	High
<i>Oral acute exposure</i>		
Animal studies		
Zhang et al. 2013 (mouse)	Moderate	
Zhai et al. 2013 (mouse)	Moderate	
Bersenyi et al. 2008 (rabbit)	Low	Moderate
Bersenyi et al. 2008 (rabbit)	Very Low	
<i>Oral intermediate exposure</i>		
Animal studies		
Fungwe et al. 1990 (rat)	Moderate	
Jeter and Davis 1954 (rat, adult)	Very Low	
Jeter and Davis 1954 (rat, weanling)	Very Low	
Lyubimov et al. 2004 (rat)	High	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		
<i>Cross-sectional studies</i>		
Vazquez-Salas et al. 2014	Low	Low
Shirai et al. 2010	Low	
<i>Oral intermediate exposure</i>		
Animal studies		
Jeter and Davis 1954 (rat, weanling)	Very Low	
Lyubimov et al. 2004 (rat)	High	High
Murray et al. 2014 (rat)	High	
Pandey and Singh 2002 (rat)	High	

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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

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- 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

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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

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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

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Table B-19. Confidence in the Body of Evidence for Molybdenum

Outcome	Confidence in body of evidence	
	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.

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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 No health effect	High Evidence of no health effect

^aMixed 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.

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- **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; Bompert et al. 1990; Murray et al. 2013; Rana and Kumar 1980c, 1983; Rana et al. 1980).

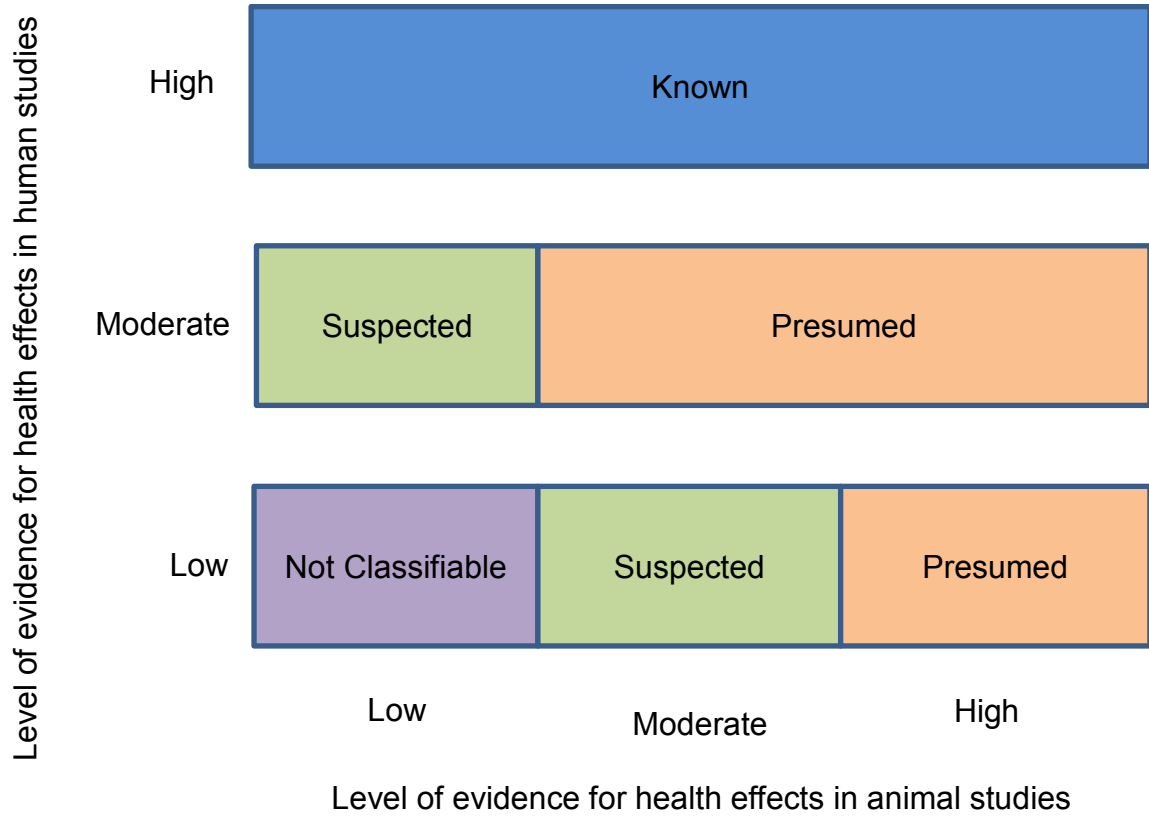
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Table B-21. Hazard Identification Conclusions for Molybdenum

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

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Figure B-2. Hazard Identification Scheme



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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.

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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.

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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").

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- (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/m³ 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.

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- (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

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

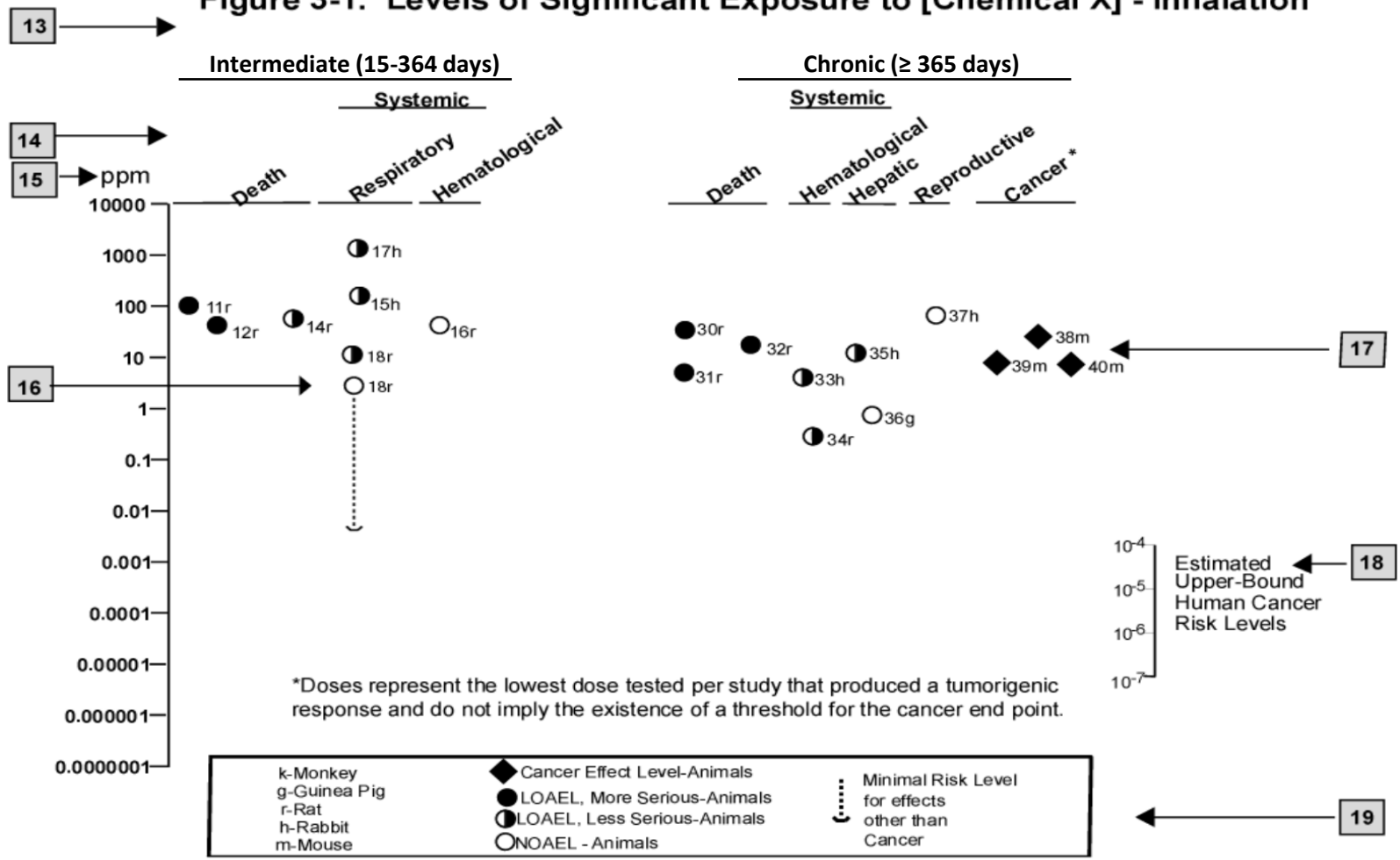
Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
3 →	Systemic	↓	↓	↓	↓	↓	↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE							
	Cancer					11 ↓	
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs) Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors) NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

12 → ^a The number corresponds to entries in Figure 3-1.

^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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 C

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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

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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
K _d	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	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

APPENDIX D

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
NIOSH TIC	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

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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

APPENDIX D

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 _i *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

