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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Hexavalent Chromium Part 1: Experimental Animal Studies

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ABBREVIATIONS

ACP	acid phosphatase
ADAFs	age-dependent adjustment factors
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CCA	chromated copper arsenate
CPSC	Consumer Product safety Commission
CrVI	hexavalent chromium
E2	estradiol
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FRN	Federal Registry Notice
FSH	follicle-stimulating hormone
GD	gestation day
GGT	γ-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GPT	glutamic-pyruvate transaminase
HCT	hematocrit
HERO	Health and Environment Research Online
Hgb	hemoglobin
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
LDH	lactate dehydrogenase
LH	luteinizing hormone
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCLG	maximum contaminant level goal
MCV	mean cell volume
MetHgb	methemoglobin
MMAD	mass median aerodynamic diameter
MMD	mass median diameter
MRL	minimum reporting level
NAS	National Academy of Sciences
NATA	National-Scale Air Toxics Assessment
NCEA	National Center for Environmental Assessments
NIOSH	National Institute for Occupational Safety and Health
NJ DEP	New Jersey Department of Environmental Protection
NOAEL	no-observed-adverse-effect level
NPDWR	National Primary Drinking Water Regulation
NPL	National Priorities List
NRC	National Research Council
NTP	National Toxicology Program
OPP	Office of Pesticides Program
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
P4	progesterone
PBPK	physiologically based pharmocokinetic
PND	postnatal day
PNW	postnatal week
RBC	red blood cell
RCRA	Resource Conservation and Recovery Act
RED	reregistration eligibility decision
RfC	reference concentration
RfD	reference dose
RTP	Research Triangle Park
SDH	sorbitol dehydrogenase
SRBC	sheep red blood cells
T	testosterone
TRI	Toxic Release Inventory
TSCATS	Toxic Substances Control Act Submission database
UCMR3	Third Unregulated Contaminant Monitoring Rule
WBC	white blood cell
WHO	World Health Organization

PREFACE

This draft document presents preliminary materials for an assessment of hexavalent chromium (CrVI), prepared by EPA's Integrated Risk Information System (IRIS) Program. These preliminary materials include a planning and scoping summary, problem formulation, information on the approaches used to identify pertinent literature, results of the literature search, approaches for selection of studies for hazard identification, and presentation of critical studies in evidence tables and exposure-response arrays. This material is being released for public review and comment prior to a public meeting, providing an opportunity for the IRIS Program to engage in early discussions with stakeholders and the public on data that may be used to identify adverse health effects and characterize dose-response relationships. This is the first of two sets of preliminary materials for hexavalent chromium, and focuses on evidence from experimental animal studies. A second set of preliminary materials will include evidence from human studies as well as an inventory of toxicokinetic and mechanistic studies of hexavalent chromium.

The planning and scoping summary includes information on the uses of hexavalent chromium, occurrence of hexavalent chromium in the environment, and the rationale for the development of the assessment. This information is responsive to recommendations in the 2009 National Research Council (NRC) report *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) related to planning and scoping in the risk assessment process.

Some problem formulation information is included to identify certain scientific elements or data that will be important for developing the assessment. This problem formulation information identifies the human health effects that the assessment will evaluate and an analysis plan that outlines the approaches envisioned for use in the assessment. The inclusion of problem formulation also addresses the recommendations in the 2009 NRC report *Science and Decisions: Advancing Risk Assessment* (NRC, 2009) related to problem formulation.

The preliminary materials are also responsive to the NRC 2011 report *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde* (NRC, 2011). The IRIS Program's implementation of the NRC recommendations is following a phased approach that is consistent with the NRC's "Roadmap for Revision" as described in Chapter 7 of the formaldehyde review report. The NRC stated that "the committee recognizes that the changes suggested would involve a multi-year process and extensive effort by the staff at the National Center for Environmental Assessment and input and review by the EPA Science Advisory Board and others." Phase 1 of implementation has focused on a subset of the short-term recommendations, such as editing and streamlining documents, increasing transparency and clarity, and using more tables, figures, and appendices to present information and data in assessments. Phase 1 also focused on assessments near the end of the development process and close to final posting. Phase 2 of

implementation is focused on assessments that are in the beginning stages of assessment development. The IRIS hexavalent chromium assessment is in Phase 2 and represents a significant advance in implementing the NRC recommendations. In the development of this assessment, many of the recommendations are being implemented in full, while others are being implemented in part. Achieving full and robust implementation of certain recommendations will be an evolving process with input and feedback from the public, stakeholders, and independent external peer review. Phase 3 of implementation will incorporate the longer-term recommendations made by the NRC, including the development of a standardized approach to describe the strength of evidence for noncancer effects. On May 16, 2012, EPA announced[1] that as a part of a review of the IRIS Program's assessment development process, the NRC will also review current methods for weight-of-evidence analyses and recommend approaches for weighing scientific evidence for chemical hazard identification. This effort is included in Phase 3 of EPA's implementation plan.

The literature search and screening strategy, which describes the processes for identifying scientific literature, screening studies for consideration, and identifying pertinent sources of health effects data, is responsive to NRC recommendations regarding the development of a systematic and transparent approach for identifying the scientific literature for analysis. The preliminary materials also describe EPA's approach for the selection of critical studies to be included in the evidence tables, as well as the approach for evaluating methodological features of studies that will be considered in the overall evaluation and synthesis of evidence for each health effect. The development of these materials is in response to the NRC recommendation to thoroughly evaluate critical studies with standardized approaches that are formulated and based on the type of research (e.g., observational epidemiology or animal bioassays). In addition, NRC recommendations for standardized presentation of key study data are addressed by the development of the preliminary evidence tables and exposure-response arrays for primary health effect information.

EPA welcomes all comments on the preliminary materials in this document, including the following:

- the clarity and transparency of the materials;
- the approach for identifying pertinent studies;
- the selection of critical studies for data extraction to preliminary evidence tables and exposure-response arrays;
- any methodological considerations that could affect the interpretation of or confidence in study results; and
- any additional studies published or nearing publication that may provide data for the evaluation of human health hazard or dose-response relationships.

The preliminary evidence tables and exposure-response arrays should be regarded solely as representing the data on each endpoint that have been identified as a result of the draft literature

[1] EPA Announces NAS' Review of IRIS Assessment Development Process. 05/16/2012. http://yosemite.epa.gov/opa/admpress.nsf/0/1ce2a7875daf093485257a000054df54?OpenDocument

search strategy and approach to selecting critical studies. They do not reflect any conclusions as to hazard identification or dose-response assessment.

After obtaining public input and conducting additional study evaluation and data integration, EPA will revise these materials to support the hazard identification and dose-response assessment in a draft Toxicological Review that will be made available for public comment.

1. INTRODUCTION

This introduction contains a planning and scoping summary and problem formulation for the IRIS assessment of hexavalent chromium. The planning and scoping summary includes information on the properties, sources and uses of hexavalent chromium, occurrence and fate of hexavalent chromium in the environment, potential for human exposure, and the rationale for the development of this assessment. Problem formulation is a process used to identify certain scientific elements or data that will be important for developing an assessment. It helps EPA collect technical and scientific input that will inform the development of that assessment. The problem formulation for hexavalent chromium uses the assessments by federal, state, and international health agencies to identify scientific issues and studies that may inform EPA's plan for updating the inhalation and oral cancer and noncancer assessment for hexavalent chromium.

1.1. Hexavalent Chromium in the Environment

1.1.1. Chemical and Physical Properties

Chromium is a transition metal element. It is present in the Earth's crust and has oxidation states ranging from -2 to +6, with the +3 (trivalent) and +6 (hexavalent) states being the most predominant. Hexavalent and trivalent chromium are also written as Cr(VI) and Cr(III), respectively.

The solubility of chromium compounds depends primarily on the compound's oxidation state and varies significantly. Most trivalent chromium compounds are insoluble in water. Some hexavalent chromium compounds on the other hand, such as chromium oxide (or chromic acid), and the ammonium and alkali metal salts (e.g., sodium and potassium) of chromic acid are readily soluble in water. Hexavalent chromium is generally reduced to trivalent chromium in the environment; however, hexavalent forms can persist under conditions where there is a low concentration of reducing materials (ATSDR, 2012). Note that toxicity experiments for hexavalent chromium use various compounds such as chromic acid, potassium dichromate, potassium chromate and sodium chromate. Even though the physical properties of these compounds are somewhat different, they are all ionized to hexavalent chromium in the body and are considered to exert the same pharmacological and toxicological effects (U.S. EPA, 2008c).

1.1.2. Sources and Uses

Chromium can originate from both natural and man-made sources, but compounds containing the hexavalent oxidation state primarily arise from anthropogenic sources, with the largest releases occurring from industrial sources (ATSDR, 2012). The United States is one of the

world's leading producers of chromium compounds. Hexavalent chromium compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless-steel production, in leather tanning, in wood preservatives, in textile dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, chemical synthesis, and plastics. Industries with the largest contribution to chromium release or disposal of chromium and chromium compounds include metal processing, tannery facilities, chromate production, stainless steel welding, electric utility companies, and ferrochrome and chrome pigment production (HSDB, 2014; U.S. EPA, 2014a). In 1996, about 52% of chromium use in the United States was for the production of wood preservatives (ATSDR, 2012), but this use has likely declined because of a 2003 voluntary phase-out of residential wood treated with chromated copper arsenate (CCA pressure-treated wood) (CPSC, 2011).

1.1.3. Environmental Fate and Transport

Land

In 2012, environmental releases to land from domestic facilities required to report to EPA's Toxics Release Inventory (TRI) Program totaled 7,760,131 lbs of chromium and 44,373,397 lbs of chromium compounds. These accounted for over 90% of the total environmental releases of chromium and chromium compounds reported to this inventory in 2012, and consisted of various on- and offsite land releases including Resource Conservation and Recovery Act (RCRA) Subtitle C landfills, other landfills and land disposals, underground injection, land treatments, and surface impoundments (U.S. EPA, 2014a). Chromium has been identified in samples from at least 1,127 of 1,699 NPL hazardous waste sites (ATSDR, 2012) and hexavalent chromium ranks 17th on ATSDR's list of 275 hazardous substances (based on a combination of the chemical's frequency, toxicity, and potential for human exposure at NPL sites).

The mobility of chromium in soil depends on the speciation of chromium, which is a function of redox potential and the pH of the soil. In most soils, chromium will be present predominantly in the trivalent oxidation state. This form has low solubility, thus generally resulting in low mobility. Under oxidizing conditions, hexavalent chromium may be present in soil as CrO_4^{-2} and $HCrO_4^-$, hexavalent forms that are relatively soluble and mobile. The leachability of hexavalent chromium in the soil generally increases with soil pH (ATSDR, 2012).

Water

In 2012, environmental releases to water from domestic facilities required to report to the TRI Program totaled 97,773 lbs of chromium and 275,565 lbs of chromium compounds. These accounted for roughly 1% of the total environmental releases in 2012 of chromium and chromium compounds in this inventory, and consisted of various on- and offsite releases to water including surface water, wastewater treatment, and publicly owned treatment works (U.S. EPA, 2014a). Chromium released into water is usually ultimately deposited in sediments. Transport of

chromium from water to the atmosphere is unlikely because of the extremely low volatility of chromium compounds (ATSDR, 2012).

Most of the soluble chromium in the aqueous phase is present as hexavalent chromium or as soluble trivalent chromium complexes. Reduction of hexavalent to trivalent chromium can occur in the aquatic environment if an appropriate reducing agent is available. The most significant reducing agents present in aquatic systems include (in order of decreasing reduction ability) organic matter, hydrogen sulfide, sulfur, iron sulfide, ammonium, and nitrate. The reduction half-life of hexavalent chromium in water can be rapid (instantaneously to a few days) when the right reducing agents are present under anaerobic conditions, but can extend much longer in water with soil and organic sediment, ranging from 4–140 days (ATSDR, 2012). Oxidation of trivalent to hexavalent chromium can also occur in the aqueous environment, but hexavalent chromium generally does not accumulate due to the concurrent presence of natural reductants. Speciation in groundwater depends on the redox potential and pH conditions of the aquifer (ATSDR, 2012). Chromium is predominantly present as trivalent chromium in surface water but as hexavalent chromium in groundwaters (Frey et al., 2004). High groundwater levels of hexavalent chromium have been reported in several areas in the Western US (California, Idaho and Arizona) (Mcneill et al., 2012).

Air

In the atmosphere, total chromium has been measured as small particulates (e.g., mass mean aerodynamic diameter ≤10 μm) that can remain airborne for days and be transported over long distances (ATSDR, 2012). Atmospheric particulate matter is deposited on land and water via wet and dry deposition. Air emissions accounted for 2% or less of total environmental releases of chromium and chromium compounds, respectively, from domestic facilities required to report to the TRI Program in 2012 (U.S. EPA, 2014a). These included 123,015 lbs (fugitive) and 56,936 lbs (point source) of chromium, and 58,952 lbs (fugitive) and 188,292 lbs (point source) of chromium compounds. It has been estimated that approximately one-third of the chromium emitted to the atmosphere in the US is hexavalent chromium, and the estimated atmospheric half-life for hexavalent chromium reduction to trivalent chromium ranges from 16 hours to 5 days (ATSDR, 2012).

1.1.4. Environmental Concentrations

The average atmospheric concentrations of total chromium compounds in the US based on EPA's National Air Toxics Assessment (NATA) for 2005 was 0.009 μg/m^3 with a range of 0.00004–0.02 μg/m^3 (U.S. EPA, 2005a). Indoor air concentrations can be 10–400 times greater than outdoor air concentrations when cigarette smoke is involved (ATSDR, 2012). In surveys of US surface waters, total chromium concentrations in rivers ranged from <1–30 μg/L, and concentrations in lakes typically were less than 5 μg/L (ATSDR, 2012).

Bioaccumulation of chromium in plants appears to be unlikely, and there is no indication of biomagnification of chromium along the terrestrial or aquatic food chain (ATSDR, 2012) .

1.1.5. General Population Exposure

Human exposure to total chromium occurs from both natural and anthropogenic sources (ATSDR, 2012). Most human exposure to chromium is from dietary intake of trivalent chromium that is naturally present in foods (Wisconsin DHS, 2010). Trivalent chromium is generally understood to be essential to normal glucose, protein, and fat metabolism and is thus an essential dietary element with prescribed dietary reference intake guidelines (IOM, 2001), although some investigators have questioned its essentiality to humans (Vincent, 2013; Stearns, 2000). Typical chromium levels in vegetables, fruits, grains, cereals, eggs, meat, and fish range from approximately 20 to 520 µg/kg (ATSDR, 2012). Dermal exposure to chromium may also occur during the use of consumer products that contain chromium, such as some metals and wood or leather treated with chromium-containing compounds (ATSDR, 2012). Chromium has been detected in various human tissues and body fluids, including serum, urine, lung, breast milk, hair, and nails (ATSDR, 2012).

The general population may be exposed to hexavalent chromium compounds via inhalation of ambient air, ingestion of water or food, or dermal contact with chromium-containing products such as pressure-treated wood (NTP, 2011). Elevated exposures to hexavalent chromium may occur among individuals who live near industrial facilities that use hexavalent chromium or near sites where chromium compounds have been disposed (NTP, 2011). However, human exposure studies generally do not identify the specific forms of chromium (NTP, 2011). Children's exposure to chromium from ingestion of soil or from contact with playground equipment constructed with chromated copper arsenate (CCA)-treated wood is of potential concern (ATSDR, 2012; Hamula et al., 2006).

Monitoring data indicate that exposure to hexavalent chromium can occur through drinking water. In 341 drinking water samples taken across 41 states where the total chromium mean level was 1.9 µg/L, hexavalent chromium levels ranged from 0–52.6 µg/L (mean, 1.1 µg/L), with 57% of samples reporting non-detectable concentrations (Seidel et al., 2012; Frey et al., 2004). Data from the California Department of Public Health indicate that 87% of samples (n=27,507) in that state had concentrations of hexavalent chromium above the minimum reporting level (MRL) of 1 µg/L (Seidel et al., 2012). It may be noted that accurate speciation methods for measuring low levels of hexavalent chromium are very recent, accounting for the relative paucity of monitoring data for hexavalent chromium (Mcneill et al., 2012). EPA's Third Unregulated Contaminant Monitoring Rule (UCMR3) Program is working with states to test systems during 2012–2015 for the presence of total chromium and hexavalent chromium; results through January 2014 indicate that 76% of the samples have hexavalent chromium concentrations greater than a MRL of 0.03 µg/L and 90% of the public water systems had hexavalent chromium concentrations greater than 0.03 µg/L (U.S. EPA, 2014b). Hexavalent chromium in water distribution systems can also occur as a disinfection by-

product because of the efficient oxidation of trivalent chromium by chlorine and other agents such as ozone and permanganate used in disinfection and odor removal (Mcneill et al., 2012).

1.2. Scope of the Assessment

Significant new epidemiologic and experimental animal toxicity information for hexavalent chromium has become available since EPA's current IRIS assessment for hexavalent chromium was posted in 1998, including updates of earlier occupational cohort studies and a National Toxicology Program bioassay that reported increased incidences of tumors in rats and mice exposed to hexavalent chromium in drinking water (NTP, 2008). The NTP (2008) bioassay findings are significant because they provide the first direct laboratory evidence of carcinogenicity for ingested hexavalent chromium. Further, the dose-response information from both new epidemiologic and experimental animal studies could result in changes to current toxicity values. Given the widespread exposure to hexavalent chromium and the availability of new studies that provide significant new health effects information, the IRIS Program is developing an updated assessment of hexavalent chromium. This updated assessment will address multiple Agency needs. Several regulatory programs and activities that would benefit from a more current IRIS assessment of hexavalent chromium are presented below:

- Hexavalent chromium has been identified as a contaminant of concern at numerous contaminated waste sites, including more than a thousand National Priority List (NPL) sites. IRIS values are used to develop screening values at NPL sites and to set remediation targets for contaminated sites.
- In its 2008 Omnibus Appropriations Bill, Congress asked EPA to develop an updated health standard for ingested hexavalent chromium, and use this standard to revise the maximum contaminant level for drinking water as soon as possible. The EPA Administrator indicated her commitment to developing a health assessment and a potential regulation for hexavalent chromium in drinking water during her testimony before the Senate Environment and Public Works Committee in 2010. An updated IRIS assessment for hexavalent chromium will be directly responsive to Congressional language and to the Administrator's commitment to developing a health assessment for hexavalent chromium.
- Currently, the EPA drinking water standard of 0.1 milligrams per liter (mg/L) is for total chromium, which includes all forms of chromium including hexavalent chromium (Federal Register, 2010). This standard is based on a 1-year drinking water study of hexavalent chromium in rats (MacKenzie et al., 1958). The Safe Drinking Water Act requires EPA to periodically review the national primary drinking water regulation (NPDWR) for each contaminant and revise the regulation, if appropriate. Following its second six-year review announced in 2010, EPA noted that it would await the updated IRIS assessment for

hexavalent chromium in order to evaluate revising the NPDWR. The Agency anticipates completing the next review of the NPDWRs by 2016.

- Chromium compounds are also listed among the original hazardous air pollutants (sometimes referred to as air toxics) under the Clean Air Act. The health risks associated with air toxics, including chromium compounds, are assessed under the National-Scale Air Toxics Assessment (NATA), EPA's ongoing comprehensive evaluation of air toxics in the U.S. NATA provides estimates of cancer and noncancer health effects based on chronic inhalation exposure from outdoor sources, and is used to identify and prioritize air toxics, emission source type, and locations that are of greatest potential concern in terms of contributing to population risk. IRIS values are used in assessing population risks (U.S. EPA, 2005a).

Accordingly, this IRIS assessment will address the needs of EPA's program and regional offices by identifying the health hazards from exposure to hexavalent chromium via inhalation and ingestion and by deriving toxicity values for these health hazards. The updated IRIS assessment will not address potential health effects from dermal exposures because EPA's Office of Pesticide Programs (OPP) previously evaluated this exposure pathway in its reregistration eligibility decision (RED) for CCA pesticides (U.S. EPA, 2008c) and no priority needs related to dermal exposure have been identified by other EPA program and regional offices.

1.3. Problem Formulation

1.3.1. Assessments by Federal, State, and International Health Agencies

EPA's current IRIS assessment of hexavalent chromium was completed in 1998 (U.S. EPA, 1998). In order to identify studies and scientific issues that may impact an updated IRIS assessment of hexavalent chromium, EPA consulted the following assessments subsequently published by federal, state, or international health agencies, with an emphasis on more recent documents:

1. International Programme of Chemical Safety (IPCS). (2013). Inorganic chromium(VI) compounds. (78). Geneva, Switzerland: World Health Organization.
2. National Institute for Occupational Safety and Health (NIOSH). (2013). Occupational exposure to hexavalent chromium. (DHHS (NIOSH) Publication No. 2013–128). Department of Health and Human Services, Centers for Disease Control and Prevention.
3. Agency for Toxic Substances and Disease Registry (ATSDR). (2012). Toxicological profile for chromium. Atlanta, GA: US Department of Health and Human Services, Public Health Service.

4. International Agency for Research on Cancer (IARC). (2012). A review of human carcinogens: Arsenic, metals, fibres, and dusts [IARC Monographs Volume 100C]. Lyon, France.
5. California EPA (Cal/EPA). (2011). Public health goal for Hexavalent Chromium (Cr VI) in drinking water. Sacramento, CA: Pesticide and Environmental Toxicology Branch, Office of Environmental Health Hazard Assessment.
6. National Toxicology Program (NTP). (2011). Report on carcinogens: Twelfth edition (12th ed.). Research Triangle Park, NC.
7. New Jersey Department of Environmental Protection (NJ DEP). (2009). Derivation of ingestion-based soil remediation criterion for Cr+6 based on the NTP chronic bioassay data for Sodium Dichromate Dihydrate.
8. U.S. EPA. (2008a, b). Evaluation of the carcinogenic potential of inorganic hexavalent chromium (Cr(VI)). Washington, DC: Health Effects Division, Office of Pesticide Programs.
9. Food and Drug Administration (FDA). (2013). Beverages: Bottle water. Code of Federal Regulations: 21 CFR 165.110.
10. Occupational Safety and Health Administration (OSHA). (2006). Occupational exposure to hexavalent chromium. Final rule. Fed Reg 71: 10099-10385.
11. World Health Organization (WHO). (2003). Chromium in drinking water. (WHO/SDE/WSH/03.04/04). Geneva, Switzerland.
12. U.S. EPA . (2009). National primary drinking water regulation [EPA Report]. (EPA/816/F-09/004). Washington, DC.
13. The Netherlands National Institute for Public Health and the Environment (RIVM). (2001). Re-evaluation of human-toxicological maximum permissible risk levels (pp. 58-61). (RIVM report 711701 025). Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu RIVM.

1.3.2. Toxicokinetics of Hexavalent Chromium

IPCS (2013), ATSDR (2012), Cal/EPA (2011) and OSHA (2006) have reviewed the absorption and metabolism of hexavalent chromium. Briefly, chromium exists in multiple oxidation states, but it is the hexavalent and trivalent states that are most prevalent biologically. Following oral or inhalation exposure (and prior to systemic absorption), hexavalent chromium can be reduced to trivalent chromium within the gastrointestinal (GI) tract or the respiratory tract, respectively. If reduced to the trivalent state prior to uptake, chromium is poorly absorbed by cells. However, chromium in the hexavalent state can be readily absorbed by cells lining the GI or respiratory tract. Systemically absorbed hexavalent chromium is rapidly absorbed and reduced by cells in the body. The reverse of this process, oxidation of trivalent chromium to hexavalent chromium, will not occur in the body. As a result, systemically circulating chromium is believed to exist primarily in the trivalent state, particularly since red blood cells can efficiently reduce hexavalent chromium to trivalent chromium.

IPCS (2013) and ATSDR (2012) raised the issue of extrapolating data on hexavalent chromium toxicity, including tumor response, from orally exposed animals to humans in light of the toxicokinetic properties of hexavalent chromium. The National Toxicology Program (NTP) rodent bioassay reported tumors in the oral cavity in rats and the small intestine in mice, as well as GI tract effects other than cancer, following chronic drinking water exposure to hexavalent chromium. GI toxicokinetics following oral exposure influences the amount of ingested hexavalent chromium that is subsequently absorbed by GI mucosae, and therefore the potential for hexavalent chromium to induce GI toxicity. In particular, inter- and intraspecies differences in reductive capacities or in rates of reduction of ingested hexavalent chromium may exist that could impact the extrapolation of rodent bioassay data to humans and the identification of potential susceptible subpopulations.[2] The updated assessment is expected to take into consideration the available hexavalent chromium toxicokinetic data in the quantitative analysis of oral toxicity data.

1.3.3. Cancer – inhalation route

EPA's 1998 IRIS assessment classified hexavalent chromium as "Group A - known human carcinogen by the inhalation route of exposure" based on evidence of a causal relationship between inhalation of hexavalent chromium and increased incidence of lung cancer in humans. The same conclusion has been reached by other federal and state health agencies and international organizations (IPCS, 2013; NIOSH, 2013; IARC, 2012; Cal/EPA, 2011; NTP, 2011; OSHA, 2006), the most recent of which was published in 2013. Consistent with this international consensus, the new studies published since 1998 do not contain results that would change EPA's conclusion to characterize hexavalent chromium as a human carcinogen via the inhalation route. Therefore, this assessment will focus on the review of the evidence for lung cancer to identify studies that might improve the quantitative dose-response analysis for human lung cancer.

EPA's 1998 IRIS assessment included an inhalation unit risk for hexavalent chromium based on increased incidence of lung cancer in chromate workers as reported in an epidemiologic study by Mancuso (1997, 1975). Since that time, several other organizations have derived inhalation toxicity values for hexavalent chromium based on more recent epidemiologic studies:

- IPCS (2013) – linearly extrapolated lung cancer risk based on Gibb et al. (2000)

[2] Because of the importance of evaluating all existing information on this topic, EPA convened a public workshop webinar on this topic on September 19 and 25, 2013. A panel of scientists discussed the available studies of extracellular reduction, absorption, and transit in the GI tract for metals in general and hexavalent chromium in particular. Some of the panelists were experts on hexavalent chromium reduction and toxicity, and were able to provide valuable insight into toxicokinetic studies. Other panelists had expertise in GI tract physiology, GI toxicokinetic modeling, toxicology, and epidemiology. The aim of the workshop was not to have the panel reach consensus on any particular topic, but to foster discussion across the different areas of expertise and viewpoints so that both EPA and the public could become better informed of the issues. Workshop materials can be obtained at www.epa.gov/iris/irisworkshops/cr6.

- NIOSH (2013) – Recommended Exposure Limit (REL) based on lung cancer data from Gibb et al. (2000)
- Cal/EPA (2011) – slope factor based on lung cancer data from Gibb et al. (2000)
- OSHA (2006) – Permissible Exposure Level (PEL) based on lung cancer data from Gibb et al. (2000)

Furthermore, some of these assessments have discussed mechanistic studies investigating the role of hexavalent chromium mutagenicity and/or genotoxicity in the induction of lung tumors (IARC, 2012; NTP, 2011; OSHA, 2006). A mutagenic mode of action for chemical-induced carcinogenicity is considered relevant to all populations and lifestages. The current understanding of biology of cancer indicates that mutagenic chemicals are expected to exhibit a greater effect in early life exposure versus later life exposure (U.S. EPA, 2005b).

Due to the availability of new data and approaches that may substantially change EPA's 1998 inhalation toxicity value for carcinogenic effects, EPA plans to update the dose-response assessment for the carcinogenic effects of inhalation exposure to hexavalent chromium. This update is expected to include the following:

- A systematic review of epidemiologic studies for the purpose of identifying studies suitable for deriving point(s) of departure for hexavalent chromium-induced lung cancer.
- Analysis of available data on toxicity pathways/modes of action for lung cancer induced by hexavalent chromium inhalation for the purposes of:
  - Supporting the choice of linear and/or non-linear extrapolation from the point(s) of departure for this endpoint.
  - Identifying potentially susceptible subpopulations or lifestages.
  - Determining if a mutagenic mode of action is operative, and therefore whether to apply age-dependent adjustment factors (ADAFs) to account for early-life susceptibility to carcinogenic effects after inhalation of hexavalent chromium.
- Dose-response analyses to derive point(s) of departure and toxicity value(s) (inhalation unit risk and/or reference concentrations) for hexavalent chromium-induced lung cancer.

1.3.4. Cancer – oral route

EPA's 1998 IRIS assessment concluded that carcinogenicity of hexavalent chromium "by the oral route of exposure cannot be determined and is classified as Group D." A toxicity value was not derived for this endpoint. Subsequent reviews by EPA and state agencies have noted that experiments in rodents conducted by NTP (2008) reported increased incidences of cancers after oral administration (Cal/EPA, 2011; NTP, 2011; NJ DEP, 2009; U.S. EPA, 2008b). Several of these reviews present oral toxicity values for hexavalent chromium-induced cancer based on these rodent studies:

- Cal/EPA (2011) – oral slope factor based on incidences of adenomas and carcinomas in the small intestine of male mice (NTP, 2008)

- NJ DEP (2009) – oral slope factor based on incidences of adenomas and carcinomas in the small intestine of male mice (NTP, 2008)
- U.S. EPA (2008b) – oral slope factor based on incidences of adenomas and carcinomas in the small intestine of female mice (NTP, 2008)

Additionally, some of these assessments have discussed mechanistic studies investigating the role of hexavalent chromium mutagenicity and/or genotoxicity in inducing these cancers (IPCS, 2013; Cal/EPA, 2011; NJ DEP, 2009; U.S. EPA, 2008b). A mutagenic mode of action for chemical-induced carcinogenicity is considered relevant to all populations and lifestages. The current understanding of biology of cancer indicates that mutagenic chemicals are expected to exhibit a greater effect in early life exposure versus later life exposure (U.S. EPA, 2005b). Furthermore, as discussed above, information on inter- and intraspecies toxicokinetic differences, particularly with respect to reduction of hexavalent chromium to trivalent chromium in the GI tract, may be important to consider in assessing the human health hazard for cancer after ingestion of hexavalent chromium.

Due to the availability of new data that may substantially change EPA's 1998 conclusions regarding cancer classification and dose-response, EPA plans to update its hazard identification and dose-response assessment of hexavalent chromium carcinogenicity by ingestion. This update is expected to include the following:

- Systematic review of available studies for the purposes of:
  - Conducting a weight-of-evidence analysis for the carcinogenicity of ingested hexavalent chromium.
  - Identifying studies and endpoints suitable for dose-response analysis.
- Analysis of available toxicokinetic data to evaluate whether toxicologically-relevant inter- and/or intraspecies differences in toxicokinetics, particularly with respect to reduction of hexavalent chromium to trivalent chromium in the GI tract, can be estimated quantitatively.
- Analysis of available data on toxicity pathways/modes of action for cancers induced by hexavalent chromium ingestion for the purposes of:
  - Supporting conclusions as to the human relevance of cancers induced in rodents by ingested hexavalent chromium.
  - Supporting the choice of linear and/or non-linear extrapolation from the point(s) of departure for this endpoint, if there is a cancer hazard by ingestion.
  - Identifying potentially susceptible subpopulations or lifestages, if there is a cancer hazard by ingestion.
  - Determining if a mutagenic mode of action is operative, and therefore whether to apply ADAFs to account for early-life susceptibility to carcinogenic effects after ingestion of hexavalent chromium, if there is a cancer hazard by ingestion.
- Dose-response analyses to derive point(s) of departure and toxicity value(s) (oral slope factor and/or reference dose) for carcinogenic effects after ingestion of hexavalent chromium.

1.3.5. Noncancer effects

EPA's 1998 IRIS assessment derived a reference concentration (RfC) for noncancer effects based on nasal effects (from chromic acid mists and dissolved hexavalent chromium aerosols) in a subchronic epidemiologic study (Lindberg and Hedenstierna, 1983) and respiratory tract effects (from hexavalent chromium particulates) in subchronic rat studies (Malsch et al., 1994; Glaser et al., 1990). EPA's 1998 IRIS assessment also derived a reference dose (RfD) for noncancer effects based on a NOAEL reported in a 1-year drinking water study in rats (MacKenzie et al., 1958). Since that time, NTP (2008) has conducted a comprehensive toxicity bioassay of the effects of orally administered hexavalent chromium in rodents. Additionally, subsequent reviews by government health agencies and international health organizations have identified a number of potential targets of toxicity from inhalation or ingestion of hexavalent chromium, including:

- ***Respiratory effects.*** IPCS (2013), NIOSH (2013), ATSDR (2012) and OSHA (2006) all reported respiratory effects in workers via inhalation. These included chronic rhinorrhea, nasal itching and soreness, nasal mucosal atrophy, epistaxis, perforations and ulceration of the nasal septum, bronchitis, pneumonoconiosis, decreased pulmonary function, and pneumonia. Animal data on respiratory effects were reported by IPCS (2013) and ATSDR (2012), including nasal septum perforation, hyperplasia and metaplasia of the larynx, trachea, and bronchus, epithelial necrosis of the bronchiolar walls, hyperplasia and fibrosis, inflammation, impaired lung function and emphysema. In bronchoalveolar lavage (BAL) fluid, increased percentage of lymphocytes, increases in the levels of total protein, albumin, and activity of lactate dehydrogenase and β-glucuronidase were reported.
- ***Gastrointestinal effects.*** ATSDR (2012) reviewed reports of oral ulcer, diarrhea, abdominal pain, indigestion, and vomiting in people who consumed hexavalent chromium-contaminated well water. Gastrointestinal effects in rats and mice, reviewed by IPCS (2013), ATSDR (2012), and Cal/EPA (2011), included duodenal histiocytic infiltration, epithelial hyperplasia of the duodenum, and ulcer and epithelial hyperplasia and metaplasia of the glandular stomach.
- ***Hepatic effects.*** ATSDR (2012) reviewed liver toxicity observed in case reports of humans exposed to hexavalent chromium by ingestion. Liver damage was evidenced by the development of jaundice, increased bilirubin, and increased serum lactate dehydrogenase and liver enzymes. Hepatic effects in animals, as summarized by ATSDR (2012) and Cal/EPA (2011), included increased serum alanine aminotransferase (ALT) and sorbital dehydrogenase (SDH) activity and histopathological changes (including cellular histiocytic infiltration, chronic focal inflammation, cytoplasmic vacuolization, increased sinusoidal space, fatty changes, clear cell and eosinophilic foci, and necrosis).
- ***Hematological effects.*** IPCS (2013), ATSDR (2012), and Cal/EPA (2011) summarized hematological effects observed in animal studies, including microcytic, hypochromic

anemia, characterized by decreased mean cell volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit (Hct), and hemoglobin (Hgb).

- ***Immunological effects.*** IPCS (2013), NIOSH (2013), ATSDR (2012), and OSHA (2006) summarized data on asthma attacks in some sensitized workers, indicating immunological effects in humans. Additionally, functional and histopathological changes to the immune system in animals were reviewed by ATSDR (2012) and Cal/EPA (2011). These effects included stimulation of the humoral immune system and increased phagocytic activity of macrophages, increased proliferative responses of splenocytes, and histiocytic cellular infiltration of pancreatic lymph nodes.
- ***Reproductive effects.*** IPCS (2013), NIOSH (2013), and ATSDR (2012) summarized data on reproductive effects in workers, including increases in the number of morphologically abnormal sperm, decreases in sperm count and motility, and greater incidences of complications during pregnancy and childbirth (toxicosis and postnatal hemorrhage). Reproductive effects in monkeys, rats and rabbits, reviewed by ATSDR (2012) and Cal/EPA (2011), included decreased sperm count and motility and histopathological changes to the epididymis (ductal obstruction, development of microcanals, depletion of germ cells, hyperplasia of Leydig cells, and Sertoli cell fibrosis). Changes in sexual behavior in rats and mice were also reported.
- ***Developmental effects.*** ATSDR (2012) and Cal/EPA (2011) reviewed developmental effects observed in rats and mice. Exposure to hexavalent chromium premating and/or in utero or during lactation was associated with increased postimplantation loss, decreased number of live fetuses/litter, decreased fetal weight, internal and skeletal malformations, and delayed sexual maturation in offspring.

Additionally, several of these reviews derived chronic inhalation or oral toxicity values, some of which are based on studies more recent than EPA's 1998 IRIS assessment:

- IPCS (2013) and ATSDR (2012) – inhalation toxicity value based on nasal irritation from chromic acid/chromium trioxide (Lindberg and Hedenstierna, 1983)
- IPCS (2013) – inhalation toxicity value based on altered lactate dehydrogenase activity in BAL fluid from salts of hexavalent chromium (Glaser et al., 1990)
- IPCS (2013) and ATSDR (2012) – oral toxicity value based on diffuse epithelial hyperplasia in the duodenal mucosa of female mice (NTP, 2008)
- Cal/EPA (2011) – oral toxicity value based on mild chronic inflammation and fatty changes in the liver of female mice (NTP, 2008)
- RIVM (2001) – oral toxicity value based on noncarcinogenic effects (not specified) from MacKenzie et al. (1958) study.

Finally, as discussed above in the Section *Toxicokinetics of hexavalent chromium*, information on inter- and intraspecies toxicokinetic differences, particularly with respect to reduction of hexavalent chromium to trivalent chromium in the gastrointestinal tract, will be important to consider in assessing the noncancer toxicity of ingested hexavalent chromium.

Therefore, due to the availability of new data that may substantially change EPA's 1998 conclusions as to the noncancer toxicity of inhaled or ingested hexavalent chromium (including the RfC and RfD), EPA will be conducting an update of its hazard identification and dose-response assessment of hexavalent chromium noncancer toxicity. Because of the availability of multiple recently completed comprehensive reviews of the noncancer health effects of hexavalent chromium, the IRIS assessment will focus its hazard identification and dose-response assessment on the health effects identified above: respiratory, gastrointestinal, hepatic, hematological, immunological, reproductive, and developmental. These cover both the "primary health effects associated with exposure to hexavalent chromium" identified by ATSDR (2012) and the health effects that have been used as the basis of noncancer toxicity values. In sum, this update is expected to include the following:

- Systematic review of available studies for the purposes of:
  - Conducting a weight-of-evidence analysis for identifying the noncancer respiratory, gastrointestinal, immunological, hepatic, hematological, reproductive, and developmental hazards of inhaled or ingested hexavalent chromium.
  - Identifying studies and endpoints among these hazards suitable for dose-response analysis.
- Analysis of available toxicokinetic data to evaluate whether toxicologically-relevant inter- and/or intraspecies differences in toxicokinetics, particularly with respect to reduction of hexavalent chromium to trivalent chromium in the gastrointestinal tract, can be estimated quantitatively.
- Analysis of available data on toxicity pathways/modes of action for noncancer effects induced by hexavalent chromium inhalation or ingestion for the purposes of:
  - Supporting conclusions as to the human relevance of noncancer effects induced in rodents by inhaled or ingested hexavalent chromium.
  - Identifying potentially susceptible subpopulations or lifestages.
- Dose-response analyses to derive point(s) of departure and toxicity value(s) (RfCs and RfDs) for noncancer effects after inhalation or ingestion of hexavalent chromium. Evaluation of the feasibility of dose-response analysis of noncancer effects to support economic benefits analyses.

2. METHODS FOR IDENTIFYING AND SELECTING STUDIES

The NRC (2011) recommended that EPA develop a detailed search strategy utilizing a graphical display documenting how initial search findings are narrowed to the final studies that are selected for further evaluation on the basis of defined inclusion and exclusion criteria. Following these recommendations, a literature search and screening strategy were used to identify literature characterizing the health effects of hexavalent chromium. This strategy consisted of a search of online scientific databases and other sources, casting a wide net in order to identify all potentially pertinent studies. In subsequent steps, references were screened to exclude papers not pertinent to an assessment of the health effects of hexavalent chromium, and remaining references were sorted into categories for further evaluation. Section 2.1 describes the literature search and screening strategy in detail.

The NRC (2011) further recommended that after studies are identified for review by utilizing a transparent search strategy, the next step is to summarize the details and findings of the most pertinent studies in evidence tables. The NRC suggested that such tables should provide a link to the references, and include details of the study population, methods, and key findings. This approach provides for a systematic and concise presentation of the evidence. The NRC also recommended that the methods and findings should then be evaluated with a standardized approach. The approach that was outlined identified standard issues for the evaluation of epidemiological and experimental animal studies. Section 2.2 describes the approach taken for hexavalent chromium for selecting studies to be included in preliminary evidence tables and exposure-response arrays. Section 3 presents the selected studies in preliminary evidence tables and exposure-response arrays, arranged by health effect.

2.1. Draft Literature Search and Screening Strategy

The literature search for hexavalent chromium was conducted in four online scientific databases, including PubMed, Toxline, Web of Science, and TSCATS, in January 2013; the search was repeated in July 2013 and in January 2014. The detailed search approach, including the search strings and number of citations identified per database, is presented in Table 2-1. This search of online databases identified 9,721 citations (after electronically eliminating duplicates). The computerized database searches were also supplemented by a manual search of citations from other regulatory documents (Table 2-2); 99 citations were obtained using these additional search strategies. In total, 9,820 citations were identified using online scientific databases and additional search strategies.

These citations were screened using the title, abstract, and in limited instances, full text for pertinence to examining the health effects of hexavalent chromium exposure. The process for screening the literature is described below and is shown graphically in Figure 2-1.

- 168 references were identified as potential sources of chronic health effects data and were considered for data extraction into evidence tables and exposure-response arrays.
- 1,773 studies were identified as supporting studies; these included 127 studies describing physiologically-based pharmacokinetic (PBPK) models and other toxicokinetic information, 805 studies providing genotoxicity and other mechanistic information, 733 dermal, acute, short-term, injection, and intratracheal instillation exposure studies, and 108 human case reports. While still considered sources of health effects information, studies investigating dermal, acute, short-term, injection, and intratracheal instillation exposures and case reports are generally less pertinent for characterizing health hazards associated with chronic oral and inhalation exposure. Therefore, information from these studies was not considered for extraction into the preliminary evidence tables. Nevertheless, these studies will still be evaluated as possible sources of supporting health effects information.
- 466 references were identified as secondary sources of health effects information (e.g., reviews and other agency assessments); these references were kept as additional resources for development of the Toxicological Review.
- 786 references were kept for further review. This category includes references that did not provide enough material to evaluate pertinence (e.g., abstract not available) and foreign language studies.
- 6,627 references were identified as not being pertinent to an evaluation of the health effects of hexavalent chromium and were excluded from further consideration (see Figure 2-1 for exclusion categories).

The literature will be regularly monitored for the publication of new studies and a formal updated literature search and screen will be conducted after the IRIS bimonthly public meeting discussing these preliminary materials. The documentation and results for the literature search and screen can be found on the Health and Environmental Research Online (HERO) website (http://hero.epa.gov/index.cfm?action=landing.main&project_id=2233).[3]

[3] HERO (Health and Environmental Research On-line) is a database of scientific studies and other references used to develop EPA's risk assessments aimed at understanding the health and environmental effects of pollutants and chemicals. It is developed and managed in EPA's Office of Research and Development (ORD) by the National Center for Environmental Assessment (NCEA). The database includes more than 300,000 scientific articles from the peer-reviewed literature. New studies are added continuously to HERO.

Note: The HERO database will be regularly updated as additional references are identified during assessment development. Therefore, the numbers of references (by tag) displayed on the HERO webpage for hexavalent chromium may not match the numbers of references identified in Figure 3-1 (current through April 2014).

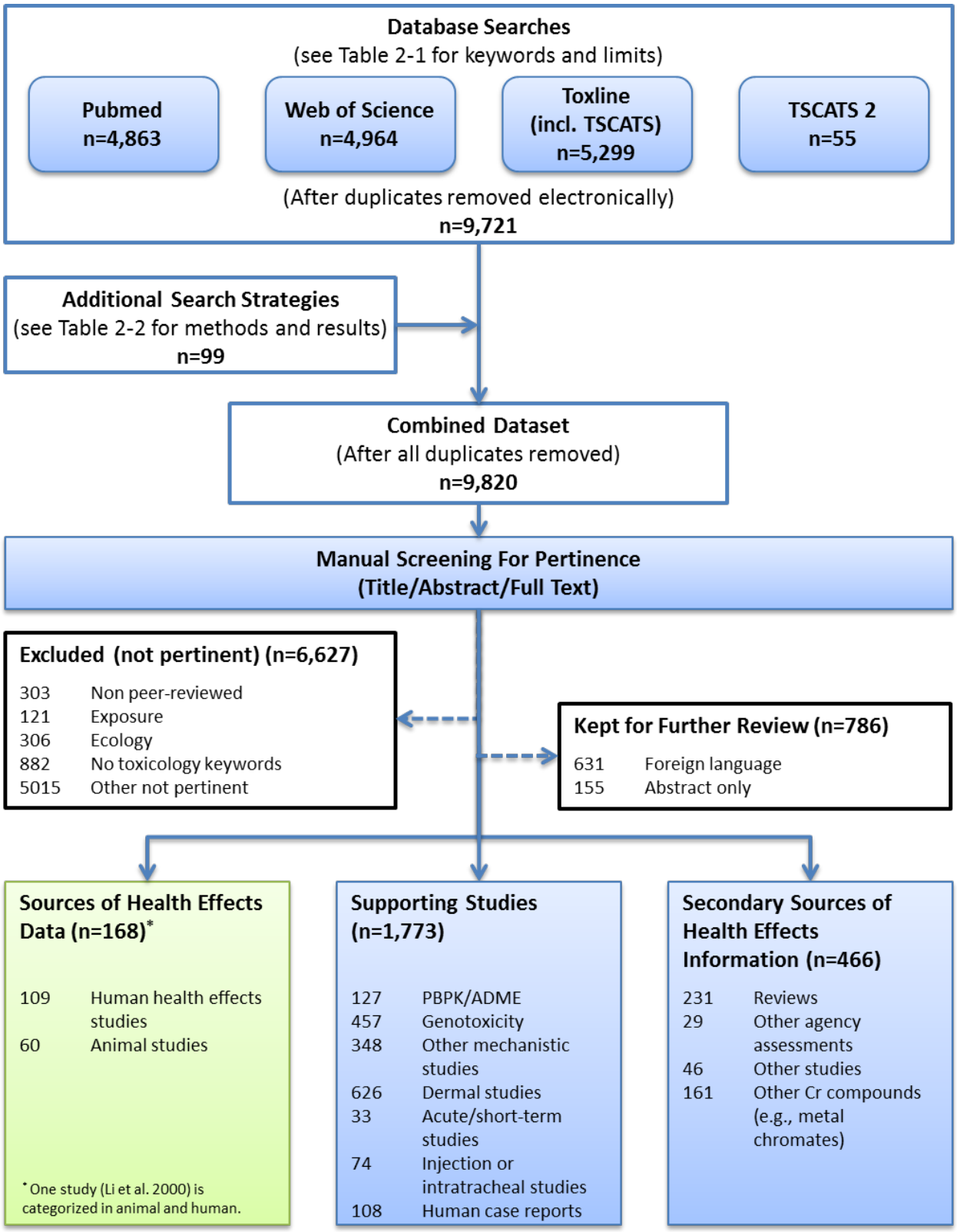

Figure 2-1. Literature search approach for hexavalent chromium.

1 **Table 2-1. Database search strategy for hexavalent chromium**

Database (Search Date)	Keywords	Limits
PubMed (1/29/2013) (7/19/2013) (2/5/2014)	*hexavalent chromium OR (hexavalent AND chromium) OR CRVI OR CR VI OR Chromium VI OR "Chromic acid" OR "Calcium chromate" OR "Potassium dichromate" OR "Potassium chromate" OR "Sodium chromate" OR "lead chromate" OR "zinc chromate" OR "strontium chromate" OR "ammonium dichromate" OR 13765-19-0[RN] OR 1333-82-0[RN] OR 7789-00-6[RN] OR 7778-50-9[RN] OR 7775-11-3[RN] OR 7789-12-0[RN] OR 13530-65-9[RN] OR 7738-94-5[rn] OR 18540-29-9[rn] OR 7758-97-6[RN] OR 11119-70-3[rn] OR 11103-86-9[rn] OR 13530-65-9[rn] OR 7788-98-9[rn] OR 77898-09-5[rn] OR 7789-06-2[rn]*	None
Web of Science (1/29/2013) (7/19/2013) (2/5/2014)	Topic = *(hexavalent chromium OR (hexavalent AND chromium) Chromium VI OR CrVI OR Cr VI OR "Chromic acid" OR "Calcium chromate" OR "Chromic trioxide" OR "Potassium dichromate" OR "Potassium chromate" OR "Sodium chromate" OR "Sodium dichromate dehydrate" OR "lead chromate" OR "zinc chromate" OR "strontium chromate" OR "ammonium dichromate" OR "ammonium chromate" OR 13765-19-0 OR 1333-82-0 OR 7789-00-6 OR 7778-50-9 OR 7775-11-3 OR 7789-12-0 OR 13530-65-9 OR 7738-94-5 OR 18540-29-9 OR 7758-97-6 OR 11119-70-3 OR 11103-86-9 OR 13530-65-9 OR 7788-98-9 OR 77898-09-5 OR 7789-06-2)*	Refined by: Research Areas = Toxicology, Biochemistry molecular biology, Public environmental occupational health, Dermatology, Cell biology, Oncology, Life sciences biomedicine other topics, Allergy, Veterinary sciences, Developmental biology, Immunology, Reproductive biology, Pathology, Physiology, Urology nephrology, Hematology, Neurosciences neurology, Respiratory system, Cardiovascular system cardiology, Obstetrics gynecology, Infections diseases, Gastroenterology hepatology, Microscopy
Web of Science[a] (1/29/2013) (7/19/2013) (2/5/2014)	Topic = *(hexavalent chromium OR (hexavalent AND chromium) Chromium VI OR CrVI OR Cr VI OR "Chromic acid" OR "Calcium chromate" OR "Chromic trioxide" OR "Potassium dichromate" OR "Potassium chromate" OR "Sodium chromate" OR "Sodium dichromate dehydrate" OR "lead chromate" OR "zinc chromate" OR "strontium chromate" OR "ammonium dichromate" OR "ammonium chromate" OR 13765-19-0 OR 1333-82-0 OR 7789-00-6 OR 7778-50-9 OR 7775-11-3 OR 7789-12-0 OR 13530-65-9 OR 7738-94-5 OR 18540-29-9 OR 7758-97-6 OR 11119-70-3 OR 11103-86-9 OR 13530-65-9 OR 7788-98-9 OR 77898-09-5 OR 7789-06-2)* AND cancer* OR carcinogen* OR chronic OR	Refined by: Research Areas = Chemistry, Environmental sciences ecology, Spectroscopy, Pharmacology pharmacy, Water resources, Genetics heredity, Science technology other topics, Biophysics, Food sciences technology, Endocrinology metabolism, Research experimental medicine, Nutrition dietetics, Zoology, General internal medicine, Construction building technology, Parasitology, Medical laboratory technology, Education educational research, Otorhinolaryngology, Rheumatology, Anatomy morphology, Emergency medicine, Mycology, Sport sciences, Psychiatry

Database (Search Date)	Keywords	Limits
	subchronic OR genotox* OR inhalation absorption OR oral absorption OR mice OR mouse OR Mutagenicity OR pharmacokinetic OR rat OR rats OR (toxic* NOT (fish OR bacteria* OR microorganism* OR plant*) OR tumor*	
Toxline (includes TSCATS) (1/29/2013) (7/19/2013) (2/5/2014)	18540-29-9 OR 7789-09-5 OR 13765-19-0 OR 1333-82-0 OR 7758-97-6 OR 7789-00-6 OR 7778-50-9 OR 7775-11-3 OR 7789-12-0 OR 7789-06-2 OR 13530-65-9 OR 7788-98-9 OR 7738-94-5 OR 13530-68-2	Not PubMed; synonyms included
TSCATS2 (1/29/2013) (7/19/2013) (2/5/2014)	18540-29-9	None

[a] For Web of Science, results were obtained by searching the research areas noted in the "Limits" column using the italicized terms in the "Keywords" column (starting with "Topic = *(hexavalent chromium…)*"), and subsequent filtering in EndNote using the additional keywords in normal text (starting with "cancer* OR …").

Table 2-2. Summary of additional search strategies for hexavalent chromium

Approach used	Source(s)	Date performed	Number of additional citations identified
Manual search of citations from reviews conducted by other international and federal agencies	ATSDR (2012). Toxicological profile for chromium. Atlanta, GA: US Department of Health and Human Services, Public Health Service.	1/2013	40
	U.S. EPA (2010). Toxicological review of hexavalent chromium (external review draft). (EPA/635/R-10/004A). Washington, DC.	1/2013	59

2.2. Selection of Critical Studies in Early Stages of Draft Development

2.2.1. General Approach

In response to the NRC recommendations, each study retained after the literature search and screen is evaluated for aspects of its design or conduct that could affect the interpretation of results and the overall contribution to the synthesis of evidence for determination of hazard potential. Much of the key information for conducting this evaluation can generally be found in the study's methods section and in how the study results are reported. Importantly, the evaluation at this stage does not consider study results, or more specifically, the direction or magnitude of any reported effects. For example, standard issues for evaluation of experimental animal data identified by the NRC and adopted in this approach include consideration of the species and sex of animals studied, dosing information (dose spacing, dose duration, and route of exposure), endpoints considered, and the relevance of the endpoints to the human endpoints of concern.

To facilitate the evaluation outlined above, evidence tables are constructed that systematically summarize the important information from each study in a standardized tabular format as recommended by the NRC (2011). In general, the evidence tables may include all studies that inform the overall synthesis of evidence for hazard potential. At this early stage of study evaluation the goal is to be inclusive. Exclusion of studies may unnecessarily narrow subsequent analyses by eliminating information that might later prove useful. Premature exclusion might also give a false sense of the consistency of results across the database of studies by unknowingly reducing the diversity of study results. However, there may be situations in which the initial review of the available data will lead to a decision to focus on a particular set of health effects and to exclude others from further evaluation. This situation could occur, for example, with a chemical with a large database that has a few well-developed areas of research, but many other areas that consist of sparse data, offering a very limited basis for drawing conclusions regarding hazard. In

this case, EPA will focus on the more developed areas of research for hazard identification. For hexavalent chromium, the identification of the health effects to be focused on was discussed in Problem Formulation, and the results of any exclusions are described below in Section 2.2.2.

Additionally, a study can be excluded at this stage if flaws in its design, conduct, or reporting are so great that the results would not be considered credible. Such study design flaws are discussed in a number of EPA's guidelines (see http://www.epa.gov/iris/backgrd.html) or summarized in the draft Preamble to the IRIS Toxicological Review ("Preamble")[4]. Examples of these flaws include studies where impurities in the test chemical are so great as to prohibit attribution of the results to the chemical, or studies where concurrent or essential historical control information is lacking. Studies with fundamental flaws in their design, conduct, or reporting are not included in evidence tables. Such exclusions in the case of experimental animal studies of hexavalent chromium are also described below in the Section 2.2.2.

The size of the database can influence both the type and number of evaluation criteria that are applied at this early stage. For example, if there are few studies on a health effect, additional evaluation criteria might not be needed, and thus the evidence tables may include all studies without severe flaws. Especially with smaller databases, it is important to consider all studies and not exclude studies unnecessarily. On the other hand, for larger databases, such as that for hexavalent chromium, additional criteria could facilitate a more efficient review of the database and help to focus on the more informative studies indicating the potential for hazard. These criteria could be specific to each type of study or a particular endpoint, and may consider factors such as those discussed in EPA's guidelines or summarized in the draft Preamble. Application of such additional criteria could result in initially setting aside some studies and not summarizing them in the evidence tables, although they would still be evaluated as possible sources of supporting health effects information during assessment development. Application of such criteria in the case of experimental animal studies of hexavalent chromium are also described below in Section 2.2.2.

2.2.2. Selection of Critical Experimental Animal Studies for Evidence Tables for Hexavalent Chromium

After the literature search was manually screened for pertinence (Figure 2-1; Sources of Chronic Health Effects Data), sixty experimental animal studies were identified as sources of health effects data and considered for data extraction to evidence tables and exposure-response arrays. From these studies, exclusions were first made if they exclusively examined health effects not identified in Problem Formulation. Next, studies were excluded if any fundamental flaws were identified in their design or conduct. The remaining studies are all sources of health effects data that may be used in the assessment. However, additional criteria were then applied to focus the

[4] See the draft Preamble in the Toxicological Review of Ammonia (revised external review draft) at http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=254524 or the Toxicological Review of Trimethylbenzenes (revised external review draft) at http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=254525.

evidence tables on the more methodologically robust studies. The studies summarized in evidence tables are considered the "critical" studies from which the study methods and results are presented in preliminary evidence tables and exposure-response arrays.

Exclusions based on results of problem formulation

As discussed in the Problem Formulation for hexavalent chromium, the hazard identification in the IRIS assessment will focus on the following health effects: respiratory, gastrointestinal, liver, immunological, hematological, reproductive, developmental, and cancer. These represent the health effects for hexavalent chromium with well-developed areas of research. A screen of the literature published after publication of the ATSDR (2012) Toxicological Profile and other recent reviews did not identify other health effect categories that should be added to those already identified. Focus on these health effects resulted in the exclusion of one study, Vyskocil et al. (1993), from the evidence tables because the study presented an evaluation of kidney endpoints only.

Exclusions due to fundamental flaws in their design or conduct

All experimental animal studies that were sources of chronic health effects data were evaluated for potential flaws in their design, reporting, or conduct. As a result, nine studies were removed from further consideration in the assessment. The specific studies and basis for exclusion are summarized in Table 2-3.

Table 2-3. Animal studies with fundamental flaws not considered further in the assessment

Rationale for exclusion	References and specific issue(s) identified
Issues with animal husbandry.	Borneff et al. (1968) The animal colony was compromised by mousepox infection, and widespread cannibalism occurred in all dose groups.
Non-reproducible animal populations used.	Anwar et al. (1961) Dogs of multiple breeds from an unspecified source. Aruldhas et al. (2006); Aruldhas et al. (2005); Aruldhas et al. (2004); Subramanian et al. (2006) Monkeys captured by local government for creating a public nuisance.
Compromised by data record-keeping anomalies.	Junaid et al. (1996a); Kanojia et al. (1996); Samuel et al. (2011) See discussion in text.

EPA determined that two of the studies listed in Table 2-3 contained datasets that were essentially identical, despite being published as separate studies of potassium dichromate in different rodent species. The studies are:

- Kanojia, RK; Junaid, M; Murthy, RC. (1996). Chromium induced teratogenicity in female rat. Toxicology letters 89: 207-213.
- Junaid, M; Murthy, RC; Saxena, DK. (1996a). Embryo- and fetotoxicity of chromium in pregestationally exposed mice. Bulletin of environmental contamination and toxicology 57: 327-334.

Incidence data for rats in Table 2 from Kanojia et al. (1996) and for mice in Table 2 from Junaid et al. (1996a) are identical for all entries (with the exception of the exposure group categories). In addition, chromium tissue concentration data for rats in Table 3 from Kanojia et al. (1996) and for mice in Table 3 from Junaid et al. (1996a) have identical means and standard deviations for all but one entry. Otherwise, the only differences between these tables from the two studies are the exposure group categories and the number of significant figures. EPA considered the similarity in the two data sets from two separate experiments in different species to be highly improbable. Related studies by the same investigators published after the two studies at issue do not contain an erratum for the data [Junaid et al. (1996b); Murthy et al. (1996); Kanojia et al. (1998)]. Requests were sent to the corresponding authors seeking clarification of the study findings, but no additional information has been received. Additionally, a search for any correspondence regarding data correction did not identify any relevant information. Finally, the journal editors were contacted, but no errata or retractions have yet been issued. Until questions regarding these studies are resolved, data from Kanojia et al. (1996) and Junaid et al. (1996a) will be excluded from further consideration.

In addition, an internal review found that data from Samuel et al. (2011) were identical to data reported in Banu et al. (2008) despite being identified as separate and independent studies. Hormone data from Table 3 of Samuel et al. (2011) appears to have been copied directly from Table 2 of Banu et al. (2008), calling into question whether the exposure and control groups were performed concurrently in the experiments described in Samuel et al. (2011). Data from Banu et al. (2008) currently remain in the tables.

Additional criteria applied to identify more methodologically robust studies

The remaining fifty references include studies designed to examine repeat-dose oral and inhalation toxicity and specialized studies of reproductive and developmental toxicity and immunotoxicity, representing a relatively large database of experimental animal literature. Given the size of the database, additional criteria were applied to focus on the more methodologically robust studies of hexavalent chromium hazard.

An initial screen was conducted to identify studies with limitations in study design, conduct, or reporting that would reduce the informativeness of the study. Specific issues were identified, as described in Table 2-4. All experimental animal studies that were categorized as sources of chronic health effects data were evaluated with respect to these methodological issues; these issues were not identified in any of the studies that were ultimately included in the evidence tables. Twelve

studies were identified as being less informative for characterizing the health effects of hexavalent chromium because of study design and reporting issues, and were not included in the evidence tables. The specific studies and basis for exclusion are summarized in Table 2-4. While not included in evidence tables, these studies will nevertheless be evaluated as possible sources of supporting health effects information during assessment development.

The remaining thirty-eight studies are considered the critical experimental animal studies for hazard identification. Data from these studies have been extracted and presented in evidence tables (Section 3). One of these studies, Stout et al. (2009), contains analyses of data presented originally in NTP (2008), so these have been listed in the tables together.

Table 2-4. Animal studies considered less informative, not included in evidence tables but retained as potential supporting information

Rationale for exclusion	References
Measurements of water consumption and/or body weight were not provided for animals exposed via drinking water (*ad libitum*) at high chromium concentrations (≥30 mg hexavalent chromium/L) known to impact palatability of the drinking water and reduce water consumption (NTP, 2008, 2007). Reported water consumption and body weight data are needed to estimate dose.	Asmatullah and Noreen (1999); Al-Hamood et al. (1998); Bataineh et al. (1997); Elbetieha and Al-Hamood (1997); Trivedi et al. (1989)
Incomplete reporting of study results and lack of water consumption measurements following drinking water exposures.	Schroeder and Mitchener (1971);MacKenzie et al. (1958)
Test animals were exposed to mixtures including or containing hexavalent chromium in the absence of a hexavalent chromium-only exposure group.	Zeidler-Erdely et al. (2013); Davidson et al. (2004)
Dose could not be estimated with confidence because of ambiguous reporting in study methods.	Zabulyte et al. (2009); Zabulyte et al. (2006)
Full study could not be obtained.	Behari et al. (1978)

2.2.3. Preliminary Evidence Tables and Exposure-Response Arrays

The evidence tables present data from studies related to a specific outcome or endpoint of toxicity. At a minimum, the evidence tables include the relevant information for comparing key study characteristics such as study design, exposure metrics, and dose-response information. Evidence tables will serve as an additional method for presenting and evaluating the suitability of the data to inform hazard identification for hexavalent chromium during the analysis of hazard potential and utility of the data for dose-response evaluation. The information in the preliminary evidence tables is also displayed graphically in preliminary exposure-response arrays. In these arrays, a significant effect (indicated by a filled circle) is based on statistical significance. The complete list of references considered in preparation of these materials can be found on the HERO website at http://hero.epa.gov/index.cfm?action=landing.main&project_id=2233.

2.2.4. Study Characteristics That Will Be Considered in the Evaluation and Synthesis of the Critical Studies for Hexavalent Chromium

Beyond the initial methodological screening described above in Sections 2.2.1 and 2.2.2, methodological aspects of a study's design, conduct, and reporting will be considered again in the overall evaluation and synthesis of the pertinent data that will be developed for each health effect. Some general questions that will be considered in evaluating experimental animal studies are presented in Table 2-5. These questions are, for the most part, broadly applicable to all experimental studies.

Table 2-5. Questions and relevant experimental information for evaluation of experimental animal studies

Methodological feature	Question(s) considered	Examples of relevant information extracted
Test animal	Based on the endpoint(s) in question, are concerns raised regarding the suitability of the species, strain, or sex of the test animals on study?	Test animal species, strain, sex
Experimental setup	Are the timing, frequency and duration of exposure, as well as animal age and experimental group allocation procedures/ group size for each endpoint evaluation, appropriate for the assessed endpoint(s)?	Age/lifestage of test animals at exposure and all endpoint testing timepoints Timing and periodicity of exposure and endpoint evaluations; duration of exposure Experimental group allocation procedures and sample size for each experimental group (e.g., animals; litters; dams) at each endpoint evaluation
Exposure	Are the exposure conditions and controls informative and reliable for the endpoint(s) in question, and are they sufficiently specific to the compound of interest?	Test article composition, stability, and vehicle control Exposure administration techniques (e.g., route; chamber type) and related controls
Endpoint evaluation procedures	Do the procedures used to evaluate the endpoint(s) in question conform to established protocols, or are they biologically sound? Are they sensitive for examination of the outcome(s) of interest?	Specific methods for assessing the effect(s) of exposure, including related details (e.g., biological matrix or specific region of tissue/organ evaluated) Endpoint evaluation controls, including those put in place to minimize evaluator bias
Outcomes and data reporting	Were data reported for all pre-specified endpoint(s) and study groups, or were any data excluded from presentation/ analyses?	Data presentation for endpoint(s) of interest

Note: "Outcome" refers to findings from an evaluation (e.g., steatosis), whereas "endpoint" refers to the evaluation itself (e.g., liver histopathology).

Evaluation of some specific methodological features identified in Table 2-5, such as exposure, is likely to be relatively independent of outcome. Other methodological features, in particular those related to experimental setup and endpoint evaluation procedures, are generally outcome specific (e.g., reproductive and developmental toxicity). In general, experimental animal studies will be compared against traditional assay formats (e.g., those used in guideline studies), with deviations from the protocol evaluated in light of how the deviations could alter interpretation of the outcome in question. A full evaluation of all critical studies will be performed as part of the critical review and synthesis of evidence for hazard identification for each of the health endpoints identified in the evidence tables presented in Section 3.

3. PRELIMINARY EVIDENCE TABLES AND EXPOSURE-RESPONSE ARRAYS

3.1. Data Extraction for Animal Studies: Preparation of Preliminary Evidence Tables and Exposure-Response Arrays

For each critical study selected, key information on the study design, including characteristics that inform study quality, and study results pertinent to evaluating the health effects from chronic oral and inhalation exposure to hexavalent chromium are summarized in preliminary evidence tables. Most results are presented as the percent change from the control group; an asterisk (*) indicates a result that has been calculated and reported by study authors to be statistically significant compared to controls (p<0.05).

The information in the preliminary evidence tables is also displayed graphically in preliminary exposure-response arrays. In these arrays, a significant effect (indicated by a filled circle) is based on statistical significance. The complete list of references considered in preparation of these materials can be found on the HERO website at http://hero.epa.gov/index.cfm?action=landing.main&project_id=2233.

3.2. Respiratory System Effects

Table 3-1. Evidence pertaining to respiratory system effects following inhalation exposure to hexavalent chromium

Reference and study design	Results
Lung Weight	
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 30 d, 90 d, or 90 d with 30 d recovery Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Percent change from control by exposure group for relative lung weight: mg/m^3 | 30 d | 90 d | 90 d with 30 d recovery 0 | -- | -- | -- 0.05 | 16.3* | 9.1 | 4.7 0.10 | 25.6* | 13.6* | 11.6* 0.20 | 27.9* | 25.0* | 23.3* 0.40 | 41.9* | 47.7* | 23.3*
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.050, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Percent change from control by exposure group: Group | Relative weight Control (0 mg/m^3) | -- Cr_5O_{12} (0.1 mg/m^3) | 26.1* $Na_2Cr_2O_7$ (0.025 mg/m^3) | No data provided $Na_2Cr_2O_7$ (0.050 mg/m^3) | No data provided $Na_2Cr_2O_7$ (0.1 mg/m^3) | 15.2 Organ weights for lung at low and mid $Na_2Cr_2O_7$ exposure groups were measured but results not reported by authors due to lack of statistical significance.
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 28 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Authors state that lung weights were statistically significantly increased above 0.025 mg/m^3 Cr VI but data were not provided.

Reference and study design	Results
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group: mg/m^3 — Relative weight 0 — -- 0.025 — -2.9 0.050 — 8.8* 0.100 — 11.8* 0.200 — 35.3*
Johansson et al. (1986a) Rabbit, Male (8/group) 0, 0.9 mg Cr VI/m^3 as Na_2CrO_4 aerosol exposure (dynamic whole-body chamber) 6 hr/d, 5 d/wk 4-6 wk Generation method (ultrasonic nebulizer), analytical method (gravimetric filter collection; atomic absorption spectrometry and modified diphenylcarbazine method), analytical concentration, and MMAD reported.	No statistically significant changes in the weight of the lower left lobe (2.4 ± 0.2 g in controls and 2.2 ± 0.2 g in treated) were reported.
Histopathology	
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 30 d Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Incidence (percent) by exposure group: mg/m^3 — Bronchioalveolar hyperplasia — Histiocytosis — Fibrosis 0 — 1/10 (10) — 1/10 (10) — 0/10 (0) 0.05 — 7/10 (70) — 5/10 (50) — 0/10 (0) 0.10 — 10/10 (100) — 8/10 (80) — 4/10 (40) 0.20 — 9/10 (90) — 5/10 (50) — 1/10 (10) 0.40 — 9/10 (90) — 3/10 (30) — 3/10 (30) Statistical significance was not assessed by study authors.
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Incidence (percent) by exposure group: mg/m^3 — Bronchioalveolar Hyperplasia — Histiocytosis — Fibrosis 0 — 0/10 (0) — 2/10 (20) — 0/10 (0) 0.05 — 3/10 (30) — 9/10 (90) — 1/10 (10) 0.10 — 2/10 (20) — 10/10 (100) — 0/10 (0) 0.20 — 3/10 (30) — 9/10 (90) — 0/10 (0) 0.40 — 7/10 (70) — 10/10 (100) — 0/10 (0) Statistical significance was not assessed by study authors.

Reference and study design	Results
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d exposure with 30 d recovery Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Incidence (percent) by exposure group: mg/m^3 | Bronchioalveolar hyperplasia | Histiocytosis | Fibrosis 0 | 0/10 (0) | 1/10 (10) | 0/10 (0) 0.05 | 1/10 (10) | 6/10 (60) | 0/10 (0) 0.10 | 0/10 (0) | 5/10 (50) | 0/10 (0) 0.20 | 7/10 (70) | 8/10 (50) | 0/10 (0) 0.40 | 3/10 (30) | 10/10 (100) | 0/10 (0) Statistical significance was not assessed by study authors.
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	No treatment-related changes in lung histopathology.
Johansson et al. (1986a) Rabbit, Male (8 /group) 0, 0.9 mg Cr VI/m^3 as Na_2CrO_4 aerosol exposure (dynamic whole-body chamber) 6 hr/d, 5 d/wk 4-6 wk Generation method (ultrasonic nebulizer), analytical method (gravimetric filter collection; atomic absorption spectrometry and modified diphenylcarbazine method), analytical concentration, and MMAD reported.	Qualitative histopathology results indicate that no increases in phospholipid accumulation or interstitial inflammation in lung tissue were observed. In Type II cells, no nodular proliferation, increased volume density, size, or number were observed. However, nodular accumulation of alveolar macrophages was observed in three of eight exposed rabbits.
Other Respiratory Histopathology	
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	There were weak accumulations of pigment-loaded macrophages in alveolar region of 8 rat lungs in the lowest $Na_2Cr_2O_7$ exposure group (0.025 mg/m^3) and moderate accumulations in the alveolar and peribronchial regions of all evaluated rats of the other chromium exposed groups, compared to no accumulation in the controls. Accumulations of eosinophilic substance inside the alveolar lumens were seen in 3 out of 18 rats in the Cr_5O_{12}-exposed group (0.063 mg Cr VI/m^3). Focal thickened septa in the lungs of 3 rats, combined with interstitial fibrosis in 2 cases, were also observed in the Cr_5O_{12}-exposed group. Focal bronchioalveolar hyperplasia was observed in one rat from each group (unclear whether this includes control or just dosed groups). No hyperplastic changes or tumors were observed in the nasal cavities of the rats.

Reference and study design	Results			
Lung: BAL Fluid				
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 28 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group:			
	mg/m^3	Macrophages	Polynuclear macrophages	Macrophages in telophase
	0	--	--	--
	0.025	9.4	57.1*	90.9*
	0.050	3.1	28.6	118.2*
	mg/m^3	Macrophage diameter	Lymphocytes	Granulocytes
	0	--	--	--
	0.025	-0.9	100.0*	14.3
	0.050	6.1	185.7*	42.9*
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group:			
	mg/m^3	Macrophages	Polynuclear macrophages	Macrophages in telophase
	0	--	--	--
	0.025	-6.3	70.0	142.9*
	0.050	-15.6*	170.0*	335.7*
	0.200	-37.5*	180.0*	114.3*
	mg/m^3	Macrophage diameter	Lymphocytes	Granulocytes
	0	--	--	--
	0.025	9.0*	36.4*	36.4
	0.050	21.3*	118.2*	145.5*
	0.200	27.9*	27.3	-54.5*

Reference and study design	Results
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 30 d Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Percent change from control by exposure group: mg/m^3 / Total Protein / Albumin / Lactate dehydrogenase 0 / -- / -- / -- 0.05 / 43.1* / 82.9* / 14.3 0.10 / 79.2* / 118.3* / 25.0* 0.20 / 116.7* / 184.1* / 75.0* 0.40 / 181.0* / 229.3* / 125.0* mg/m^3 / Total macrophages / Dividing macrophages / Cell viability 0 / -- / -- / -- 0.05 / 0.0 / 58.3 / 1.1 0.10 / 7.7 / 116.7* / 1.1 0.20 / 53.8* / 125.0* / 3.4 0.40 / 76.9* / 66.7 / 4.5*
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Percent change from control by exposure group: mg/m^3 / Total protein / Albumin / Lactate dehydrogenase 0 / -- / -- / -- 0.05 / 75.2* / 49.4* / 17.2* 0.10 / 44.2* / 11.7 / 6.9 0.20 / 211.1* / 51.9* / 117.2* 0.40 / 331.4* / 139.0* / 186.2* mg/m^3 / Total macrophages / Dividing macrophages / Cell viability 0 / -- / -- / -- 0.05 / -25.0* / 216.7* / 2.2 0.10 / -18.8 / 333.3* / 4.5 0.20 / 43.7* / 283.3* / 4.5 0.40 / 106.2* / 233.3* / 3.4

Reference and study design	Results
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d exposure with 30 d recovery Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Percent change from control by exposure group: mg/m^3 | Total protein | Albumin | Lactate dehydrogenase 0 | -- | -- | -- 0.05 | 46.7* | -14.1 | -14.8 0.10 | 28.2* | -10.9 | 0.0 0.20 | 31.3* | 51.7* | 14.8 0.40 | 53.3* | 67.2* | 7.4 mg/m^3 | Total macrophages | Dividing macrophages | Cell viability 0 | -- | -- | -- 0.05 | 0.0 | 9.1 | 1.1 0.10 | -7.1 | 36.4 | 0.0 0.20 | 0.0 | 54.5 | -1.1 0.40 | 7.1 | -9.1 | 0.0
Cohen et al. (2003) F344 Rat, Male (30/group) 0, 0.36 mg Cr VI/m^3 as calcium chromate (dynamic nose-only chamber) 5 hr/d, 5 d/wk Up to 48 wk Generation method (nebulization of aqueous $CaCrO_4$ suspension), analytical method (gravimetic filter), analytical concentration, and MMAD reported.	Percent change from control by exposure group in pulmonary immune cells ($\times 10^6$) in lavage: mg/m^3 | Neutrophils | Macrophages | Total cells 4 wk: 0 | -- | -- | -- 0.36 | 767* | -17.7 | -18.5 8 wk: 0 | -- | -- | -- 0.36 | 8000* | -45.7* | -35.7* 12 wk: 0 | -- | -- | -- 0.36 | 3800* | -13.6* | 2.1 24 wk: 0 | -- | -- | -- 0.36 | 1747* | -51.3* | 17.7* 48 wk: 0 | -- | -- | -- 0.36 | 4100* | -30.9* | 55.3*

Reference and study design	Results
Johansson et al. (1986b) Rabbit, Male (8/group) 0, 0.9 mg Cr VI/m^3 as Na_2CrO_4 aerosol exposure (dynamic whole-body chamber) 6 hr/d, 5 d/wk 4–6 wk Generation method (ultrasonic nebulizer), analytical method (atomic absorption spectrometry and diphenylcarbazine method), analytical concentration, and MMAD reported.	Percent change from control by exposure group: mg/m^3 | Number of macrophage cells ($\times 10^6$) | Macrophage cell diameter (µm) | Variance of diameter (μm^2) 0 | -- | -- | -- 0.9 | 75 | 4.4 | -7.4 Qualitative results from light microscopic findings indicate no increase in variance of cell diameter or increase in number of cells other than macrophages in lavage fluid. However, there was an increased number of alveolar macrophages (not reported to be statistically significant). Qualitative results from electron microscopic findings indicate no increased protrusions from cell surface or surface blebs, but increased intracellular laminated structures and large lysosomes (not reported to be statistically significant).
Other/Gross Findings	
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 5 hr/d, 5 d/wk, 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	Authors report the following, but do not provide data: CrO_3-treated groups showed decreased activity, peculiar sound during respiration starting at Week 1 and disappeared by Week 8. Alopecic effect seen in some animals from high dose group; 2/5 animals in high dose group experienced nasal hemorrhage from Day 10 through Week 4. No abnormal gross pathological findings in any group with exception of nasal hemorrhage from Day 10 through 4 weeks for 2 animals in 1.25-mg/m^3 group (animals recovered at Week 4 and were normal for remainder of study period).

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

1

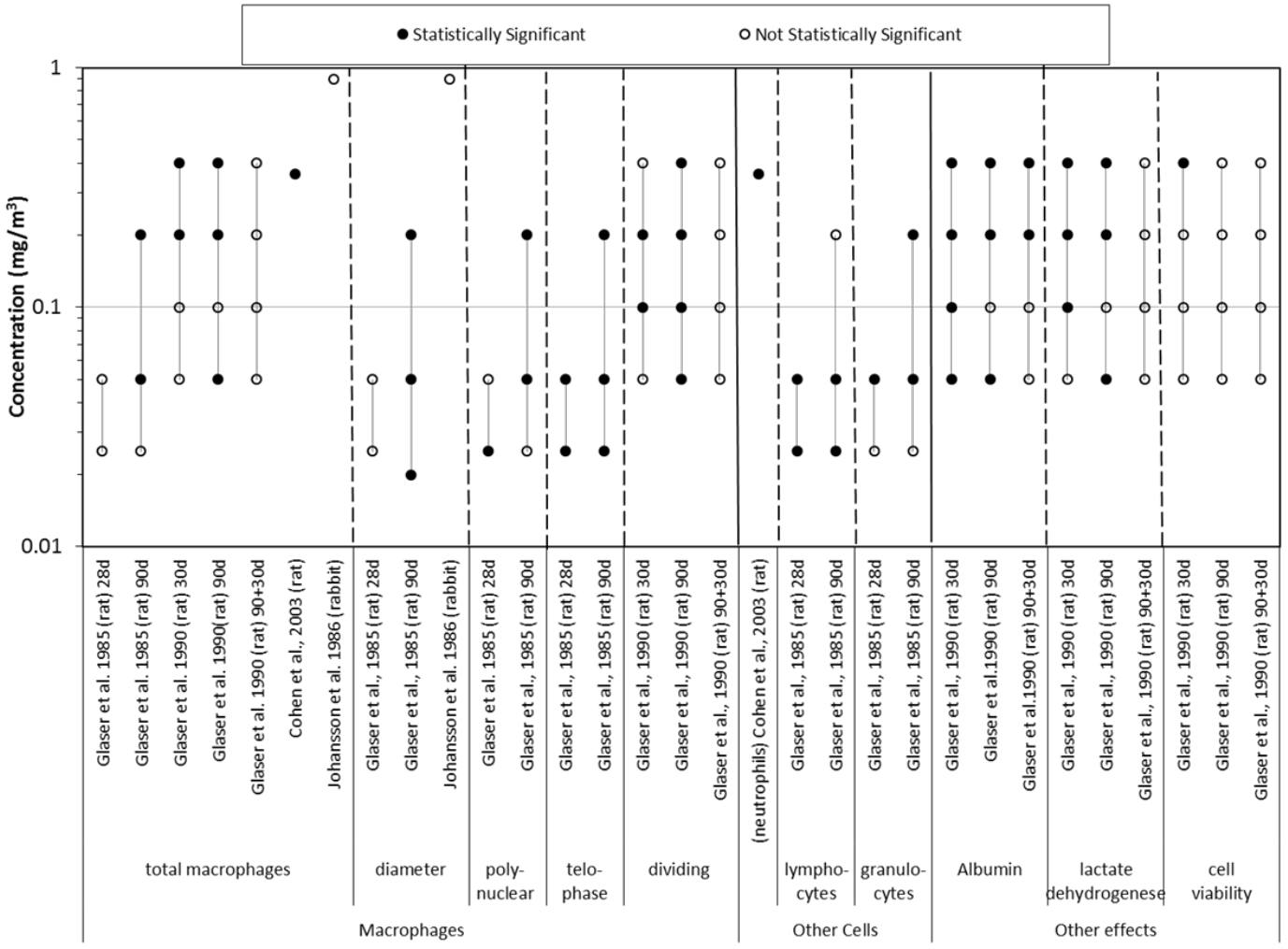

Figure 3-1. Exposure-response array of respiratory system effects (BAL fluid) following inhalation exposure to hexavalent chromium.

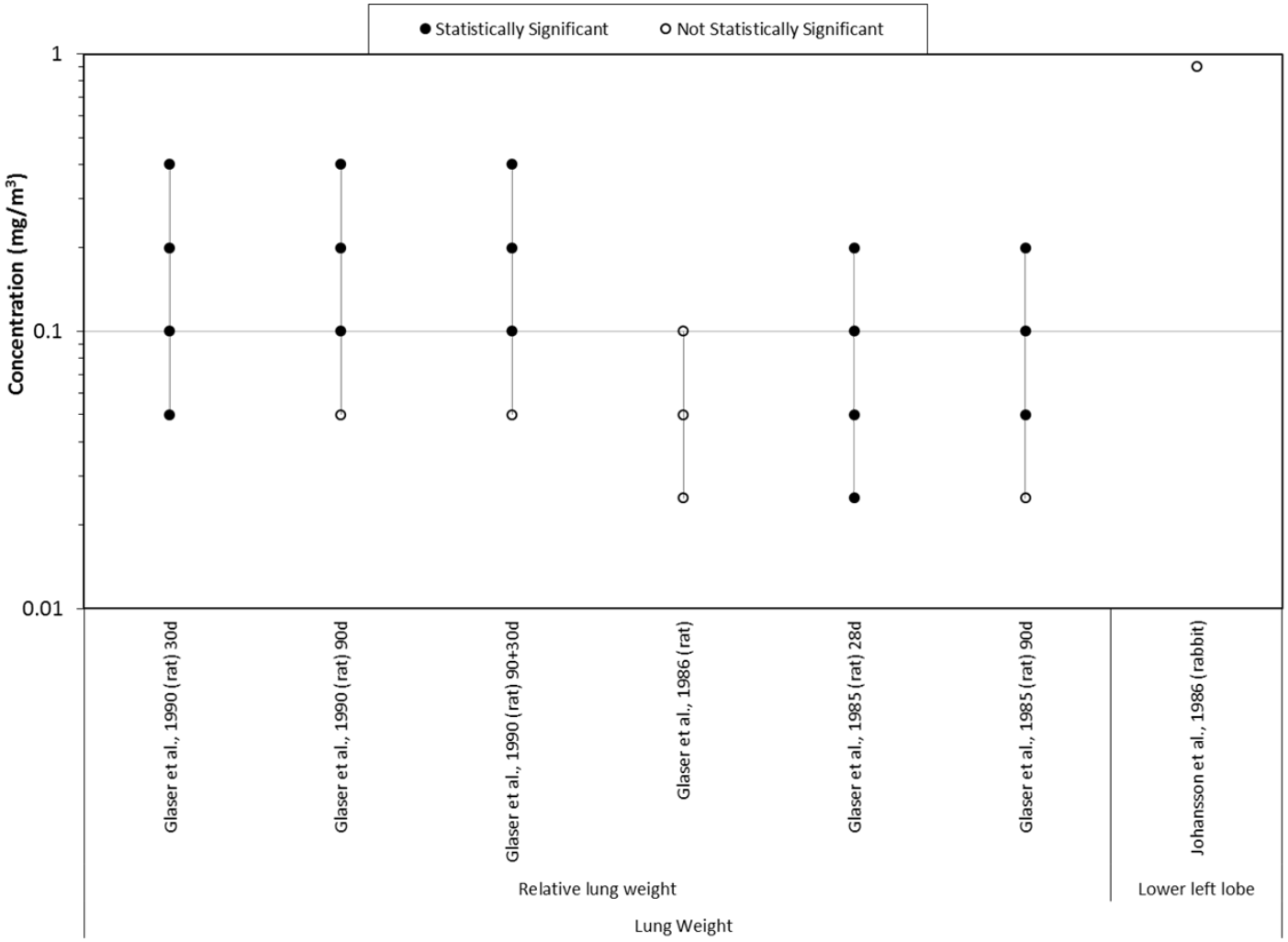

Figure 3-2. Exposure-response array of respiratory system effects (other findings) following inhalation exposure to hexavalent chromium.

3.3. Gastrointestinal Effects

Table 3-2. Evidence pertaining to gastrointestinal (GI) effects following oral exposure to hexavalent chromium

Reference and study design	Results
Small Intestine, Duodenum: Histopathology	
NTP (2008) F344 Rat (50/sex/group) Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M) 0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 0/48 (0) 0.21 — 0/48 (0) 0.77 — 6/47 (13)* 2.1 — 36/46 (78)* 5.9 — 47/48 (98)* Females mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 0/46 (0) 0.24 — 0/49 (0) 0.94 — 1/48 (2) 2.4 — 30/46 (65)* 7 — 47/50 (94)*
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Incidence (percent) by exposure group: mg Cr VI/kg-d — Males Histiocytic cellular infiltration — Females Histiocytic cellular infiltration 0 — 0/10 (0) — 0/10 (0) 1.7 — 0/10 (0) — 1/10 (10) 3.5 — 7/10 (70)* — 5/10 (50)* 5.9 — 9/10 (90)* — 7/10 (70)* 11.2 — 8/10 (80)* — 8/10 (80)* 20.9 — 7/10 (70)* — 10/10 (100)*
Thompson et al. (2012) F344 Rat, Female (15/group) Water: 0, 0.3, 4, 60, 170, 520 ppm sodium dichromate dihydrate; equivalent to 0, 0.017, 0.24, 3.54, 10.04, 30.65 mg Cr VI/kg-d 7 d/wk, 91 d	Incidence (percent) by exposure group: mg Cr VI/kg-d — Apoptosis — Crypt cell hyperplasia — Histiocytic infiltration 0 — 0/10 (0) — 0/10 (0) — 0/10 (0) 0.017 — 0/10 (0) — 0/10 (0) — 0/10 (0) 0.24 — 0/10 (0) — 0/10 (0) — 0/10 (0) 3.54 — 3/10 (30) — 0/10 (0) — 9/10 (90)* 10.04 — 4/10 (40)* — 5/10 (50)* — 10/10 (100)* 30.65 — 7/10 (70)* — 4/10 (40)* — 10/10 (100)*

Reference and study design	Results
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F); equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males mg Cr VI/kg-d | Diffuse epithelial hyperplasia | Histiocytic cellular infiltration 0 | 0/50 (0) | 0/50 (0) 0.38 | 11/50 (22)* | 2/50 (4) 0.91 | 18/50 (36)* | 4/50 (8) 2.4 | 42/50 (84)* | 37/50 (74)* 5.9 | 32/50 (64)* | 35/50 (70)* Females mg Cr VI/kg-d | Diffuse epithelial hyperplasia | Histiocytic cellular infiltration 0 | 0/50 (0) | 0/50 (0) 0.38 | 16/50 (32)* | 0/50 (0) 1.4 | 35/50 (70)* | 4/50 (8) 3.1 | 31/50 (62)* | 33/50 (66)* 8.7 | 42/50 (84)* | 40/50 (80)*
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Incidence (percent) by exposure group: Males: Histiocytic cellular infiltration; Males: Epithelial hyperplasia; Females: Histiocytic cellular infiltration; Females: Epithelial hyperplasia mg Cr VI/kg-d | Males: Histiocytic cellular infiltration | Males: Epithelial hyperplasia | Females: Histiocytic cellular infiltration | Females: Epithelial hyperplasia 0 | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) 3.1 | 4/10 (40)* | 0/10 (0) | 7/10 (70)* | 0/10 (0) 5.3 | 5/10 (50)* | 8/10 (80)* | 8/9 (89)* | 9/9 (100)* 9.1 | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* 15.7 | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* 27.9 | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* | 10/10 (100)*
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse, Male (5–10/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2, 8.7 mg Cr VI/kg-d 7 d/wk, 3 mo Strain Comparison Study	Incidence (percent) by exposure group: B6C3F1: Histiocytic cellular infiltration; B6C3F1: Epithelial hyperplasia; BALB/c: Histiocytic cellular infiltration; BALB/c: Epithelial hyperplasia mg Cr VI/kg-d | B6C3F1: Histiocytic cellular infiltration | B6C3F1: Epithelial hyperplasia | BALB/c: Histiocytic cellular infiltration | BALB/c: Epithelial hyperplasia 0 | 0/10 (0) | 0/10 (0) | 0/10 (0) | 0/10 (0) 2.8 | 8/10 (80)* | 4/10 (40)* | 4/10 (40)* | 2/10 (20) 5.2 | 10/10 (100)* | 10/10 (100)* | 8/10 (80)* | 10/10 (100)* 8.7 | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* | 10/10 (100)* am3-C57BL/6: Histiocytic cellular infiltration; am3-C57BL/6: Epithelial hyperplasia mg Cr VI/kg-d | am3-C57BL/6: Histiocytic cellular infiltration | am3-C57BL/6: Epithelial hyperplasia 0 | 0/5 (0) | 0/5 (0) 2.8 | 2/5 (40)* | 5/5 (100)* 5.2 | 5/5 (100)* | 5/5 (100)* 8.7 | 4/5 (80)* | 5/5 (100)*

Reference and study design	Results
Thompson et al. (2011) B6C3F1 Mouse, Female (15/group) Water: 0, 0.3, 4, 14, 60, 170, 520 ppm sodium dichromate dihydrate; equivalent to 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg Cr VI/kg-d 7 d/wk, 91 d	Incidence (percent) by exposure group: mg Cr VI/kg-d — Villous cytoplasmic vacuolization — Villous atrophy — Apoptosis 0 — 0/10 (0) — 0/10 (0) — 0/10 (0) 0.024 — 0/10 (0) — 0/10 (0) — 0/10 (0) 0.32 — 0/10 (0) — 0/10 (0) — 0/10 (0) 1.1 — 0/10 (0) — 0/10 (0) — 0/10 (0) 4.6 — 5/10 (50)* — 0/10 (0) — 0/10 (0) 11.6 — 10/10 (100)* — 1/10 (10) — 3/10 (30) 31.1 — 7/10 (70)* — 3/10 (30)* — 4/10 (40)* mg Cr VI/kg-d — Cryptcell hyperplasia — Histiocytic infiltration 0 — 0/10 (0) — 0/10 (0) 0.024 — 0/10 (0) — 0/10 (0) 0.32 — 0/10 (0) — 0/10 (0) 1.1 — 0/10 (0) — 0/10 (0) 4.6 — 0/10 (0) — 1/10 (10) 11.6 — 9/10 (90)* — 10/10 (100)* 31.1 — 9/10 (90)* — 10/10 (100)*
Small Intestine, Jejunum: Histopathology	
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F); equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group in females: mg Cr VI/kg-d — Diffuse epithelial hyperplasia — Histiocytic cellular infiltration 0 — 0/50 (0) — 0/50 (0) 0.38 — 2/50 (4) — 0/50 (0) 1.4 — 1/50 (2) — 0/50 (0) 3.1 — 0/50 (0) — 2/50 (4) 8.7 — 8/50 (16)* — 8/50 (16)* No significant effects observed in males.
Thompson et al. (2012) F344 Rat, Female (15/group) Water: 0, 0.3, 4, 60, 170, 520 ppm sodium dichromate dihydrate; equivalent to 0, 0.017, 0.24, 3.54, 10.04, 30.65 mg Cr VI/kg-d 7 d/wk, 91 d	Incidence (percent) by exposure group: mg Cr VI/kg-d — Histiocytic infiltration 0 — 0/10 (0) 0.017 — 0/10 (0) 0.24 — 0/10 (0) 3.54 — 3/10 (30) 10.04 — 7/10 (70)* 30.65 — 9/10 (90)*

Reference and study design	Results		
Thompson et al. (2011) B6C3F1 Mouse, Female (15/group) Water: 0, 0.3, 4, 14, 60, 170, 520 ppm sodium dichromate dihydrate; equivalent to 0, 0.024, 0.32, 1.1, 4.6, 11.6, 31.1 mg Cr VI/kg-d 7 d/wk, 91 d	Incidence (percent) by exposure group:		
	mg Cr VI/kg-d	Villous cytoplasmic vacuolization	Villous atrophy
	0	0/10 (0)	0/10 (0)
	0.024	0/10 (0)	0/10 (0)
	0.32	0/10 (0)	0/10 (0)
	1.1	0/10 (0)	0/10 (0)
	4.6	4/10 (40)*	0/10 (0)
	11.6	8/10 (80)*	3/10 (30)
	31.1	5/10 (50)*	4/10 (40)*
	mg Cr VI/kg-d	Crypt cell hyperplasia	Histiocytic infiltration
	0	0/10 (0)	0/10 (0)
	0.024	0/10 (0)	0/10 (0)
	0.32	0/10 (0)	0/10 (0)
	1.1	0/10 (0)	0/10 (0)
	4.6	0/10 (0)	0/10 (10)
	11.6	5/10 (50)*	9/10 (90)*
	31.1	7/10 (70)*	10/10 (100)*

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

1

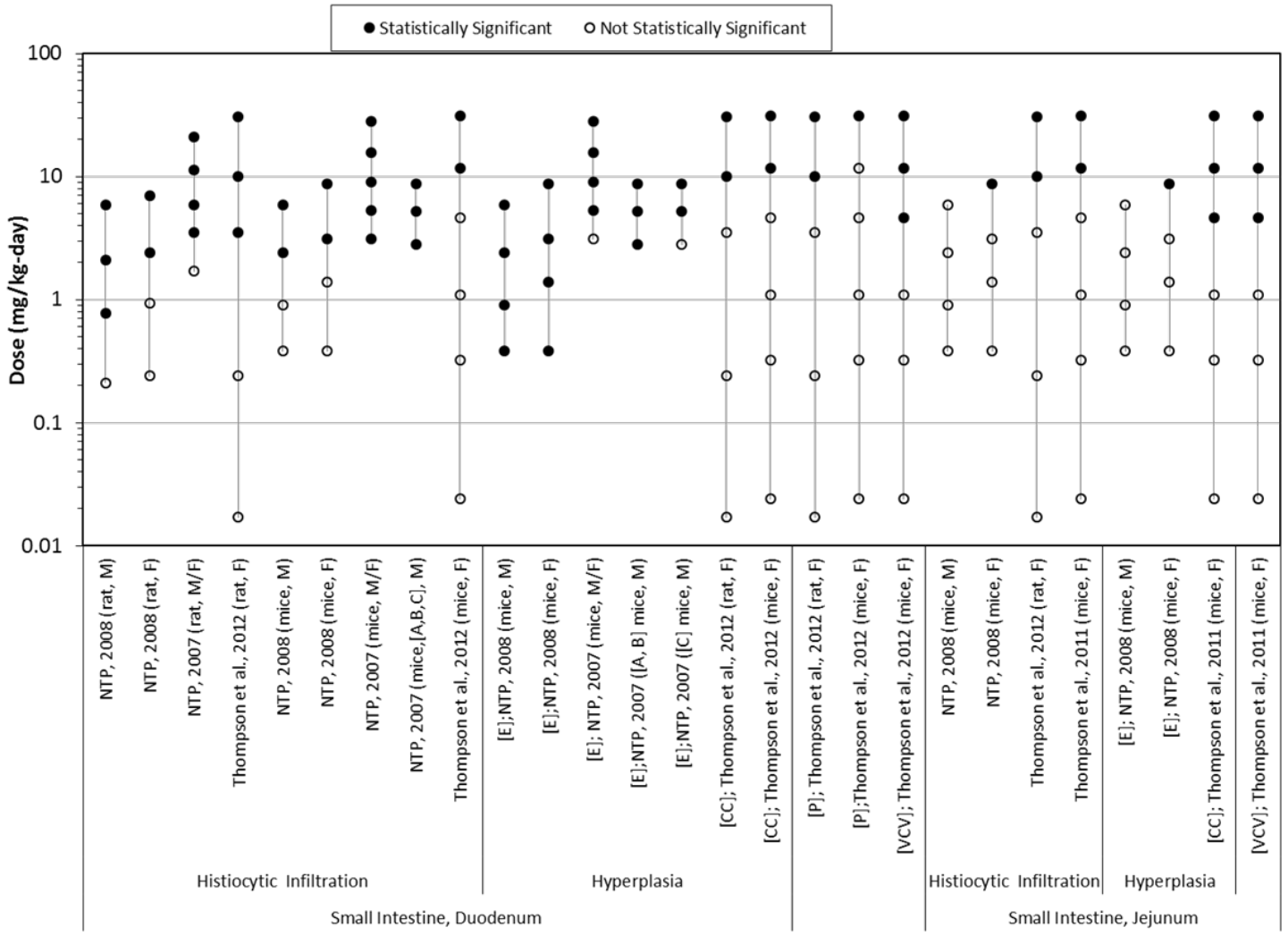

Figure 3-3. Exposure-response array of GI effects following oral exposure to hexavalent chromium. [A]: am3-C57BL/6 strain of mouse; [B]: B6C3F1; [C]: BALB/c. [P]: Apoptosis; [VCV]: villous cytoplasmic vacuolization; [E]: epithelial; [CC]: crypt cell.

3.4. Liver Effects

Table 3-3. Evidence pertaining to liver effects following oral or inhalation exposure to hexavalent chromium

Reference and study design	Results
Liver Weight – Oral	
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group for males: mg Cr VI/kg-d — Absolute liver weight — Relative liver weight 0 -- -- 1.7 -5 -3 3.5 5 3 5.9 -3 -3 11.2 -16* -11* 20.9 -18* -9* No statistically significant effects observed in females.
Chopra et al. (1996) Wistar Rat, Female (5-6/group) Water: 0, 25 ppm potassium dichromate; equivalent to 0, 1.4 mg Cr VI/kg-d 7 d/wk, 22 wk	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 -- 1.4 125*
Geetha et al. (2003) Sprague-Dawley Rat, Male (number/ group not reported) Gavage: 0, 30 mg Cr VI/kg-d given as potassium dichromate 7 d/wk, 30 d	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 -- 30 66.7*
Acharya et al. (2001) Wistar Rat, Male (5-6/group) Water: 0, 20 ppm potassium dichromate; equivalent to 0, 1.5 mg Cr VI/kg-d 7 d/wk, 22 wk	Percent change from control by exposure group: mg Cr VI/kg-d — Relative liver weight 0 -- 1.5 125*
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Absolute but not relative liver weight was statistically significantly decreased at the three highest doses in males and the two highest in females; this was attributed to a significant reduction in body weight.

Reference and study design	Results
NTP (2007) BALB/c and am3-C57BL/6 Mouse, Male (5–10/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2, 8.7 mg Cr VI/kg-d 7 d/wk, 3 mo Strain Comparison Study	Absolute but not relative liver weight was statistically significantly increased at the highest dose in both species; this was attributed to a significant reduction in body weight.
NTP (1997) BALB/c Mouse (20/sex/group) Continuous Breeding Protocol: F0 animals exposed for 7 d/wk, 13 wk total, 1 wk prior to and 12 wk during cohabitation. After cohabitation, F0 breeding pairs were separated and continued on study diets. Diet: 0, 100, 200, 400 ppm potassium dichromate (equivalent to 0, 17.6, 35.3, 141.2 ppm Cr VI) M/F (F0): 0, 19.4, 38.6, 85.7 mg potassium dichromate/kg-d (equivalent to 0, 6.8, 13.6, 30.3 mg Cr VI/kg-d) Lactating F (F0): 0, 32.8, 69.0, 143.1 mg potassium dichromate/kg-d (equivalent to 0, 11.6, 24.4, 50.5 mg Cr VI/kg-d)	Percent change from control by exposure group: mg Cr VI/kg-d | F0 males: Absolute liver weight | F0 females: Absolute liver weight 0 | -- | -- 6.8 | -5.5 | -5.9 13.6 | -11 | -5.9 30.3 | -17* | -12* There were no statistically significant changes in relative liver weights.
Liver Weight – Inhalation	
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Authors report no statistically significant changes in liver weights but do not provide data.
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 5 hr/d, 5 d/wk 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	There were no statistically significant changes in relative liver weights.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Glaser et al. (1986)
Wistar Rat, Male (40/control, 20/treatment group)
0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber)
22 hr/d, 7 d/wk
72 wk
Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.</td><td>Percent change from control by exposure group:
<u>Exposure group</u> — <u>Relative liver weight</u>
Control (0 mg/m^3) — --
Cr_5O_{12} (0.1 mg/m^3) — 2.7
$Na_2Cr_2O_7$ (0.025 mg/m^3) — No data provided
$Na_2Cr_2O_7$ (0.05 mg/m^3) — No data provided
$Na_2Cr_2O_7$ (0.1 mg/m^3) — 13.5*
Organ weights for liver at low and mid $Na_2Cr_2O_7$ exposure groups were measured but results not reported by authors due to lack of statistical significance.</td></tr>
<tr><td colspan="2">Histopathology – Oral</td></tr>
<tr><td>NTP (2008)
F344 Rat (50/sex/group)
Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M)
0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F)
7 d/wk, 104 wk
Related reference: Stout et al. (2009)</td><td>Incidence (percent) by exposure group:
<u>Males</u>
<u>mg Cr VI/kg-d</u> — <u>Histiocytic cellular infiltration</u> — <u>Chronic inflammation</u> — <u>Basophilic focus</u>
0 — 1/50 (2) — 19/50 (38) — 22/50 (44)
0.21 — 0/50 (0) — 25/50 (50) — 28/50 (56)
0.77 — 2/49 (4) — 21/49 (43) — 29/49 (60)*
2.1 — 5/50 (10) — 28/50 (56)* — 32/50 (64)*
5.9 — 34/49 (69)* — 26/49 (53) — 30/49 (61)

<u>Females</u>
<u>mg Cr VI/kg-d</u> — <u>Histiocytic cellular infiltration</u> — <u>Chronic inflammation</u> — <u>Fatty change</u>
0 — 1/50 (2) — 12/50 (24) — 3/50 (6)
0.24 — 5/50 (10) — 21/50 (42)* — 7/50 (14)
0.94 — 21/50 (42)* — 28/50 (56)* — 10/50 (20)*
2.4 — 42/50 (84)* — 35/50 (70)* — 13/50 (26)*
7 — 47/50 (94)* — 39/50 (78)* — 16/50 (32)*</td></tr>
<tr><td>Acharya et al. (2001)
Wistar Rat, Male (5-6/group)
Water: 0, 20 ppm potassium dichromate; equivalent to 0, 1.5 mg Cr VI/kg-d
7 d/wk, 22 wk</td><td>Qualitative histopathology in treated group reported as:
Centrilobular and periportal vacuolation and necrosis in hepatocytes; pronounced in periportal area.</td></tr>
<tr><td>Chopra et al. (1996)
Wistar Rat, Female (5-6/group)
Water: 0, 25 ppm potassium dichromate; equivalent to 0, 1.4 mg Cr VI/kg-d
7 d/wk, 22 wk</td><td>Qualitative histopathology in treated group reported as:
Altered hepatic architecture in the periportal area; increased sinusoidal space, vacuolation, and necrosis.</td></tr>
</table>

Reference and study design	Results
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Incidence (%) by exposure group for females: mg Cr VI/kg-d / Histiocytic cellular infiltration / Chronic focal inflammation 0 / 0/10 (0) / 3/10 (30) 1.7 / 3/10 (30) / 5/10 (50) 3.5 / 6/10 (60)* / 2/10 (20) 5.9 / 6/10 (60)* / 7/10 (70) 11.2 / 9/10 (90)* / 2/10 (20) 20.9 / 8/10 (80)* / 10/10 (100)* No statistically significant effects observed in males.
Rafael et al. (2007) Wistar Rat, Male (9 control, 19 treated) Water: 0, 20 ppm Cr VI equivalent to 0, 2.96 mg Cr VI/kg-d 7 d/wk, 10 wk	Qualitative histopathology in treated group reported as: Increased intracellular space as a result of shrinkage, increased degenerative alteration with vascularization, "little" focus of necrosis, absence of polysaccharides and carbohydrates, fibrosis.
Meenakshi et al. (1989) Wistar Rat, Male (10/group) Gavage: 0, 10 mg Cr VI/kg-d as potassium dichromate 7 d/wk, 60 d	Qualitative histopathology in treated group reported as: Marked periportal accumulation of inflammatory cells, diffuse Kupffer cell hyperplasia, focal necrosis, phagocytic cell infiltration.
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) or 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F); equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 104 wk Related reference: Stout et al. (2009)	Incidence (%) by exposure group for females: mg Cr VI/kg-d / Histiocytic cellular infiltration / Chronic inflammation 0 / 2/49 (4) / 16/49 (33) 0.38 / 15/50 (30)* / 21/50 (42) 1.4 / 23/50 (46)* / 22/50 (44) 3.1 / 32/50 (64)* / 27/50 (54)* 8.7 / 45/50 (90)* / 24/50 (48) No significant effects observed in males.
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse, Male (5–10/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2, 8.7 mg Cr VI/kg-d 7 d/wk, 3 mo Strain Comparison Study	Incidence (percent) by exposure group: mg Cr VI/kg-d / B6C3F1 Glycogen depletion / am3-C57BL/6 Glycogen depletion 0 / 1/10 (10) / 0/5 (0) 2.8 / 2/10 (20) / 4/5 (80)* 5.2 / 9/10 (90)* / 5/5 (100)* 8.7 / 10/10 (100)* / 5/5 (100)* No statistically significant effects observed in BALB/c strain.

Reference and study design	Results
NTP (1996a) BALB/c Mouse (24 males or 48 females/group, 5–6 males or 12 females/group per timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.1, 3.5, 7.4, 32.5 mg Cr VI/kg-d (M) 0, 1.8, 5.6, 12.0, 48.4 mg Cr VI/kg-d (F) Sacrificed at 3, 6, 9 wk of treatment or after 8-wk recovery period	Incidence (percent) by exposure group: Males mg Cr VI/kg-d — Cytoplasmic vacuolation 0 — 0/6 (0) 1.1 — 0/6 (0) 3.5 — 1/6 (17) 7.4 — 2/5 (40) 32.5 — 2/6 (33) Females mg Cr VI/kg-d — Cytoplasmic vacuolation 0 — 1/12 (8) 1.8 — 0/12 (0) 5.6 — 3/12 (25) 12.0 — 2/12 (17) 48.4 — 4/12 (33) Statistical significance and lesion severity not reported by study authors.
Histopathology – Inhalation	
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Authors state normal histologic findings in kidney and liver but do not provide data.
Gross Pathology – Inhalation	
Nettesheim et al. (1971) C57BL/6 Mouse (136 males/136 females) 0, 13 mg/m^3 of calcium chromate dust (equivalent to 4.33 mg Cr VI/m^3) (dynamic whole-body chamber) 5 hr/d, 5 d/wk lifespan (~2 yr) Generation method (Wright dust feed), analytical method (gravimetric filter), and analytical concentration reported; MMAD not reported. Methods: Nettesheim et al. (1970)	Markedly atrophied liver (incidence not specified).
Clinical chemistry – Oral	
Kumar and Barthwal (1991) Albino Rat, Male (10/group) Gavage: 0, 50 mg Cr VI/kg-d as potassium chromate 7 d/wk, 30 d	Results presented as figures. Triglycerides, phospholipids, cholesterol, and glucose were statistically significantly higher in treated animals compared to controls after 30 days of treatment.

Reference and study design	Results
Meenakshi et al. (1989) Wistar Rat, Male (6/group) Gavage: 0, 10 mg Cr VI/kg-d as potassium dichromate 7 d/wk, 60 d	Percent change from control by exposure group: mg Cr VI/kg-d | Total cholesterol | Phospho-lipids | Triglycerides | Total lipids 0 | -- | -- | -- | -- 10 | 36.4* | 43.1* | 26.5* | 31.9* mg Cr VI/kg-d | AST | ALT | GGT 0 | -- | -- | -- 10 | 51.6* | 60.2* | 57.5*
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group: mg Cr VI/kg-d | Males: ALT at 3 Mo | Males: SDH at 3 Mo | Females: ALT at 3 Mo | Females: SDH at 3 Mo 0 | -- | -- | -- | -- 1.7 | 180* | 77* | 583* | 359* 3.5 | 370* | 255* | 241* | 195* 5.9 | 356* | 229* | 283* | 268* 11.2 | 655* | 458* | 284* | 336* 20.9 | 95* | 90* | 288* | 368* There were also statistically significant decreases in ALP, cholesterol, and triglycerides, and increases in creatine kinase and bile acids in males and females.
Chopra et al. (1996) Wistar Rat, Female (5-6/group) Water: 0, 25 ppm potassium dichromate; equivalent to 0, 1.4 mg Cr VI/kg-d 7 d/wk, 22 wk	Percent change from control by exposure group: mg Cr VI/kg-d | AST | ALT | ALP | ACP 0 | -- | -- | -- | -- 1.4 | 50* | 143* | 167* | 120*
Meenakshi et al. (1989) Wistar Rat, Male (6/group) Gavage: 0, 10 mg Cr VI/kg-d as potassium dichromate 7 d/wk, 60 d	Percent change from control by exposure group: mg Cr VI/kg-d | Glucose 0 | -- 10 | 58.0*

Reference and study design	Results
Krim et al. (2013) Wistar Rat, Male (10/group) Gavage: 0, 15 mg/kg as potassium dichromate 7 d/wk, 30d	Percent change from control by exposure group: mg/kg / Total lipids / Triglycerides / Cholesterol / ALT 0 / -- / -- / -- / -- 15 / 128* / 70* / 56* / 48* mg/kg / AST / ALP / LDH 0 / -- / -- / -- 15 / 60* / 73* / 37*
Geetha et al. (2003) Sprague-Dawley Rat, Male (number/ group not reported) Gavage: 0, 30 mg Cr VI/kg-d given as potassium dichromate 7 d/wk, 30 d	Statistically significant increases in ALT, AST, and creatinine phosphokinase (figures only).
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse (5–10 males/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2 or 8.7 mg Cr VI/kg-d (M) 7 d/wk, 3 mo Strain Comparison Study	B6C3F1 mice: slight but statistically significant decreases in ALP, SDH, and bile acids. No other significant changes in markers of liver toxicity. BALB/c mice: slight but statistically significant increases in ALT. No other significant changes in markers of liver toxicity. am3-C57BL/6 mice: statistically significant increase in ALT at the highest dose. No other significant changes in markers of liver toxicity.
Clinical Chemistry – Inhalation	
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 6 hr/d, 5 d/wk 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	Percent change from control by exposure group: mg/m^3 / ALT / Glucose 0 / -- / -- 0.2 / -7.2 / 7.2* 0.5 / -12.2 / 11.5* 1.25 / -24.5* / 5.1 No statistically significant effects on total bilirubin, AST, LDH, ALP, glucose, or total cholesterol.
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Authors note no difference between exposed and control animals in mean serum activity of GPT or AP or in total serum cholesterol. Authors note statistically significant difference in serum triglyceride and phospholipid contents at 0.200 mg/m^3 compared to control but data not provided.

Reference and study design	Results
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Authors state no significant differences between alanine aminotransferase and alkaline phosphatase activity, serum lipids, triglycerides, phospholipids, or total cholesterol in any exposure group compared to the controls (data not provided).

1 *Significantly different from control (p<0.05) as calculated by study authors.
2 Percent change from control calculated as (Treated – Control) ÷ Control × 100.

3

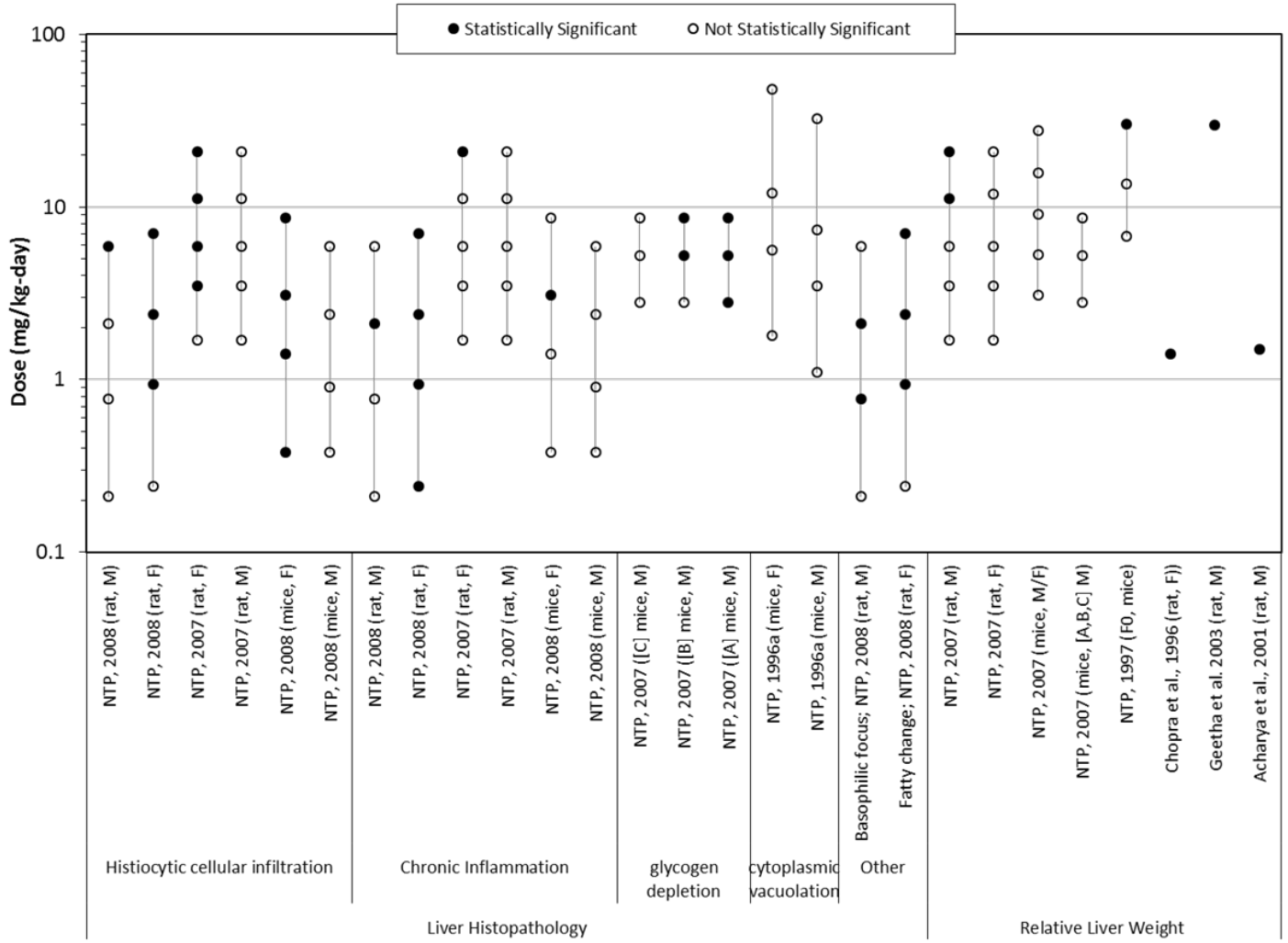

Figure 3-4. Exposure-response array of liver effects following oral exposure to hexavalent chromium. [A]: am3-C57BL/6 strain of mouse; [B]: B6C3F1; [C]: BALB/c.

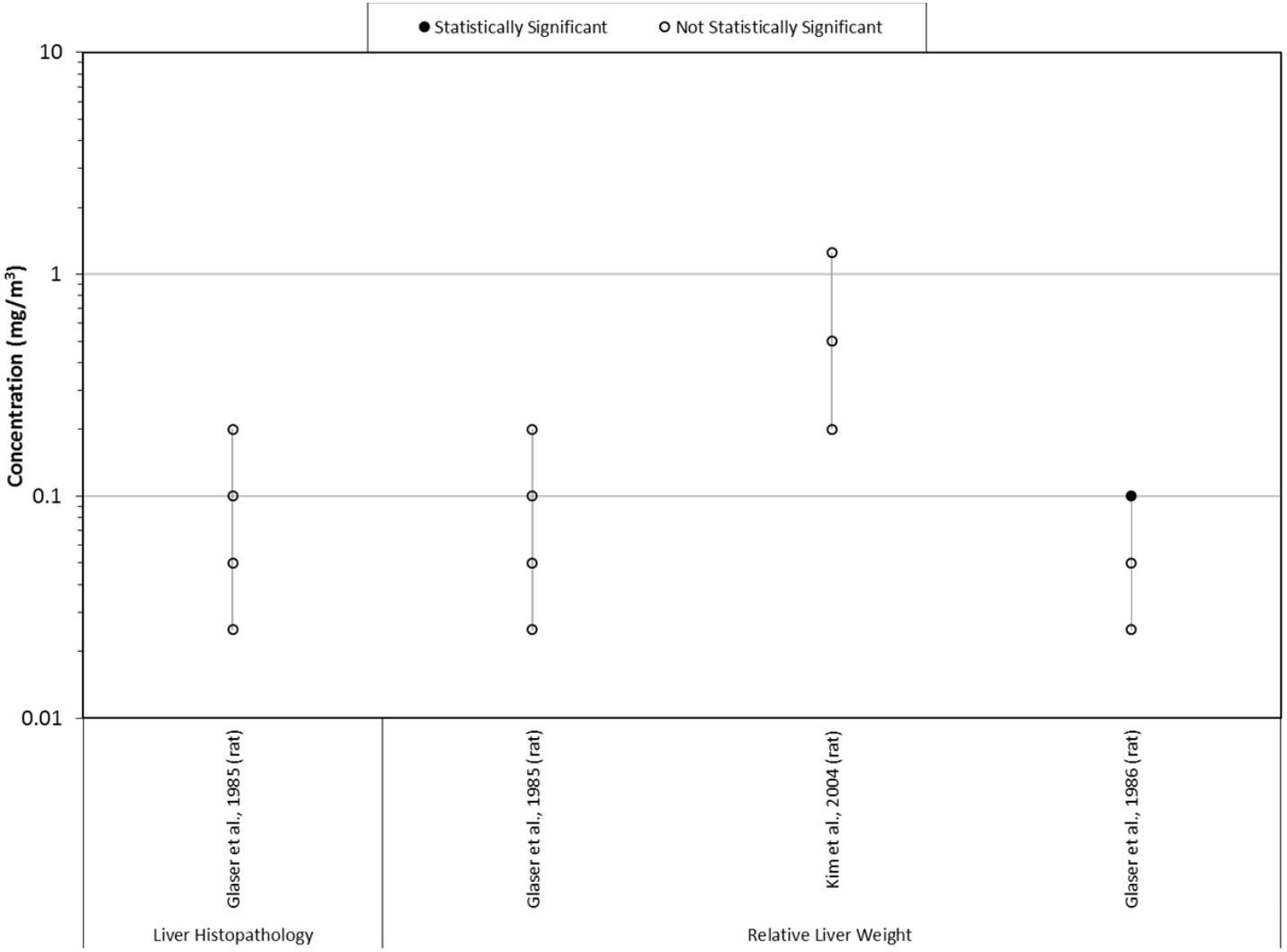

Figure 3-5. Exposure-response array of liver effects following inhalation exposure to hexavalent chromium.

3.5. Immune System and Lymphatic System Effects

Table 3-4. Evidence pertaining to immune and lymphatic system effects following oral or inhalation exposure to hexavalent chromium

Reference and study design	Results
Lymph Node, Pancreatic: Histopathology – Oral	
NTP (2008) F344 Rat (50/sex/group) Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M) 0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group in females: mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 17/29 (58.6) 0.24 — 20/36 (55.6) 0.94 — 23/30 (76.7) 2.4 — 32/34 (94.1)* 7 — 27/33 (81.8) No statistically significant effects observed in males.
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Incidence (percent) by exposure group: Males mg Cr VI/kg-d — Ectasia — Lymphoid hyperplasia — Histiocytic cellular infiltration 0 — 0/10 (0) — 0/10 (0) — 0/10 (0) 1.7 — 0/10 (0) — 0/10 (0) — 5/10 (50)* 3.5 — 0/10 (0) — 0/10 (0) — 2/10 (20) 5.9 — 0/10 (0) — 3/10 (30) — 4/10 (40)* 11.2 — 1/10 (10) — 3/10 (30) — 5/10 (50)* 20.9 — 10/10 (100)* — 6/10 (60)* — 9/10 (90)* Females mg Cr VI/kg-d — Ectasia — Lymphoid hyperplasia — Histiocytic cellular infiltration 0 — 0/10 (0) — 0/10 (0) — 4/10 (40) 1.7 — 0/10 (0) — 0/10 (0) — 8/10 (80) 3.5 — 0/10 (0) — 2/10 (20) — 7/10 (70) 5.9 — 0/10 (0) — 0/10 (0) — 7/10 (70) 11.2 — 1/10 (10) — 0/10 (0) — 7/10 (70)* 20.9 — 10/10 (100)* — 10/10 (100)* — 9/10 (90)*

Reference and study design	Results
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F); equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 0/5 (0) 0.38 — 2/13 (15) 0.91 — 2/10 (20) 2.4 — 5/8 (63)* 5.9 — 12/16 (75)* Females mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 0/14 (0) 0.38 — 1/12 (8) 1.4 — 2/15 (13) 3.1 — 7/14 (50)* 8.7 — 8/13 (62)*
Lymph Node, Mesenteric: Histopathology – Oral	
NTP (2008) F344 Rat (50/sex/group) Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M) 0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males mg Cr VI/kg-d — Histiocytic cellular infiltration — Hemorrhage 0 — 13/49 (26.5) — 2/49 (4.1) 0.21 — 11/50 (22) — 7/50 (14) 0.77 — 30/49 (61.2)* — 9/49 (18.4)* 2.1 — 39/50 (78)* — 8/50 (16)* 5.9 — 41/49 (83.7)* — 17/49 (34.7)* Females mg Cr VI/kg-d — Histiocytic cellular infiltration — Hemorrhage 0 — 21/50 (42) — 11/50 (22) 0.24 — 18/50 (36) — 13/50 (26) 0.94 — 27/50 (54) — 16/50 (32) 2.4 — 36/50 (72)* — 14/50 (28) 7 — 42/50 (84)* — 21/50 (42)*
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Incidence (percent) by exposure group: mg Cr VI/kg-d — Males: Histiocytic cellular infiltration — Females: Histiocytic cellular infiltration 0 — 0/10 (0) — 0/10 (0) 3.1 — 0/9 (0) — 0/10 (0) 5.3 — 4/9 (44)* — 6/10 (60)* 9.1 — 6/8 (75)* — 6/10 (60)* 15.7 — 3/8 (38) — 4/9 (44)* 27.9 — 8/10 (80)* — 9/10 (90)*

Reference and study design	Results
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse, Male (5–10/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2, 8.7 mg Cr VI/kg-d (M) 7 d/wk, 3 mo Strain Comparison Study	Incidence (percent) by exposure group in am3-C57BL/6: mg Cr VI/kg-d — Histiocytic cellular infiltration 0 — 0/5 (0) 2.8 — 0/5 (0) 5.2 — 0/5 (0) 8.7 — 4/5 (80)* No statistically significant effects observed in B6C3F1 or BALB/c strains.
Immune System Effects – Inhalation	
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 6 hr/d, 5 d/wk 7 d/wk, 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	Authors report macrophage aggregation and foamy cells in alveolar region in "all animals of the 1.25 mg/m^3 treated group, but in only a few animals of the 0.5 mg/m^3 treated group and none in the 0.2 mg/m^3 group."
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group: mg/m^3 — Serum immunoglobulin levels 0 — -- 0.025 — 8.3 0.050 — 66.7* 0.100 — 91.7* 0.200 — 0 Values approximated from Figure 2. Text states that "the differences in the mean total immunoglobulin levels between control and experimental groups became significant at exposures above 25 µg/m^3 Cr. Aerosols with chromium concentrations higher than 100 µg/m^3 produced depression of the stimulating effect."
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate; 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr(III) oxide (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Mean serum immunoglobulin was measured at 6, 15, and 24 months; lower levels were measured in all exposure groups compared to control but only significant ($p < 0.001$) for Cr_5O_{12}-exposed groups at 6 months (data not provided).

Reference and study design	Results
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group for mitogen-simulated T-lymphocyte response to concanavalin: mg/m^3 — 15 µg/ml concanavalin — 30 µg/ml concanavalin 0 — -- — -- 0.200 — 53.1* — 51.4* Values were approximated from a figure, actual data not provided.
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050 mg Cr VI/m^3 (28 and 90 d) and 0.200 mg Cr VI/m^3 (90 d only) as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 28 and 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Percent change from control by exposure group: SRBC antibody response by spleen cells mg/m^3 — 28 d — 90 d 0 — -- — -- 0.025 — 52.2* — 60.5* 0.050 — 34.8* — 181* 0.200 — Not measured — 128* in vitro phagocytosis of 2 µm latex particles mg/m^3 — 28 d — 90 d 0 — -- — -- 0.025 — Not reported — 159.5* 0.050 — 462.5* — 439.7* 0.200 — Not measured — -73.2* Values were approximated from a figure, actual data not provided.
Spleen Weight – Oral	
Geetha et al. (2003) Sprague-Dawley Rat, Male (number/group not reported) Gavage: 0, 30 mg Cr VI/kg-d given as potassium dichromate 7 d/wk (assumed), 30 d	Percent change from control by exposure group: mg Cr VI/kg-d — Relative spleen weight 0 — -- 30 — 47.6*

Reference and study design	Results		
NTP (2007) F344 Rat (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group: Males		
	mg Cr VI/kg-d	Absolute spleen weight	Relative spleen weight
	0	--	--
	1.7	-6.3	-4.6
	3.5	-3.1	-5.7
	5.9	-6.3	-6.7*
	11.2	-17.2*	-12.9*
	20.9	-6.3*	3.1
	Females		
	mg Cr VI/kg-d	Absolute spleen weight	Relative spleen weight
	0	--	--
	1.7	7.3	−3.8
	3.5	4.9	1.9
	5.9	7.3	4.7
	11.2	7.3	6.1*
	20.9	7.3	12.7*
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group: Males		
	mg Cr VI/kg-d	Absolute spleen weight	Relative spleen weight
	0	--	--
	3.1	-1.5	4.3
	5.3	-5.9	4.5
	9.1	-5.9	10.6
	15.7	-7.4	16.5*
	27.9	-11.8	10.5*
	Females		
	mg Cr VI/kg-d	Absolute spleen weight	Relative spleen weight
	0	--	--
	3.1	8.1	6.8
	5.3	8.1	16.3*
	9.1	9.5	14.1
	15.7	-4.1	7.7
	27.9	0	13.6

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>NTP (2007)
B6C3F1, BALB/c, am3-C57BL/6 Mouse (5–10 males/group)
Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2 or 8.7 mg Cr VI/kg-d (M)
7 d/wk, 3 mo
Strain Comparison Study</td><td>Percent change from control by exposure group:
B6C3F1
mg Cr VI/kg-d | Absolute spleen weight | Relative spleen weight
0 | -- | --
2.8 | -7.1 | -5.9
5.2 | -8.2 | 1.8
8.7 | -20.0* | 3.8
BALB/c
mg Cr VI/kg-d | Absolute spleen weight | Relative spleen weight
0 | -- | --
2.8 | -4.5 | -2.3
5.2 | -6.7 | -0.9
8.7 | -9.0 | 1.7
am3-C57BL/6
mg Cr VI/kg-d | Absolute spleen weight | Relative spleen weight
0 | -- | --
2.8 | -7.3 | 9.2
5.2 | -3.7 | 15.0
8.7 | -22.0* | 21.2*</td></tr>
<tr><td colspan="2">Spleen Weight – Inhalation</td></tr>
<tr><td>Glaser et al. (1985)
Wistar Rat, Male (10/group)
0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber)
22 hr/d, 7 d/wk
28 d
Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported.
Related reference: Glaser et al. (1988)</td><td>Authors state that spleen weights were statistically significantly increased after 28 day inhalation exposure to chromate aerosol concentrations above 0.025 mg/m^3 Cr VI but data were not provided.</td></tr>
<tr><td>Glaser et al. (1985)
Wistar Rat, Male (10/group)
0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber)
22 hr/d, 7 d/wk
90 d
Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported.
Related reference: Glaser et al. (1988)</td><td>Percent change from control by exposure group:
mg/m^3 | Relative spleen weight
0 | --
0.025 | 0
0.050 | 33.3*
0.100 | 50.0*
0.200 | 41.7*</td></tr>
</table>

Reference and study design	Results
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk (dynamic whole-body chamber) Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Organ weights for kidney, adrenal glands, spleen, and testes at all exposure groups and for lung and liver at low and mid $Na_2Cr_2O_7$ exposure groups were measured but results not reported (assumed to be not significant).
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 6 hr/d, 5 d/wk 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	Authors report no statistically significant changes in relative spleen weights but data were not provided.
Nettesheim et al. (1971) C57BL/6 Mouse (136 males/136 females) 0, 13 mg/m^3 of calcium chromate dust (equivalent to 4.33 mg Cr VI/m^3) (dynamic whole-body chamber) 5 hr/d, 5 d/wk lifespan (~2 yr) Generation method (Wright dust feed), analytical method (gravimetric filter), and analytical concentration reported; MMAD not reported. Methods: Nettesheim et al. (1970)	Atrophied spleen (incidence not specified).

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

1

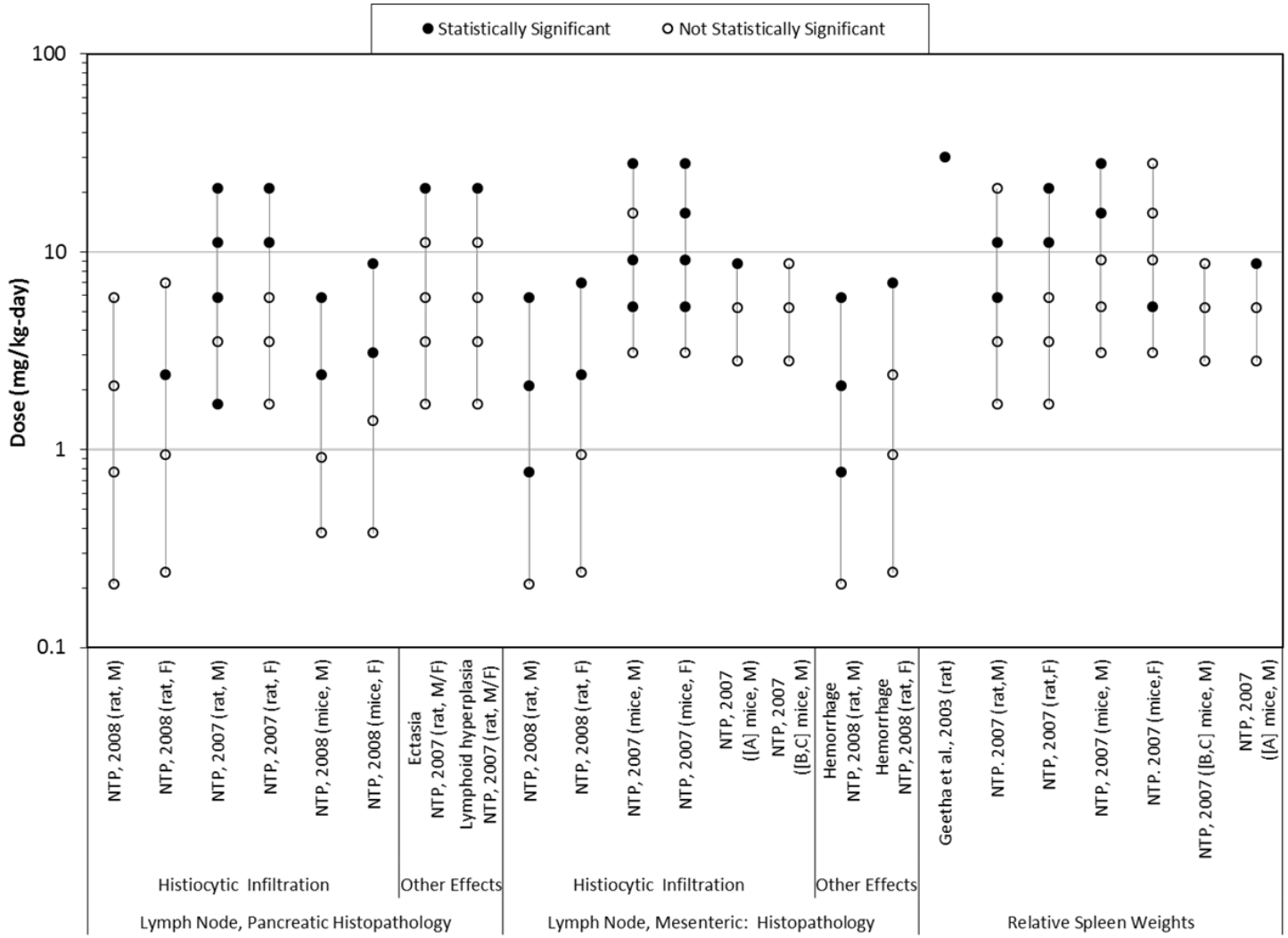

Figure 3-6. Exposure-response array of immune and lymphatic system effects following oral exposure to hexavalent chromium. [A]: am3-C57BL/6 strain of mouse; [B]: B6C3F1; [C]: BALB/c.

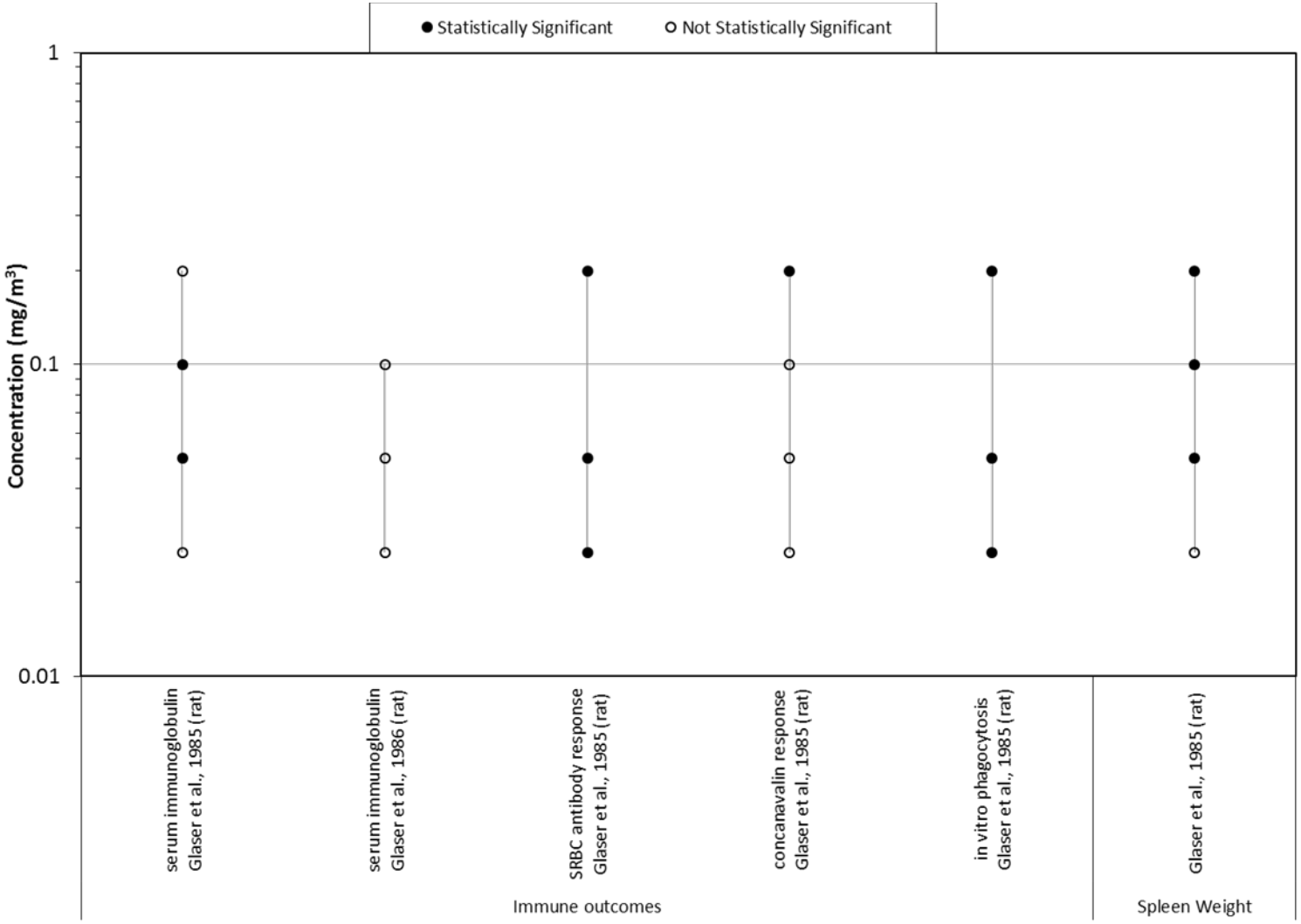

Figure 3-7. Exposure-response array of immune and lymphatic system effects following inhalation exposure to hexavalent chromium.

3.6. Hematological Effects

Table 3-5. Evidence pertaining to hematological effects following oral or inhalation exposure to hexavalent chromium

Reference and study design	Results
Oral	
NTP (2008) F344 Rat (50/sex/group) Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M) 0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Percent change from control by exposure group in males at 12 mo: mg Cr VI/kg-d / Hgb / MCV / MCH / MCHC / RBC 0 / -- / -- / -- / -- / -- 0.21 / -2.5 / -0.4 / -1.2 / -0.6 / -1.1 0.77 / -1.3 / -1.3 / -2.4* / -0.9 / 1.4 2.1 / -1.3 / -2.3* / -4.7* / -2.2* / 3.7 5.9 / -3.2* / -5.1* / -7.6* / -2.5* / 5.1* There were intermittent decreases in hematocrit and increases in reticulocytes, nucleated erythrocytes, and platelets that were resolved by 12 months. There were no consistent changes in WBCs. Hematological data not collected in female rats.

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>NTP (2007)
F344 Rat (10/sex/group)
Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d (M/F)
7 d/wk, 3 mo</td><td>Percent change from control by exposure group:
Male
<table>
<tr><th>mg Cr VI/kg-d</th><th>Hct (automated)</th><th>Hgb</th><th>RBC</th><th>Reticulocytes</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>1.7</td><td>-1.1</td><td>-0.7</td><td>1.8*</td><td>4.3</td></tr>
<tr><td>3.5</td><td>-1.5</td><td>-2.0</td><td>4.2*</td><td>-4.3</td></tr>
<tr><td>5.9</td><td>-2.4</td><td>-5.9*</td><td>14.3*</td><td>4.3</td></tr>
<tr><td>11.2</td><td>-6.3*</td><td>-13.1*</td><td>22.4*</td><td>0.0</td></tr>
<tr><td>20.9</td><td>-33.0*</td><td>-28.8*</td><td>-4.1*</td><td>34.8*</td></tr>
</table>
<table>
<tr><th>mg Cr VI/kg-d</th><th>Nucleated erythrocytes</th><th>MCV</th><th>MCH</th><th>MCHC</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>1.7</td><td>200.0</td><td>-2.9*</td><td>-2.3*</td><td>1.8</td></tr>
<tr><td>3.5</td><td>0.0</td><td>-5.4*</td><td>-6.4*</td><td>-0.9</td></tr>
<tr><td>5.9</td><td>0.0</td><td>-14.3*</td><td>-17.9*</td><td>-4.2*</td></tr>
<tr><td>11.2</td><td>100.0</td><td>-23.4*</td><td>-28.9*</td><td>-7.2*</td></tr>
<tr><td>20.9</td><td>1100.0*</td><td>-30.5*</td><td>-24.9*</td><td>8.7*</td></tr>
</table>
Female
<table>
<tr><th>mg Cr VI/kg-d</th><th>Hct (automated)</th><th>Hgb</th><th>RBC</th><th>Reticulocytes</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>1.7</td><td>3.6</td><td>1.3</td><td>3.6*</td><td>29.4*</td></tr>
<tr><td>3.5</td><td>-0.5</td><td>-2.0</td><td>1.2*</td><td>23.5*</td></tr>
<tr><td>5.9</td><td>-3.2*</td><td>-5.9*</td><td>2.0*</td><td>23.5*</td></tr>
<tr><td>11.2</td><td>-3.2*</td><td>-7.2*</td><td>7.6*</td><td>23.5*</td></tr>
<tr><td>20.9</td><td>-13.1*</td><td>-21.1*</td><td>15.9*</td><td>41.2*</td></tr>
</table>
<table>
<tr><th>mg Cr VI/kg-d</th><th>Nucleated erythrocytes</th><th>MCV</th><th>MCH</th><th>MCHC</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>1.7</td><td>-63.3</td><td>0.0</td><td>-2.7*</td><td>-2.3*</td></tr>
<tr><td>3.5</td><td>33.3</td><td>-1.7*</td><td>-3.3*</td><td>-1.7*</td></tr>
<tr><td>5.9</td><td>-33.3</td><td>-5.3*</td><td>-8.2*</td><td>-2.9*</td></tr>
<tr><td>11.2</td><td>-100.0</td><td>-9.9*</td><td>-13.6*</td><td>-4.3*</td></tr>
<tr><td>20.9</td><td>-63.3</td><td>-25.0*</td><td>-32.1*</td><td>-9.6*</td></tr>
</table>
There was also a significant increase in platelets in both males and females, but NTP stated that a platelet estimate performed on blood smears indicate that there was no increase at Week 14.</td></tr>
<tr><td>Kumar and Barthwal (1991)
Albino Rat, Male (10/group)
Gavage: 0, 50 mg Cr VI/kg-d as potassium chromate
7 d/wk, 30 d</td><td>Results presented as figures. Hemoglobin, red blood cells, and plasma corpuscular volume were statistically significantly lower in treated group compared to control at 30 days. White blood cells in treated animals were lower than controls but the measurement did not achieve statistical significance.</td></tr>
</table>

Reference and study design	Results
Krim et al. (2013) Wistar Rat, Male (10/group) Gavage: 0, 15 mg/kg as potassium dichromate 7 d/wk, 30 d	Percent change from control by exposure group: mg/kg potassium dichromate: RBC: Hgb: Hct: MCV 0: -- : -- : -- : -- 15: -25* : -15* : -32* : -9* There were no significant changes in WBC, MCHC, or platelets.
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse, Male (5–10/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2 or 8.7 mg Cr VI/kg-d (M) 7 d/wk, 3 mo Strain Comparison Study	Percent change from control by exposure group for MCH at 3 mo: mg Cr VI/kg-d: B6C3F1: BALB/c: am3-C57BL/6 0: -- : -- : -- 2.8: -3* : -3* : -2* 5.2: -4* : -5* : -4* 8.7: -7* : -7* : -6* Percent change from control by exposure group for MCV at 3 mo: mg Cr VI/kg-d: B6C3F1: BALB/c: am3-C57BL/6 0: -- : -- : -- 2.8: -2* : -2* : -3 5.2: -3 : -4 : -5* 8.7: -6 : -5 : -12
NTP (1996a) BALB/c Mouse (24 males or 48 females/group, 5–6 males or 12 females/group per timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.1, 3.5, 7.4, 32.5 mg Cr VI/kg-d (M) 0, 1.8, 5.6, 12.0, 48.4 mg Cr VI/kg-d (F) Sacrificed at 3, 6, 9 wk of treatment or after 8-wk recovery period	Percent change from control by exposure group: Male mg Cr VI/kg-d: MCV at 9 weeks 0: -- 1.1: -1.4 3.5: -1.2 7.4: -2.1 32.5: -4.3* Female mg Cr VI/kg-d: MCV at 9 weeks 0: -- 1.8: 0.0 5.6: 0.2 12.0: -1.0 48.4: -2.0* MCH was significantly decreased in males but not females at Week 9. There were no other significant changes in hematology parameters ay Week 9. The MCV resolved after the 8-week recovery period in females, but was increased in males.

Reference and study design	Results
NTP (2007) B6C3F1 Mouse (10/sex/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d (M/F) 7 d/wk, 3 mo	Percent change from control by exposure group: Male mg Cr VI/kg-d / MCV / MCH / Hgb 0 / -- / -- / -- 3.1 / -1.8* / -2.0* / -4.9 5.3 / -3.6* / -3.3* / 0 9.1 / -4.9* / -4.6* / -3.1 15.7 / -5.6* / -5.9* / -4.3 27.9 / -7.3* / -7.8* / -5.5 Female mg Cr VI/kg-d / MCV / MCH / Hgb 0 / -- / -- / -- 3.1 / -0.9 / -1.3* / -1.3 5.3 / -1.9* / -3.2* / 0.6 9.1 / -3.9* / -5.7* / -0.6 15.7 / -5.8* / -7.6* / -3.2* 27.9 / -7.3* / -9.5* / -4.5* There were no significant changes in hematocrit, RBCs, nucleated erythrocytes, platelets, or WBCs in either males or females. Females had a slight but significant decrease in MCHC that was not observed in males.
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F); equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Percent change from control by exposure group: Female mg Cr VI/kg-d / RBC / MCV / MCH 0 / -- / -- / -- 0.38 / 1.5 / 0.0 / 1.3 1.4 / 2.0 / -1.3 / 0.0 3.1 / 3.9* / -3.6* / -2.6* 8.7 / 7.5* / -6.4* / -7.1* There were intermittent increases in WBC and decreases in MCHC that were resolved by 12 months. No changes were observed in hemoglobin, reticulocytes, or nucleated erythrocytes. There was a decrease in platelets observed only after 12 months. Hematological data not collected in male mice.
Shrivastava et al. (2005) Swiss Mouse, sex not specified (12–24/group) Water: 0, 250 ppm as potassium dichromate; equivalent to 0, 14.8 mg/kg-d 9 wk	Percent change from control by exposure group: mg Cr VI/kg-d / 3 wk: platelets / 9 wk: platelets 0 / -- / -- 14.8 / 68* / 99* WBCs were significantly decreased at 3 wk, but not at 6 or 9 wk; RBCs were significantly increased at 3 wk, but not at 6 or 9 wk; at 9 wk there was a significant decrease in MCV and significant increase in Hgb and Hct, but no change in MCHC.

Reference and study design	Results
Inhalation	
Glaser et al. (1990) Wistar Rat, Male (10/group) 0, 0.050, 0.10, 0.20, 0.40 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 30 d, 90 d, or 90 d with 30 d recovery Generation method (cyclone nebulizer), analytical concentration, and MMD reported; analytical method not reported.	Percent change from control for leukocytes in blood (10^9/L) by exposure group: mg/m^3 — 30 d — 90 d — 90 d with 30 d recovery 0 — -- — -- — -- 0.05 — 83.9* — -84.3* — -11.2 0.10 — 87.5* — 70.4* — -5.6 0.20 — 132.1* — 255.6* — 3.4 0.40 — 248.2* — 374.1* — 27.0
Glaser et al. (1985) Wistar Rat, Male (10/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), analytical concentration, and MMD reported. Related reference: Glaser et al. (1988)	Authors state that red and white blood cell counts were not affected but data were not provided.
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Percent change from control by exposure group: Group — 17-18 mo: leukocyte count Control (0 mg/m^3) — -- Cr_5O_{12} (0.1 mg/m^3) — 35.6* Authors stated that there were no statistically significant differences in hematological parameters between the controls and $Na_2Cr_2O_7$-exposed groups, no data provided. Authors note statistically significant increases in red blood cell count, hematocrit, and blood hemoglobin levels in the Cr_5O_{12}-exposed group at 27 mo but no data were provided.

Reference and study design	Results			
Kim et al. (2004) Sprague-Dawley Rat, Male (5/group) 0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber) 6 hr/d, 5 d/wk 90 d Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.	Percent change from control by exposure group:			
	mg/m^3	Hgb	Hct	Mean RBC count
	0	--	--	--
	0.2	-5.3	-8.2*	-3.4
	0.5	-6*	-6.8	-4.6
	1.25	-7.9*	-11*	-8*
	No statistically significant effects on WBC, MCV, MVHC, or platelets.			

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

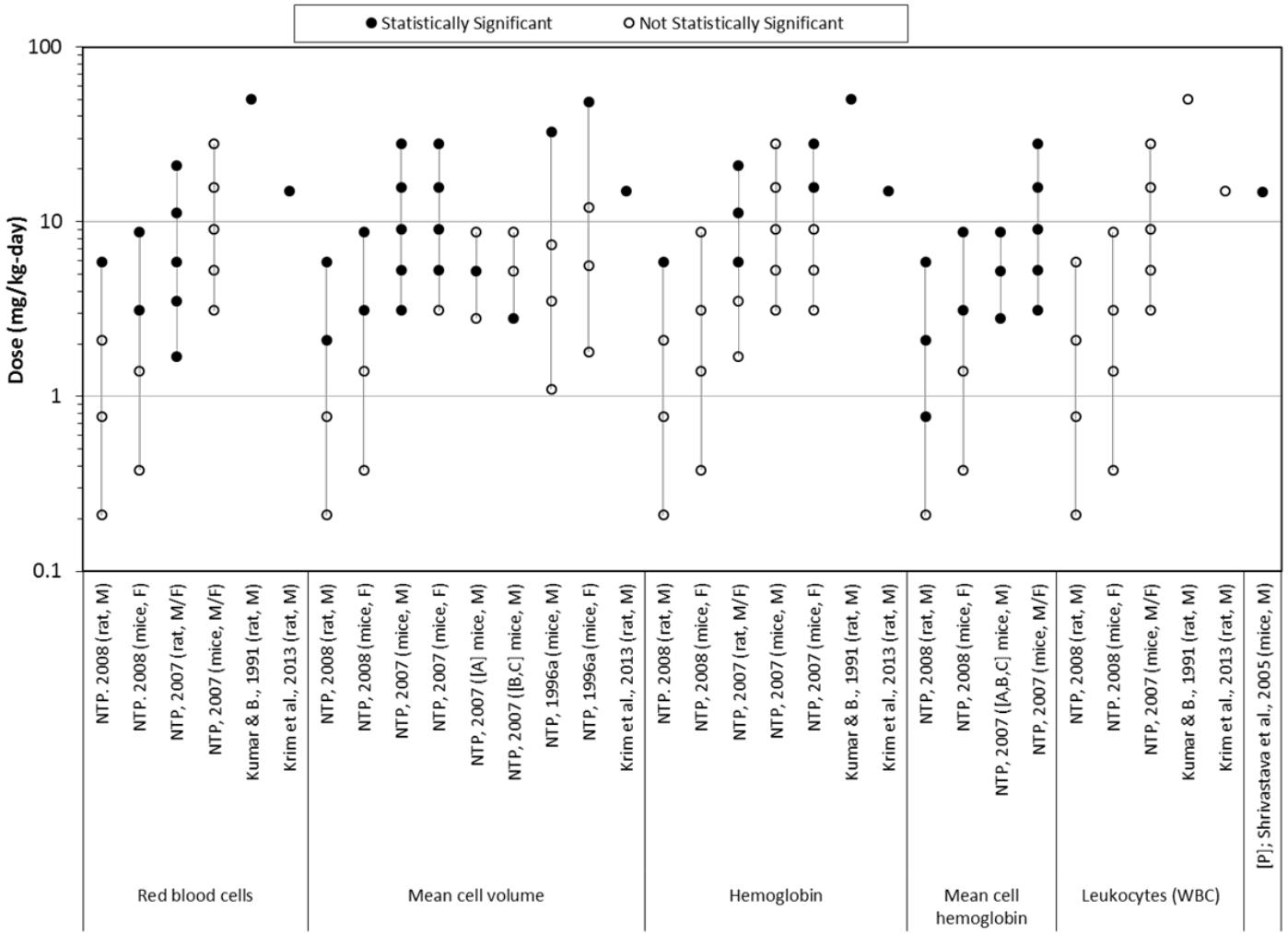

Figure 3-8. Exposure-response array of hematological effects following oral exposure to hexavalent chromium. [Kumar & B., 1991] denotes Kumar and Barthwal (1991). [A]: am3-C57BL/6 strain of mouse; [B]: B6C3F1; [C]: BALB/c.

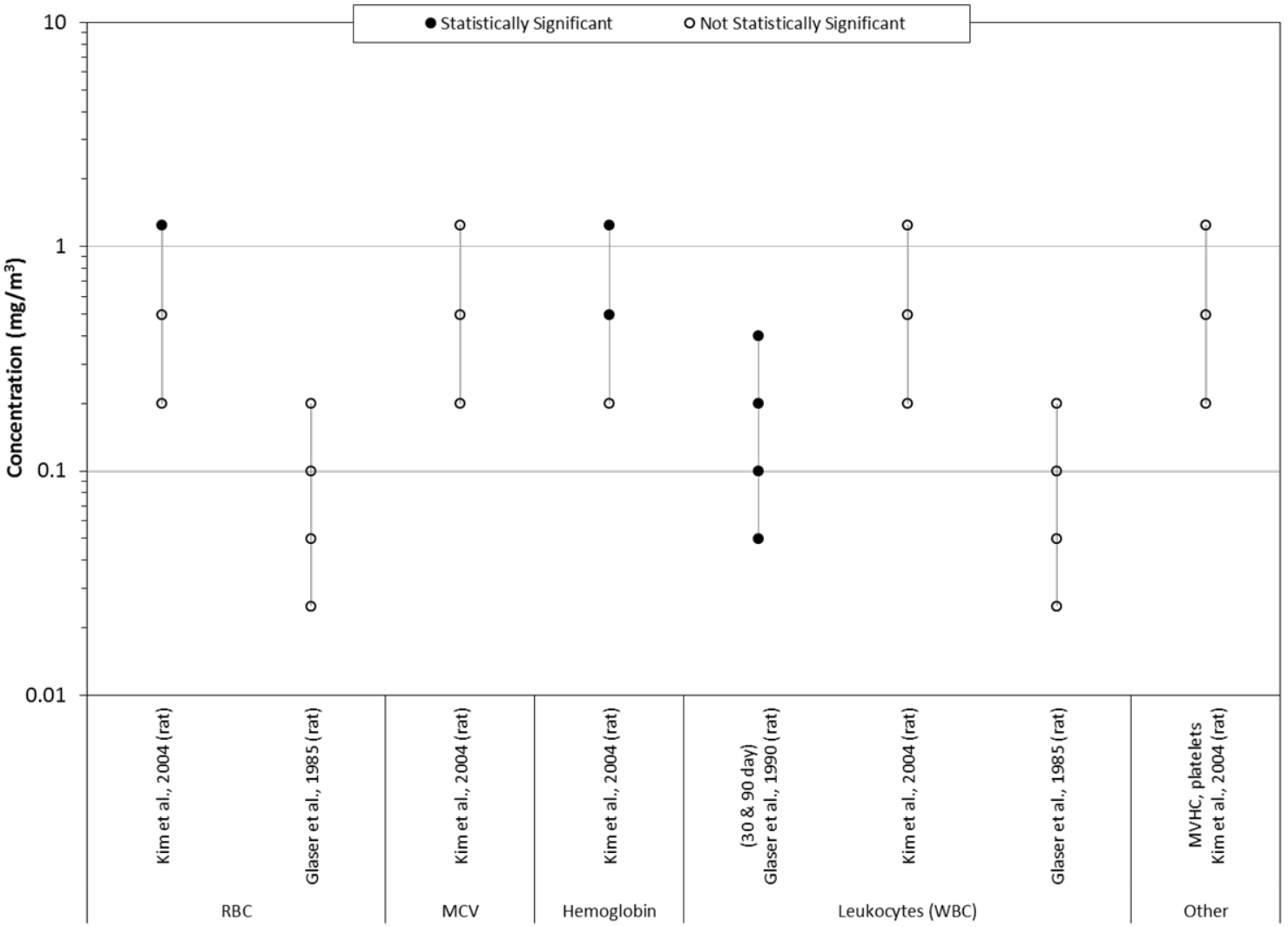

Figure 3-9. Exposure-response array of hematological effects following inhalation exposure to hexavalent chromium.

3.7. Male Reproductive Effects

Table 3-6. Evidence pertaining to male reproductive effects following oral or inhalation exposure to hexavalent chromium

Reference and study design	Results
Male Reproductive Organ Weights – Oral	
NTP (2007) F344 Rat (10 males/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d 7 d/wk, 3 mo	No statistically significant effects observed on absolute male testis weight.
Chowdhury and Mitra (1995) Charles Foster Rat (10 males/group) Gavage: 0, 20, 40, 60 mg Cr VI/kg-d; administered as sodium dichromate 7 d/wk, 90 d	Percent change from control by exposure group: mg Cr VI/kg-d — Testis: absolute weight 0 — -- 20 — -2.7 40 — -27.7* 60 — -35.0*
NTP (1996b) Sprague-Dawley Rat (24 males/group; 6 males/group/timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 0.35, 1.1, 2.1, 8.5 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed on male testis weight.
NTP (2007) B6C3F1 Mouse (10 males/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg Cr VI/kg-d 7 d/wk, 3 mo	No statistically significant effects observed on male absolute testis weight.
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse (5–10 males/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2 or 8.7 mg Cr VI/kg-d 7 d/wk, 3 mo Strain Comparison Study	No treatment-related effects were observed for weights of left cauda, left epididymis, and left testis weight; the statistically significant (11%) decrease observed in the absolute testes weight of am3-C57BL/6 mice was attributed to a 36% decrease in body weight.

Reference and study design	Results
NTP (1997) BALB/c Mouse (20 males/group) Continuous Breeding Protocol: F0 animals exposed for 13 wks total, 1 wk prior to and 12 wks during cohabitation. After cohabitation, F0 breeding pairs were separated and continued on study diets. Diet: 0, 100, 200, 400 ppm potassium dichromate (equivalent to 0, 17.6, 35.3, 141.2 ppm Cr VI) (F0): 0, 19.4, 38.6, 85.7 mg potassium dichromate/kg-d (equivalent to 0, 6.8, 13.6, 30.3 mg Cr VI/kg-d) (F1): 0, 22.4, 45.5, 104.9 mg potassium dichromate/kg-d (equivalent to 0, 7.9, 16.1, 37.1 mg Cr VI/kg-d)	No effects on F0 reproductive organ weights (right testis weight, right epididymis weight, right cauda epididymis weight, prostate weight, seminal vesicle weight). No statistically significant effects on F1 reproductive organ weights (right testis weight, right epididymis weight, right cauda epididymis weight, prostate weight, seminal vesicle weight). Treatment-related decrease in maternal weights at delivery reported for some of the litters.[a] No treatment-related differences reported in pregnancy index.
NTP (1996a) BALB/c Mouse (24 males/group, 5–6 males/group per timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.1, 3.5, 7.4, 32.5 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed on male testis weight.
Zahid et al. (1990) BALB/c Mouse (7 males/group) Diet: 0, 100, 200, 400 mg potassium dichromate/kg diet equivalent to 0, 6.4, 12.7, 25.5 mg CrVI/kg-d (calculated) 35 d	Testes and epididymis weights were stated to be comparable across all treatment groups but data were not provided.
Yousef et al. (2006) New Zealand White Rabbit (6 males/group) Gavage: 0, 5 mg potassium dichromate/kg-d; equivalent to 0, 3.6 mg Cr VI/kg-d 7 d/wk, 10 wk	Percent change from control by exposure group: mg Cr VI/kg-d — Testis: relative weight — Epididymis: relative weight 0 — -- — -- 3.6 — -22.2* — -22.2*

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Testis: Weight – Inhalation</td></tr>
<tr><td>Glaser et al. (1986)
Wistar Rat (40 males/control, 20 males/treatment group)
0, 0.025, 0.05, 0.1 mg Cr VI/m^3 as sodium dichromate ($Na_2Cr_2O_7$); 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber)
22 hr/d, 7 d/wk
72 wk
Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.</td><td>Authors stated no statistically significant effects observed but data were not provided.</td></tr>
<tr><td>Kim et al. (2004)
Sprague-Dawley Rat (5 males/group)
0, 0.2, 0.5, 1.25 mg/m^3 as CrO_3 (dynamic whole-body chamber)
6 hr/d, 5 d/wk
91 d
Generation method (mist generator), analytical method (gravimetric filter, flame atomic absorption spectrophotometry), and analytical concentration reported; MMAD not reported.</td><td>There were no statistically significant changes in relative testes weights.</td></tr>
<tr><td colspan="2">Male Reproductive Organ Histopathology – Oral</td></tr>
<tr><td>Chowdhury and Mitra (1995)
Charles Foster Rat (10 males/group)
Gavage: 0, 20, 40, 60 mg Cr VI/kg-d; administered as sodium dichromate
7 d/wk, 90 d</td><td>Percent change from control by exposure group for testis endpoints:
<table>
<tr><th>mg Cr VI/kg-d</th><th>Seminiferous tubular diameter</th><th>Stage-7 spermatid</th><th>Leydig cell population - entry 1</th><th>Leydig cell population - entry 2</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>20</td><td>-0.8</td><td>-0.2</td><td>-3.7</td><td>0</td></tr>
<tr><td>40</td><td>-10.8*</td><td>-19.5*</td><td>-21.4*</td><td>-12.1*</td></tr>
<tr><td>60</td><td>-15.3*</td><td>-45*</td><td>-37.3*</td><td>-19.7*</td></tr>
</table>
<table>
<tr><th>mg Cr VI/kg-d</th><th>Pachytene spermatocyte</th><th>Resting spermatocyte</th><th>Spermato-gonia</th></tr>
<tr><td>0</td><td>--</td><td>--</td><td>--</td></tr>
<tr><td>20</td><td>-3.6</td><td>-2.3</td><td>-1</td></tr>
<tr><td>40</td><td>-25.7*</td><td>-3.3</td><td>-0.8</td></tr>
<tr><td>60</td><td>-28*</td><td>-5*</td><td>-0.6</td></tr>
</table>
Study authors provided two separate entries for leydig cell population.</td></tr>
</table>

Reference and study design	Results
NTP (2007) F344 Rat (10 males/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d 7 d/wk, 3 mo	No statistically significant effects observed upon microscopic examination of testis.
NTP (1996a) BALB/c Mouse (24 males/group, 5–6 males/group per timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.1, 3.5, 7.4, 32.5 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed on male reproductive organ histopathology (testes and epididymis examined for Sertoli nuclei and preleptotene spermatocyte counts in Stage X or XI tubules; sperm analyzed for chromatin structure).
Zahid et al. (1990) BALB/c Mouse (7 males/group) Diet: 0, 100, 200, 400 mg potassium dichromate/kg diet equivalent to 0, 6.4, 12.7, 25.5 mg CrVI/kg-d (calculated) 35 d	mg Cr VI/kg-d: 0; 6.4; 12.7; 25.5 Degenerated tubules (incidence (%)): 0/1400 (0); 21/1774 (1.2)*; 26/1129 (2.3)*; 33/1372 (2.4)* Undegenerated tubules without spermatogonia (incidence (%)): 18/90 (20); 45/90 (50)*; 54/90 (60)*; 81/90 (90)* Spermatogonia (% change): --; -80*; -89*; -95* Resting spermatocytes (% change): --; 159*; 151*; 192*
Male Reproductive Organ Histopathology – Inhalation	
Glaser et al. (1985) Wistar (TNO-W-74) Rat (10 males/group) 0, 0.025, 0.050, 0.100, 0.200 mg Cr VI/m^3 as $Na_2Cr_2O_7$ aerosol exposure (dynamic whole-body chamber) 22 hr/d, 7 d/wk 28 d and 90 d Generation method (jet nebulizer and cyclone), analytical method (atomic absorption spectrometry; gravimetric filter), concentration, and MMD reported. Related reference: Glaser et al. (1988)	No statistically significant effects observed.
Sperm and Reproductive Parameters – Oral	
Li et al. (2001) Wistar Rat (8–11 males/group) Gavage: 0, 10, 20 mg CrO_3/kg-d; equivalent to 0, 5.2, 10.4 mg Cr VI/kg-d 6 d (sacrificed after 6 wk)	Percent change from control by exposure group: mg Cr VI/kg-d: 0; 5.2; 10.4 Sperm count: --; -75.5*; -80* Sperm abnormality: --; 142.9*; 176.4*

Reference and study design	Results
NTP (2007) B6C3F1, BALB/c, am3-C57BL/6 Mouse (5–10 males/group) Water: 0, 62.5, 125, 250 ppm sodium dichromate dihydrate; equivalent to 0, 2.8, 5.2 or 8.7 mg Cr VI/kg-d (M) 7 d/wk, 3 mo Strain Comparison Study	No treatment-related effects were observed for spermatids per testis and per mg testis, spermatids per cauda and per mg cauda, sperm motility.
NTP (1997) BALB/c Mouse (20 males/group) Continuous Breeding Protocol: F0 animals exposed for 13 wks total, 1 wk prior to and 12 wks during cohabitation. After cohabitation, F0 breeding pairs were separated and continued on study diets. Diet: 0, 100, 200, 400 ppm potassium dichromate (equivalent to 0, 17.6, 35.3, 141.2 ppm Cr VI) (F0): 0, 19.4, 38.6, 85.7 mg potassium dichromate/kg-d (equivalent to 0, 6.8, 13.6, 30.3 mg Cr VI/kg-d) (F1): 0, 22.4, 45.5, 104.9 mg potassium dichromate/kg-d (equivalent to 0, 7.9, 16.1, 37.1 mg Cr VI/kg-d)	No statistically significant effects on F0 sperm parameters (vas deferens sperm motion data, epididymal sperm density, epididymal sperm morphology, number of spermatids per mg testis, total number of sperm heads per testis). No statistically significant effects on F1 sperm parameters (vas deferens sperm motion data, epididymal sperm density, epididymal sperm morphology, number of spermatids per mg testis, total number of sperm heads per testis). Treatment-related decrease in maternal weights at delivery reported for some of the litters.[a] No treatment-related differences reported in pregnancy index.
NTP (1996a) BALB/c Mouse (24 males/group, 5–6 males/group per timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.1, 3.5, 7.4, 32.5 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed on Sertoli nuclei and preleptotene spermatocyte counts in Stage X or XI tubules or chromatin structure of sperm.
Zahid et al. (1990) BALB/c Mouse (7 males/group) Diet: 0, 100, 200, 400 mg potassium dichromate/kg diet equivalent to 0, 6.4, 12.7, 25.5 mg CrVI/kg-d (calculated) 35 d	mg Cr VI/kg-d / Sperm count (% change) / Abnormal sperm/number sperm examined (incidence (%)) 0 / -- / 385/3193 (12.1) 6.4 / -44 / 165/1242 (13.3) 12.7 / -56* / 304/1607 (18.9)* 25.5 / -57* / 318/1296 (24.5)*

Reference and study design	Results
Yousef et al. (2006) New Zealand White Rabbit (6 males/group) Gavage: 0, 5 mg potassium dichromate/kg-d; equivalent to 0, 3.6 mg Cr VI/kg-d 7 d/wk, 10 wk	Percent change from control by exposure group: mg Cr VI/kg-d / Seminal fluid pH / Packed sperm volume / Sperm concentration / Total sperm output / Sperm motility 0 / -- / -- / -- / -- / -- 3.6 / 4.1* / -9.9* / -18* / -26* / -4.6* mg Cr VI/kg-d / Total motile sperm per ejaculation / Dead sperm / Normal sperm / Total functional sperm fraction 0 / -- / -- / -- / -- 3.6 / -34* / 24* / -3.5* / -37*
Hormone Changes – Oral	
Chowdhury and Mitra (1995) Charles Foster Rat (10 males/group) Gavage: 0, 20, 40, 60 mg Cr VI/kg-d; administered as sodium dichromate 7 d/wk, 90 d	Percent change from control by exposure group: mg Cr VI/kg-d / Serum testosterone 0 / -- 20 / -31.3* 40 / -31.3* 60 / -46.9*
Yousef et al. (2006) New Zealand White Rabbit (6 males/group) Gavage: 0, 5 mg potassium dichromate/kg-d; equivalent to 0, 3.6 mg Cr VI/kg-d 7 d/wk, 10 wk	Percent change from control by exposure group: mg Cr VI/kg-d / Serum testosterone 0 / -- 3.6 / -20.8*
Changes in Reaction Time to Mounting – Oral	
Yousef et al. (2006) New Zealand White Rabbit (6 males/group) Gavage: 0, 5 mg potassium dichromate/kg-d; equivalent to 0, 3.6 mg Cr VI/kg-d 7 d/wk, 10 wk	Percent change from control by exposure group: mg Cr VI/kg-d / Reaction time 0 / -- 3.6 / 110*

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

[a] NTP (1997) maternal body weight at delivery (percent change from control):

Mg Cr VI/kg-d	Litter 1	Litter 2	Litter 3	Litter 4	Litter 5
0	--	--	--	--	--
6.8	1	1	-2	-2	-4
13.6	5*	4	4	2	3
30.3	5*	7*	5*	5	4

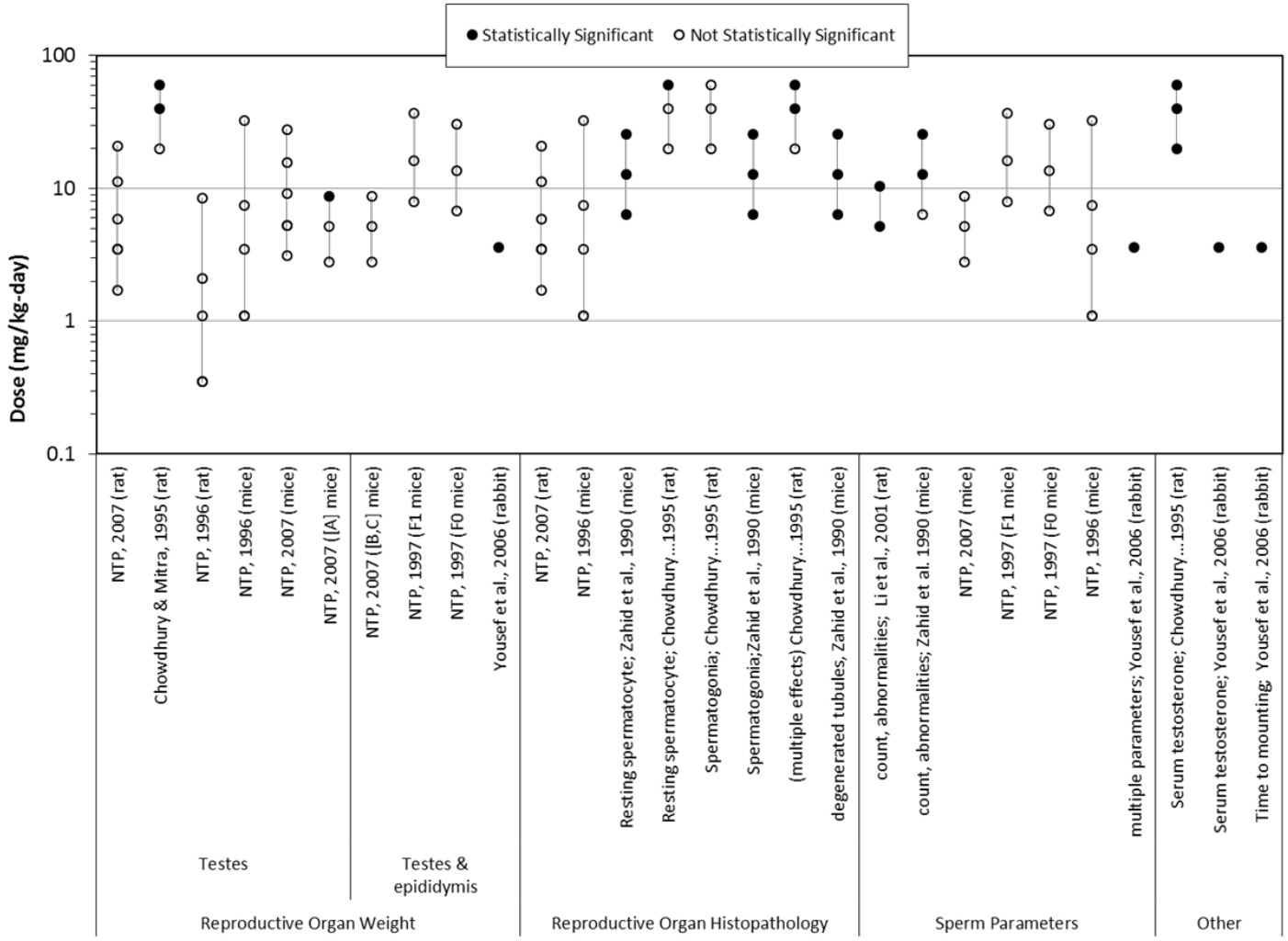

Figure 3-10. Exposure-response array of male reproductive effects following oral exposure to hexavalent chromium. [Chowdhury...1995] denotes Chowdhury & Mitra, 1995. [A]: am3-C57BL/6 strain of mouse; [B]: B6C3F1; [C]: BALB/c.

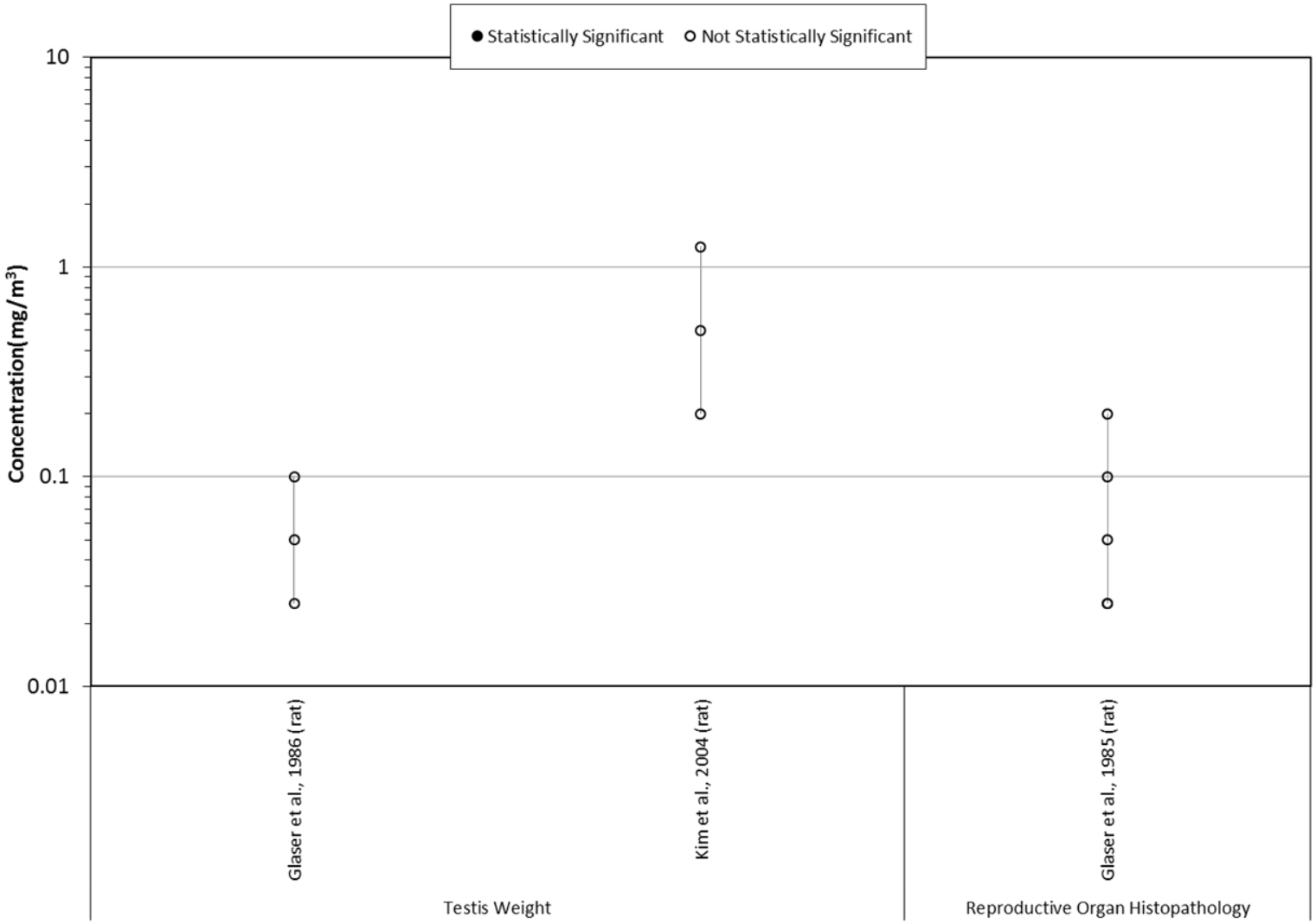

Figure 3-11. Exposure-response array of male reproductive effects following inhalation exposure to hexavalent chromium.

3.8. Female Reproductive Effects

Table 3-7. Evidence pertaining to female reproductive organ effects following oral exposure to hexavalent chromium

Reference and study design	Results
Ovarian Effects	
NTP (1996b) Sprague-Dawley Rat (48 females/group; 12 females/group/timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 0.35, 1.1, 2.5, 9.9 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed upon microscopic examination of ovaries.
NTP (2007) F344 Rat (10 females/group) Water: 0, 62.5, 125, 250, 500, 1,000 ppm sodium dichromate dihydrate; equivalent to 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg Cr VI/kg-d 7 d/wk, 3 mo	No statistically significant effects observed upon microscopic examination of ovaries.
NTP (1996a) BALB/c Mouse (48 females/group, 12 females/group/timepoint) Diet: 0, 15, 50, 100, 400 ppm potassium dichromate; equivalent to 0, 1.8, 5.6, 12.0, 48.4 mg Cr VI/kg-d Sacrificed after 3, 6, 9 wks of treatment or after 8-wk recovery period	No statistically significant effects observed upon microscopic examination of ovaries.
NTP (1997) BALB/c Mouse (20 females/group) Continuous Breeding Protocol: F0 animals exposed for 13 wks total, 1 wk prior to and 12 wks during cohabitation. After cohabitation, F0 breeding pairs were separated and continued on study diets. 0, 100, 200, 400 ppm potassium dichromate (equivalent to 0, 17.6, 35.3, 141.2 ppm Cr VI) (F0): 0, 19.4, 38.6, 85.7 mg potassium dichromate/kg-d (equivalent to 0, 6.8, 13.6, 30.3 mg Cr VI/kg-d) Lactating F (F0): 0, 32.8, 69.0, 143.1 mg potassium dichromate/kg-d (equivalent to 0, 11.6, 24.4, 50.5 mg Cr VI/kg-d) (F1): 0, 22.4, 45.5, 104.9 mg potassium dichromate/kg-d (equivalent to 0, 7.9, 16.1, 37.1 mg Cr VI/kg-d)	No statistically significant effects on F0 or F1 ovarian weight. Treatment-related decrease in maternal weights at delivery reported for some of the litters.[a] No treatment-related differences reported in pregnancy index.

Reference and study design	Results
Murthy et al. (1996) Swiss Albino Mouse (30 females/group in the 20-d study; 10 females/group in the 90-d study) Water: 0, 250, 500, 750 mg Cr VI/L (as potassium dichromate) in the 20-d study; equivalent to 0, 64, 128, 192 mg Cr VI/kg-d 0, 0.05, 0.5, 5 mg Cr VI/L (as potassium dichromate) in the 90-d study; equivalent to 0, 0.0128, 0.128, 1.28 mg Cr VI/kg-d 7 d/wk, 20 or 90 d	Percent change from control by exposure group at 20 d: mg Cr VI/kg-d | Number of small follicles | Number of large follicles | Number of medium follicles | Ovarian response to gonadotropin | Duration of estrous cycle 0 | -- | -- | -- | -- | -- 64 | -8.1 | -13.2* | -22.4* | -3.1 | 6.8 128 | -13.7* | -31.6* | -36.7* | -29.8* | 31.8 192 | -36* | -68.4* | -53.1* | -90.8* | 75* Quantitative data not provided for 90-day study.
Reproductive Performance	
NTP (1997) BALB/c Mouse (20 females/group) Continuous Breeding Protocol: F0 animals exposed for 13 wks total, 1 wk prior to and 12 wks during cohabitation. After cohabitation, F0 breeding pairs were separated and continued on study diets. 0, 100, 200, 400 ppm potassium dichromate (equivalent to 0, 17.6, 35.3, 141.2 ppm Cr VI) (F0): 0, 19.4, 38.6, 85.7 mg potassium dichromate/kg-d (equivalent to 0, 6.8, 13.6, 30.3 mg Cr VI/kg-d) Lactating F (F0): 0, 32.8, 69.0, 143.1 mg potassium dichromate/kg-d (equivalent to 0, 11.6, 24.4, 50.5 mg Cr VI/kg-d) (F1): 0, 22.4, 45.5, 104.9 mg potassium dichromate/kg-d (equivalent to 0, 7.9, 16.1, 37.1 mg Cr VI/kg-d)	No significant effects on F0 reproductive parameters (average litters per pair, average live pups per litter, proportion of pups born alive, adjusted live pup weight, cumulative days to litter). No significant effects on F1 reproductive parameters (mating index, pregnancy index, fertility index, live pups per litter, proportion of pups born alive, adjusted live pup weight, gestation length, estrous cycle length). Treatment-related decrease in maternal weights at delivery reported for some of the litters.[a] No treatment-related differences reported in pregnancy index.

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

[a] NTP (1997) maternal body weight at delivery (percent change from control):

Mg Cr VI/kg-d	Litter 1	Litter 2	Litter 3	Litter 4	Litter 5
0	--	--	--	--	--
6.8	1	1	-2	-2	-4
13.6	5*	4	4	2	3
30.3	5*	7*	5*	5	4

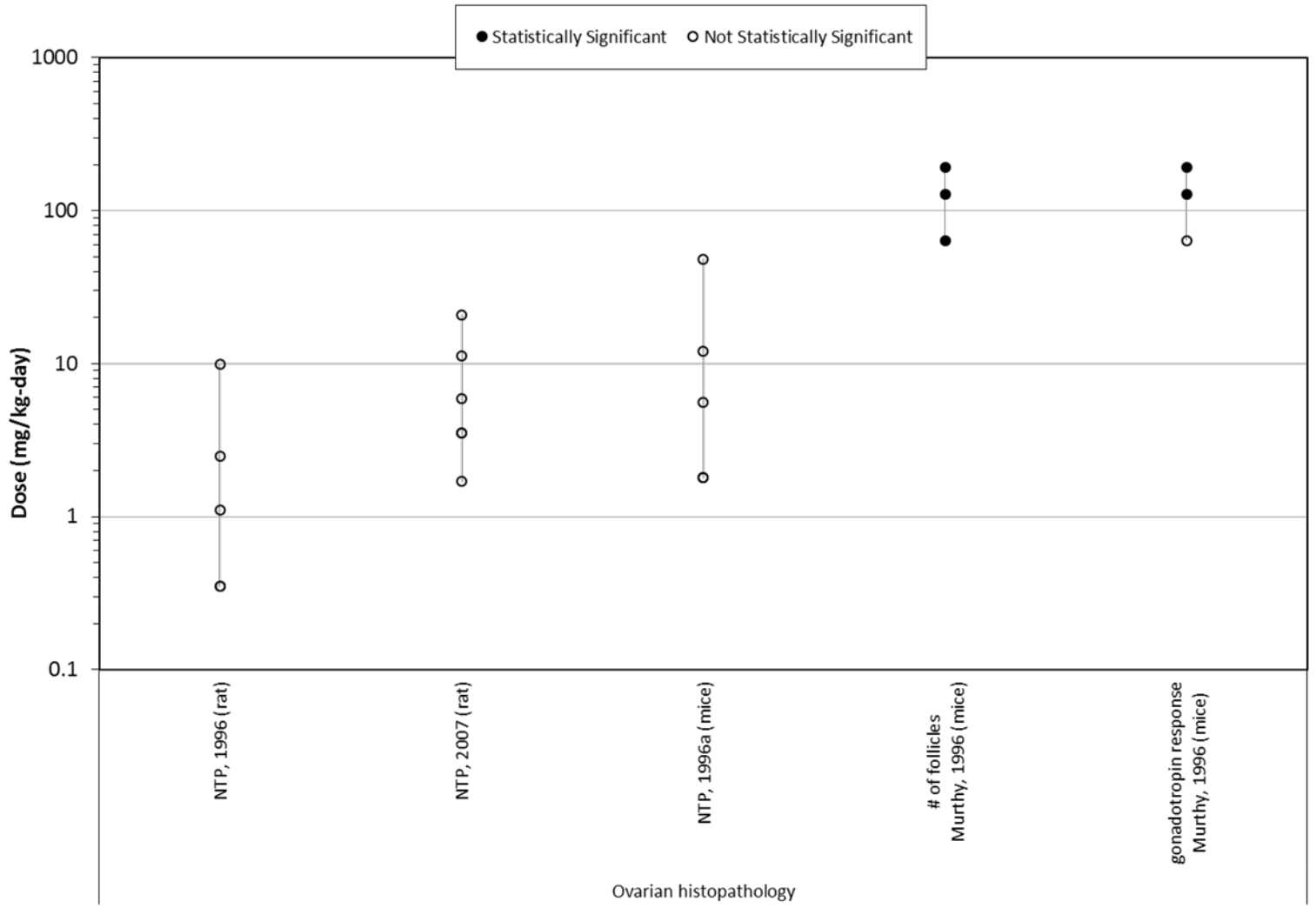

Figure 3-12. Exposure-response array of female reproductive organ effects following oral exposure to hexavalent chromium.

3.9. Reproductive and Fetal Outcomes – Dosing Prior to Gestation

Table 3-8. Evidence pertaining to reproductive/fetal outcomes resulting from oral dosing prior to gestation

Reference and study design	Results
Implantation Loss, Number of Implants, and Number of Corpora Lutea	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percent change from control by exposure group: mg Cr VI/kg-d | % Pre-implantation loss | % Post-implantation loss | Number of implantations | Number of corpora lutea 0 | -- | -- | -- | -- 70 | 103* | 127* | -15.4 | -8.95 127 | 176* | 281* | -30.2* | -20.7* 170 | 214* | 323* | -42.0* | -32.1* Treatment-related decrease in maternal weight gain reported.[a]
Resorptions	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percent change from control by exposure group: mg Cr VI/kg-d | Resorptions 0 | -- 70 | 92 127 | 166* 170 | 215* Treatment-related decrease in maternal weight gain reported.[a]
Estrous Cycle Length	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percent change from control by exposure group: mg Cr VI/kg-d | Postpartum estrous cycle length 0 | -- 70 | 24 127 | 40* 170 | 68* Treatment-related decrease in maternal weight gain reported.[a]

Reference and study design	Results
Number of Live Fetuses	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percent change from control by exposure group: mg Cr VI/kg-d — Live fetuses per litter 0 — -- 70 — -22 127 — -41* 170 — -55* Treatment-related decrease in maternal weight gain reported.[a]
Fetal Body Weight and Length	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percent change from control by exposure group: mg Cr VI/kg-d — Fetal weight — Fetal crown-rump length 0 — -- — -- 70 — -21* — -14 127 — -30* — -25* 170 — -37* — -28* Treatment-related decrease in maternal weight gain reported.[a]
Fetal Gross External Abnormalities	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percentage of total pups observed with abnormality: mg Cr VI/kg-d — Drooping wrist — Subdermal hemorrhagic patches — Kinky tail — Short tail 0 — 0 — 0 — 0 — 0 70 — 5* — 8* — 0 — 0 127 — 15* — 17* — 11* — 13* 170 — 28* — 24* — 20* — 48* Treatment-related decrease in maternal weight gain reported.[a]
Fetal Skeletal Abnormalities	
Kanojia et al. (1998) Druckrey Rat, Female (10/group) Water: 0, 70, 127, 170 mg Cr VI/kg-d 3 mo prior to gestation	Percentage of total pups observed with abnormality: mg Cr VI/kg-d — Reduced parietal ossification — Reduced interparietal ossification — Reduced caudal ossification 0 — 0 — 0 — 12 70 — 0 — 0 — 25* 127 — 24* — 28* — 59* 170 — 50* — 45* — 91* Treatment-related decrease in maternal weight gain reported.[a]

*Significantly different from control (p<0.05) as calculated by study authors.
Unless otherwise noted, results shown are percent change from control calculated as (Treated – Control) ÷ Control × 100.

[a] Kanojia et al. (1998) maternal body weight gain (percent change from control):

mg Cr VI/kg-d	Maternal body weight gain at end of treatment
0	--
70	-8
12	-18*
170	-24*

3.10. Reproductive and Fetal Outcomes – Dosing During Gestation Only

Table 3-9. Evidence pertaining to reproductive/fetal outcomes resulting from oral dosing during gestation only

Reference and study design	Results
Number of Pregnancies	
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10 /group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 1–3	mg Cr VI/kg-d — Incidence of pregnancy 0 — 10/10 35 — 0/10* Maternal toxicity not evaluated.
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 4–6	mg Cr VI/kg-d — Incidence of pregnancy 0 — 9/10 35 — 7/10 Maternal toxicity not evaluated.
Implantation Loss, Number of Implants, and Number of Corpora Lutea	
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 1–3	mg Cr VI/kg-d — Number of implants (mean±SD) 0 — 8.20±1.68 35 — 0* Maternal toxicity not evaluated.
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 4–6	mg Cr VI/kg-d — Number of implants (mean±SD) 0 — 9.22±2.06 35 — 7.50±2.97 Maternal toxicity not evaluated.
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	mg Cr VI/kg-d — Number of preimplantation losses/litter (mean±SE) — Number of postmplantation losses/litter (mean±SE) 0 — 0 — 0 7.9 — 2.1±0.36* — 1.5±0.34* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	mg Cr VI/kg-d — % Postimplantation loss (mean±SE) 0 — 4.32±2.34 53 — 10.60±2.11 101 — 21.93±3.96* 152 — 34.60±2.54* No statistically significant change in the number of corpora lutea observed. Treatment-related decrease in maternal weight gain reported.[b]

Reference and study design	Results
Junaid et al. (1995) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 14–19	mg Cr VI/kg-d — % Postimplantation loss (mean±SE) 0 — 0 53 — 3.51±2.30 101 — 18.80±3.85* 152 — 27.30±2.82* No statistically significant change in the number of corpora lutea, resorptions, or fetuses per litter observed. Treatment-related decrease in maternal weight gain reported.[c]
Number of Resorptions	
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 1–3	mg Cr VI/kg-d — Number of resorptions/total implantations 0 — 0/82 35 — 0 Maternal toxicity not evaluated.
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 4–6	mg Cr VI/kg-d — Number of resorptions/total implantations (%) 0 — 2/83 (2.4) 35 — 41/53 (77.3)* Maternal toxicity not evaluated.
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	mg Cr VI/kg-d — Number of resorptions/litter (mean±SE) 0 — 0 7.9 — 1.2±0.13* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	mg Cr VI/kg-d — Number of resorption sites (mean±SE) 0 — 0.30±0.21 53 — 1.00±0.21* 101 — 1.70±0.3* 152 — 2.30±0.273* Treatment-related decrease in maternal weight gain reported.[b]
Fetal Viability	
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 1–3	mg Cr VI/kg-d — Number of viable fetuses/female (mean±SD) 0 — 8.20±1.68 35 — 0* Maternal toxicity not evaluated.

Reference and study design	Results
Bataineh et al. (2007) Sprague-Dawley Rat, Female (10/group) Gavage: 0, 25 mg potassium dichromate/rat; equivalent to 0, 35 mg Cr VI/kg-d GD 4–6	mg Cr VI/kg-d: Number of viable fetuses/female (mean±SD) 0: 9.04±2.14 35: 2.80±0.83* Maternal toxicity not evaluated.
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	mg Cr VI/kg-d: Number of live fetuses/litter (mean±SE); Number of dead fetuses/litter (mean±SE) 0: 6.8±0.44; 0.1±0.099 7.9: 1.5±0.29*; 1.2±0.24* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	mg Cr VI/kg-d: Number of live and dead fetuses (mean±SE) 0: 8.8±0.29 53: 8.20±0.20 101: 7.00±0.36* 152: 7.20±0.24* Treatment-related decrease in maternal weight gain reported.[b]
Junaid et al. (1995) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 14–19	No statistically significant change in the number of fetuses per litter or the number of dead fetuses (number of litters) observed. Treatment-related decrease in maternal weight gain reported.[c]
Fetal Body Weight and Length	
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	Percent change from control by exposure group: mg Cr VI/kg-d: Fetal weight 0: -- 7.9: -33* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	Percent change from control by exposure group: mg Cr VI/kg-d: Fetal weight 0: -- 53: -3 101: -13* 152: -19* Treatment-related decrease in maternal weight gain reported.[b]

Reference and study design	Results
Junaid et al. (1995) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 14–19	Percent change from control by exposure group: mg Cr VI/kg-d / Fetal weight / Fetal crown-rump length 0 / -- / -- 53 / -18* / -4* 101 / -37* / -15* 152 / -47* / -29* Treatment-related decrease in maternal weight gain reported.[c]
Fetal Gross External Abnormalities	
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	mg Cr VI/kg-d / Visceral anomalies/litter (mean±SE) 0 / 0 7.9 / 2.1±0.39* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	Percentage of total pups observed with abnormality : mg Cr VI/kg-d / Drooping wrist / Subdermal hemorrhagic patches / Kinky tail / Short tail 0 / 0 / 0 / 0 / 0 53 / 8 / 0 / 0 / 0 101 / 10 / 10 / 7 / 12 152 / 16* / 16* / 12 / 8 Treatment-related decrease in maternal weight gain reported.[b]
Junaid et al. (1995) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 14–19	Percentage of total pups observed with abnormality: mg Cr VI/kg-d / Drooping wrist / Subdermal hemorrhagic patches / Kinky tail / Short tail 0 / 0 / 0 / 0 / 0 53 / 5 / 0 / 8 / 0 101 / 13* / 8 / 8 / 0 152 / 19* / 19* / 15* / 23* Treatment-related decrease in maternal weight gain reported.[c]

Reference and study design	Results
Fetal Skeletal Abnormalities	
Elsaieed and Nada (2002) Wistar Rat, Female (10/group) Water: 0, 50 ppm Cr VI as potassium chromate; equivalent to 0, 7.9 mg Cr VI/kg-d GD 6–15	mg Cr VI/kg-d — Skeletal anomalies/litter (mean±SE) 0 — 0 7.9 — 1.0±0.34* Treatment-related decrease in maternal weight gain reported.[a]
Junaid et al. (1996b) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 6–14	Percentage of total pups observed with abnormality: mg Cr VI/kg-d — Reduced nasal ossification — Reduced frontal ossification — Reduced parietal ossification 0 — 0 — 0 — 0 53 — 0 — 0 — 0 101 — 0 — 0 — 0 152 — 32* — 40* — 32* mg Cr VI/kg-d — Reduced interparietal ossification — Reduced caudal ossification — Reduced tarsals ossification 0 — 0 — 3 — 0 53 — 0 — 8 — 0 101 — 0 — 47* — 0 152 — 40* — 84* — 76* Treatment-related decrease in maternal weight gain reported.[b]

Reference and study design	Results
Junaid et al. (1995) Swiss Albino Mouse, Female (10/group) Water: 0, 250, 500, 750 ppm Cr VI as potassium dichromate; equivalent to 0, 53, 101, 152 mg Cr VI/kg-d GD 14–19	Percentage of total pups observed with abnormality: mg Cr VI/kg-d / Reduced nasal ossification / Reduced parietal ossification / Reduced interparietal ossification / Reduced caudal ossification 0 / 0 / 0 / 0 / 5 53 / 0 / 0 / 0 / 38* 101 / 0 / 0 / 0 / 67* 152 / 31* / 35* / 76* / 80* mg Cr VI/kg-d / Reduced carpal ossification / Reduced metacarpal ossification / Reduced tarsal ossification 0 / 0 / 0 / 0 53 / 0 / 0 / 0 101 / 0 / 0 / 67* 152 / 50* / 80* / 84* Treatment-related decrease in maternal weight gain reported.[c]

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.
GD = gestation day

[a] Elsaieed and Nada (2002) maternal body weight gain (percent change from control):

mg Cr VI/kg-d	Maternal gestational weigh gain
0	--
7.9	-40*

[b] Junaid et al. (1996b) maternal body weight gain (percent change from control):

mg Cr VI/kg-d	Maternal gestational weight gain
0	--
53	-2
101	-8*
152	-24*

[c] Junaid et al. (1995) maternal body weight gain (percent change from control):

mg Cr VI/kg-d	Maternal gestational weight gain
0	--
53	0
101	-11*
152	-26*

3.11. Offspring Outcomes – Dosing During Gestation and Lactation or Lactation Only

Table 3-10. Evidence pertaining to offspring outcomes resulting from oral dosing during gestation and lactation or lactation only [a]

Reference and study design	Results
EXPOSURE DURING GESTATION AND LACTATION	
Offspring Parameters	
Soudani et al. (2011b) Wistar Rat (6 F0 dams/group) Water: 0, 700 ppm potassium dichromate; equivalent to 62.4 mg Cr VI/kg-d[b] GD 14–PND 14 Offspring sacrificed on PND 14	Percent change from control by exposure group: mg Cr VI/kg-d: 0; 62.4 Pup final body weight: --; -25* Pup femur weight: --; -24* Pup femur length: --; -17* Statistically significant decrease in food consumption and water consumption in dosed dams relative to control.[c] Maternal weight not reported in this study.
Soudani et al. (2011c) Wistar Rat (6 F0 dams/group) Water: 0, 700 ppm potassium dichromate; equivalent to 62.4 mg Cr VI/kg-d[b] GD 14–PND 14 Offspring sacrificed on PND 14	Percent change from control by exposure group: mg Cr VI/kg-d: 0; 62.4 Pup relative kidney weight: --; -12* Statistically significant decrease in maternal weight, food consumption, and water consumption in dosed dams relative to control.[c]
Soudani et al. (2013) Wistar Rat (6 F0 dams /group) Water: 0, 700 ppm potassium dichromate; equivalent to 62.4 mg Cr VI/kg-d[b] GD 14–PND 14 Offspring sacrificed on PND 14	Percent change from control by exposure group in pups: mg Cr VI/kg-d: 0; 62.4 Final body weight: --; -26* Relative liver weight: --; -14* For serum data, n = 8 pups/group mg Cr VI/kg-d: 0; 62.4 ALT: --; 41* AST: --; 72* Bilirubin: --; 31* Qualitative histopathology of liver sections of the pups indicated severe infiltration of mononuclear cells, parenchyma dilatation, and moderate vacuolization, but no hemorrhage or necrosis. Statistically significant decrease in maternal weight, food consumption, and water consumption in dosed dams relative to control; histopathological lesions of the liver; elevated ALT, AST, and bilirubin relative to controls.[c]

Reference and study design	Results
EXPOSURE DURING LACTATION ONLY	
Number of Follicles in Female Offspring	
Banu et al. (2008) Wistar Rat (18 dams/group; 4 female pups/dam) Water: 0, 200 ppm potassium dichromate; equivalent to 0, 70.6 ppm Cr VI[d] Dams exposed postpartum days 1–21 Offspring evaluated on PND 21, 45, 65	Percent change from control by exposure group: PND 21 ppm Cr VI / Primordial follicles / Primary follicles / Secondary follicles / Antral follicles 0 / -- / -- / -- / -- 70.6 / -25* / -338* / -36* / -100* PND 45 ppm Cr VI / Primordial follicles / Primary follicles / Secondary follicles / Antral follicles 0 / -- / -- / -- / -- 70.6 / -31* / -35* / -48* / -85* PND 65 ppm Cr VI / Primordial follicles / Primary follicles / Secondary follicles / Antral follicles 0 / -- / -- / -- / -- 70.6 / -19* / -33* / -7 / -7 Study did not report whether maternal toxicity was evaluated.
Sexual Maturation in Female Offspring	
Banu et al. (2008) Wistar Rat (18 dams/group; 4 female pups/dam) Water: 0, 200 ppm potassium dichromate; equivalent to 0, 70.6 ppm Cr VI[d] Dams exposed postpartum days 1–21 Offspring evaluated on PND 21, 45, 65	ppm Cr VI / Onset of puberty / Duration of diestrous 0 / -- / -- 70.6 / -25* / -338* Cr VI exposure did not change the length of proestrous, estrous, or metestrous phases of the estrous cycle. Study did not report whether maternal toxicity was evaluated.

Reference and study design	Results
Hormone Changes in Female Offspring	
Banu et al. (2008) Wistar Rat (18 dams/group; 4 female pups/dam) Water: 0, 200 ppm potassium dichromate; equivalent to 0, 70.6 ppm Cr VI[d] Dams exposed postpartum days 1–21 Offspring evaluated on PND 21, 45, 65	Percent change from control by exposure group: PND 21 ppm Cr VI: E2 / T / P4 / LH / FSH / GH / PRL 0: -- / -- / -- / -- / -- / -- / -- 70.6: -63* / -60* / -55* / 15 / 60* / -52* / -36* PND 45 ppm Cr VI: E2 / T / P4 / LH / FSH / GH / PRL 0: -- / -- / -- / -- / -- / -- / -- 70.6: -45* / -51* / -42* / 11 / 67* / -47* / -42* PND 65 ppm Cr VI: E2 / T / P4 / LH / FSH / GH / PRL 0: -- / -- / -- / -- / -- / -- / -- 70.6: -33.2* / -48* / -42* / 15 / 8.6 / -29* / -48* Study did not report whether maternal toxicity was evaluated.

*Significantly different from control (p<0.05) as calculated by study authors.
Percent change from control calculated as (Treated – Control) ÷ Control × 100.

[a]No exposure-response array was prepared for these results because only single-dose studies were available.

[b]To estimate mg/kg-d, a body weight value of 0.15kg was assumed based on review of similar studies (Soudani et al., 2011a) in adult female Wistar rats by the same investigators.

[c]Soudani et al. (2013); Soudani et al. (2011b); Soudani et al. (2011c) maternal weight change, maternal food intake, and maternal water consumption (percent change from control), ALT, AST, bilirubin.

mg Cr VI/kg-d	Maternal Body Weight	Maternal Food Intake	Maternal Water Consumption	ALT	AST	Bilirubin
0	--	--	--	--	--	--
62.4	-4	-9	-8	+83	+69	+79

[d]Doses in mg/kg-d were not estimated from this drinking water study because study authors had reported decreased body weight but body weights were not reported.

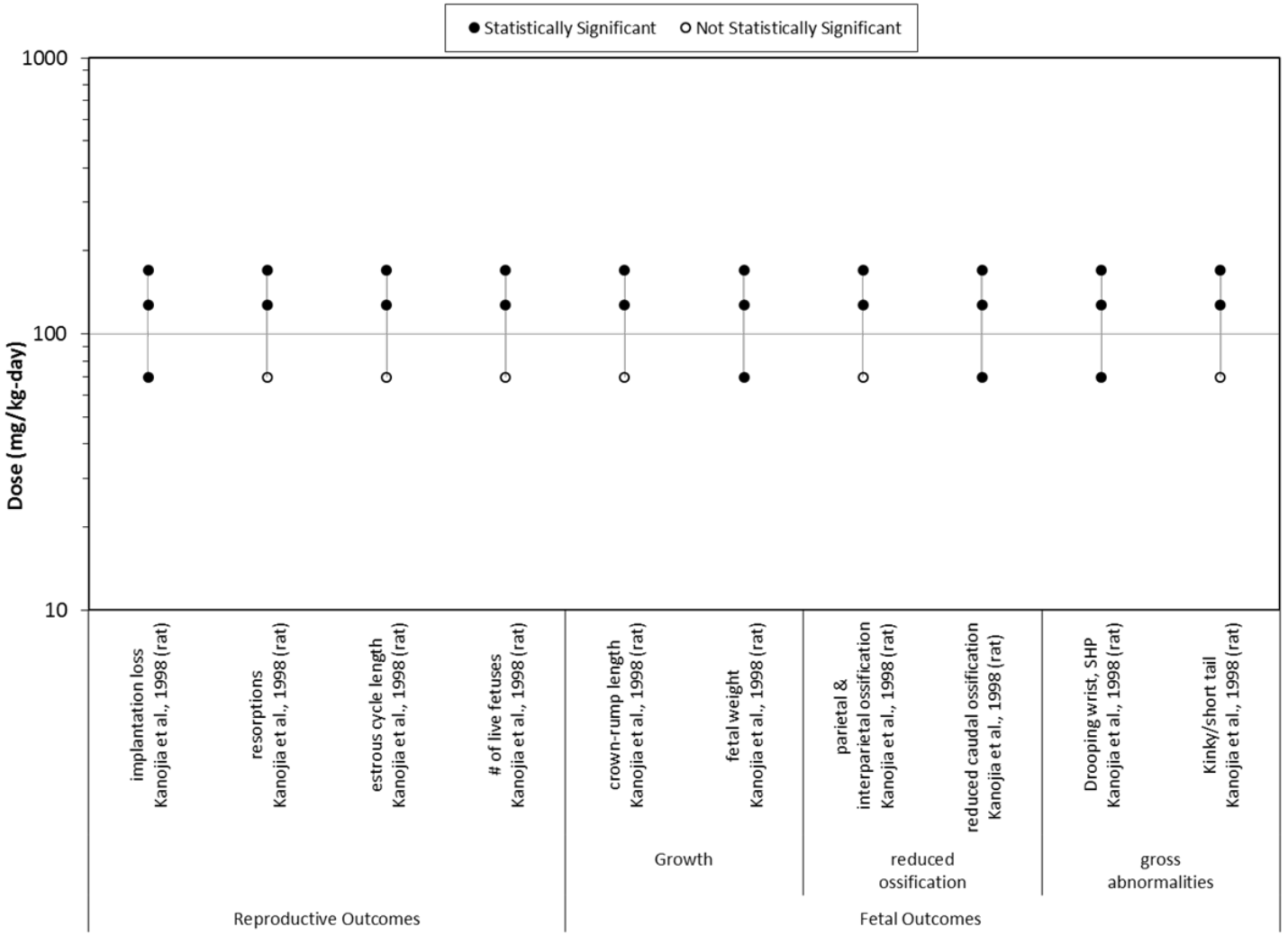

Figure 3-13. Exposure-response array of reproductive and fetal outcomes (dosing prior to gestation) following oral exposure to hexavalent chromium. [SHP]: subdermal hemorrhagic patches.

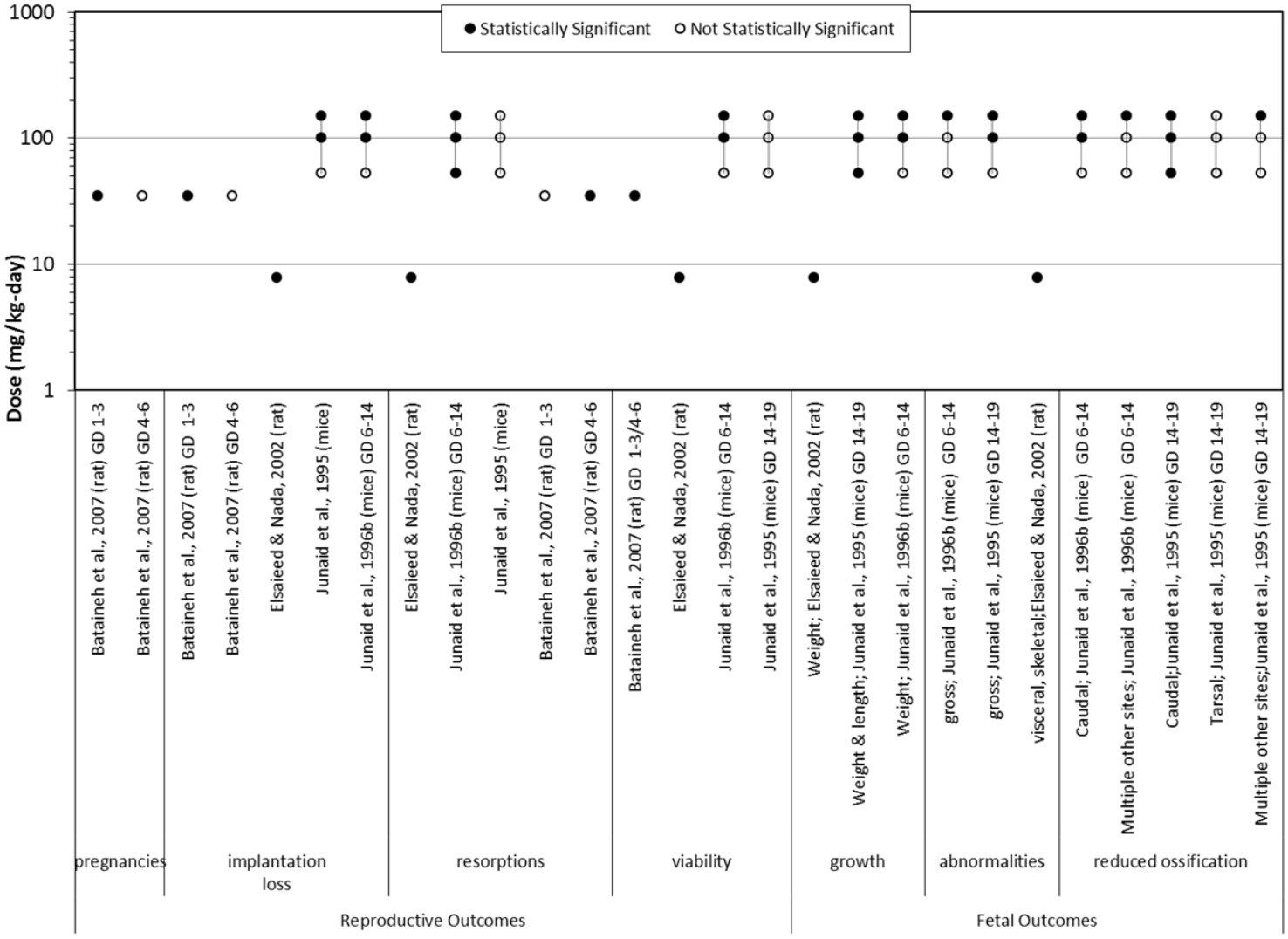

Figure 3-14. Exposure-response array of reproductive and fetal outcomes (dosing during gestation only) following oral exposure to hexavalent chromium.

3.12. Carcinogenic Effects

Table 3-11. Evidence pertaining to carcinogenic effects following oral or inhalation exposure to hexavalent chromium

Reference and study design	Results		
Oral Mucosa Tumors – Oral			
NTP (2008) F344 Rat (50/sex/group) Water: 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate; equivalent to 0, 0.21, 0.77, 2.1, 5.9 mg Cr VI/kg-d (M) 0, 0.24, 0.94, 2.4, 7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males		
	mg Cr VI/kg-d	Oral mucosa: squamous cell carcinoma	Oral mucosa or tongue: Squamous cell papilloma or carcinoma
	0	0/50 (0)	0/50 (0)
	0.21	0/50 (0)	1/50 (2)
	0.77	0/49 (0)	0/49 (0)
	2.1	0/50 (0)	0/50 (0)
	5.9	6/49 (12.2)*	7/49 (14.3)*
	Females		
	mg Cr VI/kg-d	Oral mucosa: squamous cell carcinoma	Oral mucosa or tongue: Squamous cell papilloma or carcinoma
	0	0/50 (0)	1/50 (2)
	0.24	0/50 (0)	1/50 (2)
	0.94	0/50 (0)	0/50 (0)
	2.4	2/50 (4)	2/50 (4)
	7	11/50 (22)*	11/50 (22)*

Reference and study design	Results
Digestive System Tumors – Oral	
NTP (2008) B6C3F1 Mouse (50/sex/group) Water: 0, 14.3, 28.6, 85.7, 257.4 ppm sodium dichromate dihydrate (M) 0, 14.3, 57.3, 172, 516 ppm sodium dichromate dihydrate (F), equivalent to 0, 0.38, 0.91, 2.4, 5.9 mg Cr VI/kg-d (M) 0, 0.38, 1.4, 3.1, 8.7 mg Cr VI/kg-d (F) 7 d/wk, 104 wk Related reference: Stout et al. (2009)	Incidence (percent) by exposure group: Males mg Cr VI/kg-d: 0 Small intestine, duodenum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: carcinoma: 0/50 (0) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 1/50 (2) mg Cr VI/kg-d: 0.38 Small intestine, duodenum: adenoma: 0/50 (0) Small intestine, duodenum, jejunum, ileum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: carcinoma: 2/50 (4) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 3/50 (6) mg Cr VI/kg-d: 0.91 Small intestine, duodenum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: carcinoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 2/50 (4) mg Cr VI/kg-d: 2.4 Small intestine, duodenum: adenoma: 5/50 (10) Small intestine, duodenum, jejunum, ileum: adenoma: 5/50 (10) Small intestine, duodenum, jejunum, ileum: carcinoma: 3/50 (6) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 7/50 (14)* mg Cr VI/kg-d: 5.9 Small intestine, duodenum: adenoma: 15/50 (30)* Small intestine, duodenum, jejunum, ileum: adenoma: 17/50 (34)* Small intestine, duodenum, jejunum, ileum: carcinoma: 5/50 (10)* Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 20/50 (40)* Females mg Cr VI/kg-d: 0 Small intestine, duodenum: adenoma: 0/50 (0) Small intestine, duodenum: carcinoma: 0/50 (0) Small intestine, jejunum: adenoma: 0/50 (0) Small intestine, duodenum, jejunum, ileum: adenoma: 0/50 (0) mg Cr VI/kg-d: 0.38 Small intestine, duodenum: adenoma: 0/50 (0) Small intestine, duodenum: carcinoma: 0/50 (0) Small intestine, jejunum: adenoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: adenoma: 1/50 (2) mg Cr VI/kg-d: 1.4 Small intestine, duodenum: adenoma: 2/50 (4) Small intestine, duodenum: carcinoma: 0/50 (0) Small intestine, jejunum: adenoma: 0/50 (0) Small intestine, duodenum, jejunum, ileum: adenoma: 2/50 (4) mg Cr VI/kg-d: 3.1 Small intestine, duodenum: adenoma: 13/50 (26)* Small intestine, duodenum: carcinoma: 1/50 (2) Small intestine, jejunum: adenoma: 2/50 (4) Small intestine, duodenum, jejunum, ileum: adenoma: 15/50 (30)* mg Cr VI/kg-d: 8.7 Small intestine, duodenum: adenoma: 12/50 (24)* Small intestine, duodenum: carcinoma: 6/50 (12)* Small intestine, jejunum: adenoma: 5/50 (10)* Small intestine, duodenum, jejunum, ileum: adenoma: 16/50 (32)* mg Cr VI/kg-d: 0 Small intestine, duodenum, jejunum, ileum: carcinoma: 1/50 (2) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 1/50 (2) mg Cr VI/kg-d: 0.38 Small intestine, duodenum, jejunum, ileum: carcinoma: 0/50 (0) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 1/50 (2) mg Cr VI/kg-d: 1.4 Small intestine, duodenum, jejunum, ileum: carcinoma: 2/50 (4) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 4/50 (8) mg Cr VI/kg-d: 3.1 Small intestine, duodenum, jejunum, ileum: carcinoma: 3/50 (6) Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 17/50 (34)* mg Cr VI/kg-d: 8.7 Small intestine, duodenum, jejunum, ileum: carcinoma: 7/50 (14)* Small intestine, duodenum, jejunum, ileum: adenoma or carcinoma: 22/50 (44)*

Reference and study design	Results
Pharyngeal Tumors – Inhalation	
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI /m^3 as sodium dichromate (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Incidence (percent) by exposure group: mg/m^3 — Squamous cell carcinoma 0 — 0/37 (0) 0.025 — 0/18 (0) 0.05 — 0/18 (0) 0.1 — 1/19 (5)
Lung Tumors – Inhalation	
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.025, 0.05, 0.1 mg Cr VI /m^3 as sodium dichromate (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Incidence (percent) by exposure group: mg/m^3 — Adenocarcinoma — Adenoma 0 — 0/37 (0) — 0/37 (0) 0.025 — 0/18 (0) — 0/18 (0) 0.05 — 0/18 (0) — 0/18 (0) 0.1 — 1/19 (5) — 2/19 (11)
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr(III) oxide (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Incidence (percent) by exposure group: mg/m^3 — Adenoma 0 — 0/37 (0) 0.063 — 1/18 (5.6)

Reference and study design	Results
Nettesheim et al. (1971) C57BL/6 Mouse (136 males/136 females) 0, 13 mg/m^3 of calcium chromate dust (equivalent to 4.33 mg Cr VI/m^3) (dynamic whole-body chamber) 5 hr/d, 5 d/wk lifespan (~2 yr) Generation method (Wright dust feed), analytical method (gravimetric filter), analytical concentration reported; MMAD not reported. Methods: Nettesheim et al. (1970)	% incidence of lung tumors by exposure group: mg/m^3 — Males — Females 0 — 3/136 (2.2) — 2/137 max (1.5) 4.33 — 6/136 (4.4) — 2/137 max (1.5) Authors state that 15 mice per chamber underwent histopathological examination at 6, 12, and 18 months. It is unclear how many mice per exposure group were examined at these points. It is unclear whether these mice are included in the data presented for lung tumor incidence or if incidence was for the remaining animals that underwent examination at the end of the study only (data presented is number with tumors but it does not say what total number is). It is also unclear whether the female groups contained 136 or 137 total mice (authors report 273 per chamber, ½ treated with irradiation and ½ not). Results for lung tumors were only pathological data reported. Authors provide qualitative statements for epithelial changes in the bronchial tree, bronchiolization of alveoli and alveolar lesions, and morphological changes in tracheal and submandibular lymph nodes, but do not provide data and do not specify results for non-irradiated, non-flu infected mice.
Other Tumors – Inhalation	
Glaser et al. (1986) Wistar Rat, Male (40/control, 20/treatment group) 0, 0.063 mg Cr VI/m^3 as pyrolized mixture of 3:2 Cr VI/Cr III oxide (Cr_5O_{12}) (dynamic whole-body chamber) 22 hr/d, 7 d/wk 72 wk Generation method (jet nebulizer and cyclone), analytical method (photometric, by diphenylcarbazine complexation), analytical concentration, and MMD reported.	Authors state that all of the following observed tumor locations "gave no indication of a carcinogenicity of the chromium compound": pituitary gland, pancreas, liver, spleen, parathyroid, adrenal glands, bladder, testes, kidney, gastrointestinal tract, heart or muscle, skin and appendices.

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