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Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Hexavalent Chromium Part 2: Human, Toxicokinetic, and Mechanistic Studies

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National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

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ABBREVIATIONS

ACP	acid phosphatase
ADAFs	age-dependent adjustment factors
ADME	adsorption, distribution, metabolism, elimination
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
CBC	complete blood count
CCA	chromated copper arsenate
CPSC	Consumer Product Safety Commission
Cr VI	hexavalent chromium
Cr III	trivalent chromium
E2	estradiol
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEF	forced expiratory volume
FEV	forced expiratory flow
FRN	Federal Register Notice
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GD	gestation day
GGT	γ-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GPT	glutamic-pyruvate transaminase
HCT	hematocrit
HERO	Health and Environmental Research Online
Hb	hemoglobin
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
Ig	immunoglobulin
INF	interferon
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOD	limit of detection
LOQ	limit of quantitation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCLG	maximum contaminant level goal
MCV	mean cell volume
MEFR	maximum expiratory flow rate
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 Assessment
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
OR	odds ratio
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
P4	progesterone
PBPK	physiologically-based pharmacokinetic
PEF	peak expiratory flow
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
RR	relative risk
RTP	Research Triangle Park
SD	standard deviation
SDH	sorbitol dehydrogenase
SMR	standard mortality rate
SRBC	sheep red blood cells
T	testosterone
TRI	Toxic Release Inventory
TSCATS	Toxic Substances Control Act Submission database

UCMR3	Third Unregulated Contaminant Monitoring Rule
VC	vital capacity
VCL	curvilinear velocity
VSL	straight line velocity
WBC	white blood cell
WHO	World Health Organization

PREFACE

This draft document presents the second of two sets of preliminary materials for an assessment of hexavalent chromium (Cr VI) prepared by EPA's Integrated Risk Information System (IRIS) Program. The first set of preliminary materials released in April 2014, "Preliminary Materials for the Integrated Risk Information System (IRIS) Toxicological Review of Hexavalent Chromium Part 1: Experimental Animal Studies" ("Part 1 Preliminary Materials") presented the planning and scoping summary, problem formulation information, and a summary of the experimental animal evidence for the health effects of hexavalent chromium. This second set of preliminary materials presents updated information on the literature search and screening strategy, approaches for the selection of human studies of hexavalent chromium for hazard identification, presentation of critical human studies in evidence tables, and a preliminary summary of toxicokinetic and mechanistic studies pertinent to the assessment of hexavalent chromium. 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.

The preliminary materials are responsive to the National Research Council (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. In May 2014, the NRC released their report reviewing the IRIS assessment development process. As part of this review, the NRC reviewed current methods for evidence-based reviews and made several recommendations with respect to integrating scientific evidence for chemical hazard and dose-response assessments. In their report, the NRC states that EPA should continue to improve its evidence-integration process incrementally and enhance the transparency of its process. The committee did not offer a preference but suggests that EPA consider which approach best fits its plans for the IRIS process. The NRC recommendations will inform the IRIS Program's efforts in this area going forward. 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;
- 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 should be regarded solely as representing the data on each endpoint identified as a result of the literature search strategy and approach to selecting critical studies. Similarly, the tables of toxicokinetic and mechanistic studies should be regarded as representing inventories of studies on these topics identified as a result of the literature search strategy. These studies 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. 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 1.1 describes the literature search and screening strategy in detail and updates the literature search and screening strategy presented in the Part 1 Preliminary Materials.

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 1.2 describes the approach taken for selecting studies to be included in preliminary evidence tables of the epidemiology literature for hexavalent chromium. Section 2 presents the selected studies in preliminary human evidence tables arranged by health effect.

1.1. 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 February 2014. The detailed search approach, including the search strings and number of citations identified per database, is presented in Table 1-1. This search of online databases identified 9,708 citations (after electronically eliminating duplicates). The computerized database searches were also supplemented by a manual search of citations from other regulatory documents (Table 1-2); 108 citations were obtained using these additional search

strategies. In total, 9,816 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 an evaluation of the health effects of hexavalent chromium exposure. The process for screening the literature is described below and is shown graphically in Figure 1-1.

- 169 references were identified as potential sources of chronic health effects data and were considered for data extraction into evidence tables.
- 1,774 studies were identified as supporting studies; these included 126 studies describing physiologically-based pharmacokinetic (PBPK) models and other toxicokinetic information, 806 studies providing genotoxicity and other mechanistic information, 735 dermal, acute, short-term, injection, and intratracheal instillation exposure studies, and 107 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.
- 468 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.
- 781 references were kept for further review. This category includes conference abstracts that did not provide enough material to evaluate pertinence and foreign language studies.
- 6,624 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 1-1 for exclusion categories). The majority of studies categorized as not being pertinent were excluded based on one or more of the following criteria:
    - study did not evaluate chromium
    - extraction or remediation studies
    - physical or chemical property studies
    - analytical methods for measuring chromium levels without exposure data
    - chromium not evaluated for effects (e.g., used in sample preparation)
    - bacterial metabolism studies; or
    - interaction studies (i.e., independent effects of chromium not evaluated).

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).[1]

[1] HERO (Health and Environmental Research Online) 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 1,400,000 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 and as more appropriate tags are assigned to individual studies already in the HERO database for hexavalent chromium. 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 1-1.

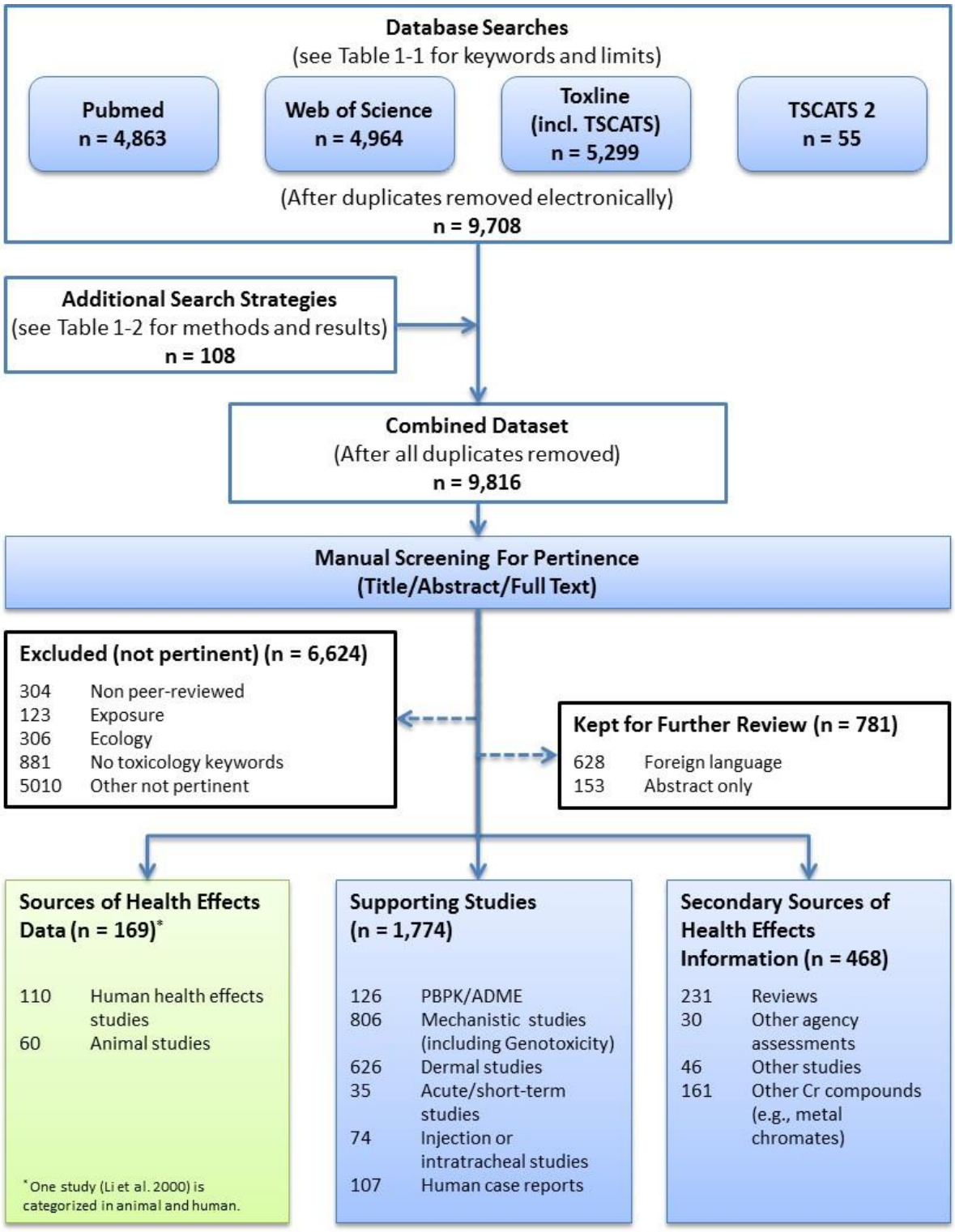

Figure 1-1. Literature search approach for hexavalent chromium.

Table 1-1. 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	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
	cancer* OR carcinogen* OR chronic OR 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 1-2. 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 (Agency for Toxic Substances and Disease Registry). (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
	OSHA (Occupational Safety & Health Administration). (2006). Occupational exposure to hexavalent chromium. Final rule. Fed Reg 71: 10099-10385.	5/2014	3
	IPCS (International Programme on Chemical Safety). (2013). Inorganic chromium (VI) compounds. (78). Geneva, Switzerland: World Health Organization.	5/2014	5
	NIOSH (National Institute for Occupational Safety and Health). (2013). Occupational exposure to hexavalent chromium. (DHHS (NIOSH) Publication No. 2013–128). Department of Health and Human Services, Centers for Disease Control and Prevention.	5/2014	1

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

1.2.1. General Approach

In response to the NRC recommendations, each study retained after the literature search and screen is evaluated for aspects of its design, conduct, or reporting 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.

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 that will serve as the focus of this health assessment was discussed in Problem Formulation in the Part 1 Preliminary Materials.

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")[2]. An example of these flaws includes studies where a control or referent group is lacking. Studies with flaws in their design, conduct, or reporting are not included in evidence tables.

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 in evaluating 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. The inclusion criteria used to identify the critical epidemiology literature for hexavalent chromium are discussed in Section 1.2.2.

1.2.2. Selection of Human Studies for Evidence Tables for Hexavalent Chromium

After the literature search was manually screened for pertinence (Figure 1-1; Sources of Chronic Health Effects Data), 110 human studies were identified as sources of health effects data and considered for data extraction to evidence tables. As discussed in the Problem Formulation for hexavalent chromium in the Part 1 Preliminary Materials, the hazard identification in the IRIS Toxicological Review will focus on the following health effects that may be associated with chronic exposure: respiratory, gastrointestinal (GI) tract, hepatic, immunological, hematological, reproductive, developmental, lung cancer associated with inhalation exposure, and GI cancer associated with oral exposure. These represent the health effects for hexavalent chromium with well-developed areas of research. A screen of the literature published after the publication of the

[2] 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.

ATSDR (2012) Toxicological Profile and other recent reviews (IPCS, 2013; NIOSH, 2013) did not identify other health effect categories that should be added to those already identified.

The specific inclusion criteria for each health-related endpoint are summarized in Table 1-3. Studies with noncancer endpoints were included in the evidence tables if they included a measure of one or more primary health effect endpoints identified in Problem Formulation. Inhalation studies examining lung cancer incidence or mortality risk with dose-response data or usable exposure data were included in the lung cancer table (either as a table entry or notation regarding related studies within a table entry) consistent with the criteria in Table 1-3. Oral studies that provided data on cancer incidence or mortality risk of the GI tract or related sites, including oral cavity, stomach, colon, liver, pancreas, or urinary tract, were included in the oral exposure cancer table.

An additional 11 studies were not included in evidence tables because they were meta-analyses (n = 5) or were only published in a language other than English (n = 6). Meta-analyses are not considered primary source studies, but are reviewed to assess the completeness of EPA's literature search. The non-English language studies will be reviewed individually to determine their potential contribution to the health assessment of hexavalent chromium.

Table 1-3. Inclusion criteria used to identify epidemiology studies of health-related endpoints of hexavalent chromium

Noncancer inclusion criteria
1. Is the study population humans? *AND* 2. Is exposure to chromium: • measured in air, water, or biological tissue; • based on knowledge of industrial hygiene (occupational settings); or • based on knowledge of specific contamination sites or accidental exposure? *AND* 3. Does the study compare a health effect in higher versus lower or no exposure groups? *AND* 4. Does the study include a measure of one or more primary health effect endpoints relating to: • hepatic effects (e.g., liver enzymes, mortality due to liver cirrhosis) • GI tract effects (e.g., mortality due to diseases of the digestive system) • hematological effects (e.g., red blood cell counts) • immune effects (e.g., serum immunoglobulin levels, lymphocyte subpopulations, cytokines) • respiratory effects (e.g., nasal ulcerations, pulmonary function) • reproductive and developmental effects (e.g., steroidal or gonadotropin hormones, sperm parameters, pregnancy outcomes including spontaneous abortion, neonatal mortality)

Inhalation exposure – lung cancer inclusion criteria
1. Is the study population humans? *AND* 2. Is exposure to chromium measured in air or biological tissue? *AND* 3. Does the study examine quantitative measures of chromium exposure in relation to lung cancer incidence or mortality risk? *AND* 4. Does the study estimate lung cancer risk at lower exposures than used in exposure-response modeling in the previous EPA assessment?
Oral exposure – cancer inclusion criteria
1. Is the study population humans? *AND* 2. Is exposure to chromium: • measured in water or biological tissue; or • based on knowledge of specific contamination sites or accidental exposure? *AND* 3. Does the study compare cancer risk in higher versus lower or no exposure groups? *AND* 4. Does the study examine oral cavity, liver, GI tract, pancreas or urinary tract cancer incidence or mortality risk?

1.2.3. Preliminary Evidence Tables

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 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.

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

Several considerations will be used in EPA's evaluation of hexavalent chromium epidemiology studies, including aspects of the study design affecting the internal or external validity of the results (e.g., population characteristics and representativeness, exposure and outcome measures, confounding, data analysis), focusing on specific types of bias (e.g., selection bias; information bias due to exposure misclassification), and other considerations that could otherwise influence or limit the interpretation of the data. A study is externally valid if the study results for the study population can be extrapolated to external target populations. An internally valid study is free from different types of biases, and is a prerequisite for generalizing study results

beyond the study population. These issues are outlined in the IRIS Preamble, and are described below.

Study population

Evaluation of study population characteristics, including key socio-demographic variables and study inclusion criteria, can be used to evaluate external validity (i.e., generalizability) and to facilitate comparison of results across different study populations. Some aspects of the selection process may also affect the internal validity of a study, resulting in a biased effect estimate.

The general considerations for evaluating issues relating to the study population include adequate documentation of participant recruitment, including eligibility criteria and participation rates, missing data, and loss to follow-up. This information is used to evaluate internal study validity related to selection bias. Different types of selection bias that may occur include the healthy worker effect, differential loss to follow up, Berkson bias (relating to selection of participants in hospital-based case-control studies), and participation bias. It is important to note that low participation rates, or differences in participation rates between exposed and non-exposed groups or between cases and controls, is not evidence of selection bias. Rather, selection bias arises from a differential pattern of participation with respect to both the exposure and the outcome, i.e., patterns of participation that would result in a biased effect estimate. This could occur, for example, if people with high exposure and the outcome of interest are more likely to participate than people with low exposure and the outcome.

Most of the available hexavalent chromium studies examined health outcomes among occupationally exposed workers. EPA will consider the implications of this type of study population with respect to the generalizability of the observed effects. EPA will also consider whether reported effect estimates are impacted by a healthy worker or healthy worker survivor effect. These types of selection biases may result in an underestimation of risk among occupational populations if their health is compared to that of a less healthy general population. Information to be used to assess the potential influence of these types of bias on observed results include data on the duration of work or exposure prior to recruitment into the study, literature pertaining to the susceptibility of specific outcomes to these biases, and analytic approaches used to assess or address these biases.

Exposure measures

General considerations for evaluating exposure include: (1) how exposure can occur (e.g., exposure sources, routes and media), (2) appropriate critical exposure period(s) for the outcomes under study, (3) variability in the exposure metrics of interest (e.g., temporal and spatial variability for environmental measures or inter-individual variability for biomonitoring data) that can impact the choice of exposure metric (e.g., cumulative, average, or peak exposure), (4) analytical methodology employed (e.g., choice of biological matrix, sampling protocol, quantification

approach, etc.), (5) choice of exposure surrogate evaluated (e.g., constituent chemical or group/mixture), and (6) classification of individuals into exposure categories. These considerations help determine how accurate and precise the exposure estimates are, and how likely measurement error is with respect to the exposure metrics used. Nondifferential misclassification of exposure categories, for example, can also result from measurement error and is expected to predominantly result in attenuated effect estimates (Blair et al., 2007).

Chromium exposure can occur in a variety of occupational settings, including production of chromium metal and metal alloys, chromium electroplating, stainless steel welding, and production or use of chromium pigments and other compounds containing chromium (OSHA, 2006). The studies identified through EPA's literature search reflect this array of occupational settings, and generally include one or more measures of exposure (e.g., air monitoring or blood or urine samples). EPA will consider the distribution of exposure in evaluating individual studies and when comparing results among groups of studies. One consideration is the contrast of exposure levels (i.e., the difference between "high" and "low"); a study with a very narrow contrast may not have sufficient variability to detect an effect that would be seen over a broader range. Another consideration is the absolute level of exposure, as different effect estimates may be expected in studies examining different exposure levels even if they had similar exposure contrasts.

Primary outcome measures

The general considerations for evaluating issues relating to accuracy, reliability, and biological relevance of outcomes include adequate duration of exposure and follow-up in order to evaluate the outcomes of interest, and use of appropriate ascertainment methods to classify individuals with regard to the outcome (e.g., high sensitivity and specificity). Issues relating to assessment of the specific primary health effects are discussed below and summarized in Table 1-4.

Hepatic, hematologic, and immune effects

Most of the measures used in the categories of hepatic, hematologic and immune effects are serologic or urinary parameters related to enzymes, differential blood cell counts, and other measures of target organ function or damage. Details of the laboratory procedures used to measure these parameters, including their normal reference range (by sex and age), are important considerations in the interpretation of these measures. With respect to the immune system measures, EPA will evaluate these as a set, examining evidence of dysregulation, rather than focusing on one specific marker.

In addition to assessing whether reported parameters are outside normal physiological range, EPA will also consider evidence of smaller changes in the distribution of a parameter that may represent an effect on a population level [e.g., as is the case for early childhood exposure to lead and decrements in intelligence as measured by IQ (U.S. EPA, 2013)].

The studies assessing hepatic, hematologic and immune effects typically include several related measures (e.g., several measures of Th1 cytokines, or several measures of liver enzymes). EPA recognizes that the interpretation of consistency across studies can be difficult when different findings are seen among a set of related outcome measures (e.g., several studies, each with different liver enzyme measures; one measure is elevated in each study but the specific enzyme that is elevated differs among the studies). In general, EPA does not consider this type of variability in observed effects to be evidence of a lack of consistency. Expert professional judgment will be used to evaluate and clarify, if possible, any inconsistencies.

Reproductive and pregnancy outcomes

The chromium literature includes studies of reproductive and gonadotropin hormone levels in men and studies of semen parameters that can be indicative of reduced fertility. The details of the laboratory procedures, including information on the basic methods, level of detection, and coefficient of variation, are important considerations for hormone assays and measures of semen parameters. The World Health Organization (WHO) laboratory methods for analysis of sperm counts and semen parameters (see, for example, WHO, 1999) are generally recognized as standards in this field. EPA will consider studies that reference these methods, regardless of which revision used, to be reliable measures.

Expectant mothers can encounter pregnancy loss either through a stillbirth (fetal death after 20 gestational weeks) or from a spontaneous abortion also known as a miscarriage (fetal death during the first 20 gestational weeks). Pregnancy loss can occur even before a clinically recognized pregnancy; early pregnancy (or "subclinical") loss, determined by measurement of human chorionic gonadotropin, is very common, accounting for approximately 20% of pregnancies (Wilcox et al., 1988). Spontaneous abortions, particularly those occurring in the first trimester, may not require medical intervention and thus medical records may not be a reliable source for this outcome (Slama et al., 2014). In addition to medical records, interview data can be used to ascertain pregnancy losses at later stages of gestation. However, these ascertainment methods are more prone to measurement error since they are subject to maternal recall. Validation studies indicate that recall of previous spontaneous abortions is relatively complete, particularly for losses that occurred after the 8th week of gestation (>80% of recorded spontaneous abortions were recalled) (Wilcox and Horney, 1984).

Infant birth weight, a common health outcome in reproductive epidemiological studies, is dependent on both gestational duration and fetal growth rate. Gestational duration can be measured as a continuous outcome or dichotomous outcome such as preterm birth. Preterm births include infants delivered earlier than 37 gestational weeks. Infants born between 32 and 36 gestational weeks are considered moderate preterm births, while those delivered earlier than 32 gestational weeks are classified as very preterm births. Different measures of fetal growth restriction are often examined in epidemiological studies. In addition to the continuous measure of

birth weight, another commonly used measure is the categorical variable of low birth weight (defined as <2500 g). Small for gestational age (defined as birth weight < the 10th percentile for the gestational birth weight distribution) is considered a better measure of fetal growth rate as it takes into consideration gestational duration, and would be preferred over a measure of birth weight in a study that includes preterm births. Birth weight and gestational duration can also be examined as continuous variables, often in analysis that excludes preterm or low birth weight births, so that the focus of the analysis is on variability within the "normal" range. EPA considers analyses of these various indices for both outcomes (fetal growth and gestational age) to be informative with respect to hazard identification, but will consider each separately as they address different issues. EPA considers birth weight obtained from medical records to be a reliable source as this is a very accurate and precise measurement.

Although more prone to measurement error than birth weight measures, gestational age can be estimated from several approaches. Some of these include ultrasonography, estimates based on date of last menstrual period based on maternal recall, or from clinical examination based on antenatal or newborn assessments (which may include an ultrasound). Menstrual dating of gestational age dependent on maternal recall of the last menstrual period can be subject to considerable measurement error in some cases, so ultrasonography-based estimates may be considered more accurate (Savitz et al., 2002; Taipale and Hiilesmaa, 2001).

Respiratory effects (noncancer)

Pulmonary function

The American Thoracic Society has published guidelines for equipment performance requirements, validation, quality control, test procedures, and reference equations for each type of spirometric measurement (Miller et al., 2005), as well as the interpretation of testing results (Pellegrino et al., 2005). Lung function varies by race or ethnic origin, gender, age, and height, and is best compared when normalized to the expected lung function based on these variables (Pellegrino et al., 2005; Hankinson et al., 1999). Some measures (e.g., FEV_1 and PEF) exhibit diurnal variation (Chan-Yeung, 2000; Lebowitz et al., 1997); thus time of day of the lung function measures should also be considered.

Cancer

Studies of cancer risk in relation to chromium exposure typically examine cancer diagnosis ascertained using cause of death data from death certificates. EPA will examine evidence pertaining to the accuracy of cause of death data (from underlying or multiple causes of death fields) for specific cancers. An additional issue is the validity of mortality data as a representation of cancer incidence; mortality data for cancer types with a high survival rate may underrepresent disease incidence, require additional considerations with respect to determining appropriate time windows of exposure, and may lead to biased risk estimates if survival is related to exposure. Five-year

survival rates for lung cancer and stomach cancer, the primary cancers evaluated in this health assessment for hexavalent chromium, are low (17% and 28%, respectively, for lung and stomach cancer, based on U.S. Surveillance, Epidemiology and End Results data (http://seer.cancer.gov/; last accessed August 14, 2014), and EPA does not consider use of mortality data to be a limitation in studies of these endpoints.

In 1998, EPA classified hexavalent chromium as a "known human carcinogen by the inhalation route of exposure" based on consistent evidence that inhaled chromium causes lung cancer in humans and hexavalent chromium causes cancer in animals. The same conclusion has been reached by other federal, state, and international health agencies. Accordingly, and as discussed in the Problem Formulation in the Part 1 Preliminary Materials, this assessment plans to adopt this conclusion and focus its review of the lung cancer evidence on identifying studies that might improve the quantitative dose-response analysis. Although the considerations with respect to selection of study population, confounding, and analysis are important, considerable focus will be placed on evaluation of issues relating to exposure measurement, and the exposure range encompassed in a study. EPA will consider the extent to which exposure estimates are supported by ambient monitoring and/or biological monitoring, ability to capture changes in exposure over time, and the potential for measurement or assignment of exposure to be influenced by knowledge of outcome (e.g., lung cancer mortality).

Confounding

The general considerations for evaluating issues relating to potential confounding include consideration of which factors may be potential confounders (i.e., those strongly related to both the exposure and the outcome under consideration, and are not intermediaries on a causal pathway), adequate control for these potential confounders in the study design or analysis, and where appropriate, quantification of the potential impact of mismeasured or unmeasured confounders. Uncontrolled confounding by factors that are positively associated with both the exposure and health endpoint of interest, and those that are inversely associated with both exposure and health endpoint, will result in an upward bias of the effect estimate. Confounding by factors that are positively associated with either exposure or the health endpoint, and inversely associated with the other axis, will result in a downward bias of the effect estimate.

Potential confounding by other worksite exposures

EPA will review literature pertaining to potential co-exposures in the occupational settings included in these preliminary materials, and the literature pertaining to the relation between any of these exposures and the outcome(s) examined. For co-exposures that are known or likely to be associated with the outcome, EPA will review the study details to determine the extent to which potential confounding was addressed in the design or analysis.

Potential confounding by other factors

Age and sex are considered important explanatory factors for most types of outcomes to be considered in this assessment; race or ethnicity may also influence some measures (such as some hematological parameters). Some of the health effects under consideration may also have strong associations with other risk factors. For example, smoking is a very strong risk factor for lung cancer, and is also, to a lesser degree, associated with various measures of immune function. Alcohol consumption is a known contributing factor to the development of liver cirrhosis. In evaluating the potential for confounding by any of these factors, EPA will review evidence pertaining to comparison of these factors with respect to the chromium exposed workers and the referent group used in a particular study.

Data Analysis

The general considerations for evaluating issues relating to data analysis include adequate documentation of statistical assumptions and analytic approach (including addressing skewness of exposure or outcome variables), consideration of sample size and statistical power, and use of appropriate statistical methods for the study design.

Table 1-4. General and outcome-specific considerations for chromium study evaluation

General considerations	
Study population	- Study population and setting: geographic area, site, time period, age and sex distribution, other details as needed (may include race/ethnicity, socioeconomic status) - Recruitment process; exclusion and inclusion criteria, knowledge of study hypothesis; knowledge of exposure and outcome - For worker populations – duration of work, incidence or prevalence sampling - Participation rates: Total eligible; participation at each stage and for final analysis group and denominators used to make these calculations - Length of follow-up, loss to follow-up - Comparability: Participant characteristic data by group, data on non-participants
Exposure	- Industrial hygiene measures - Biological matrix or target tissue/organ (e.g., urine) - Level of detection (LOD) or level of quantitation (LOQ) - Exposure distribution (e.g., central tendency, range), proportion < LOD - Contrast between “exposed” and “referent” comparisons
Analysis	- Consideration of data distribution including skewness of exposure and outcome measures - Consideration of influence of “tails” in analysis based on continuous exposure measure - Consideration of values below LOD or LOQ - Presentation of effect estimates, rather than statement regarding presence or absence of statistical significance

Outcome-specific considerations	
Hepatic, hematological, immune **Measures**	- - Type of assay - Sensitivity/detection limits, coefficient of variation
Consideration of confounding	- Age, sex, smoking history
Relevant exposure time window(s)	- Up to 6 months preceding blood or urine sample collection for assays
Steroidal and gonadotropin hormones (adults; sex-specific) **Measures**	- - - Type of assay - Sensitivity/detection limits, coefficient of variation
Consideration of confounding	- Age, smoking, body mass index (consider if these are related to exposure)
Relevant exposure time window(s)	- Up to 6 months preceding hormone sample collection
Sperm parameters **Measures**	- - Type of assay (e.g., WHO protocol)
Consideration of confounding	- Age, smoking, body mass index, abstinence time (consider if these are related to exposure)
Relevant exposure time window(s)	- Up to 6 months preceding semen sample collection; could also consider cycle-specific (or lagged cycle-specific) window
Spontaneous abortion **Measures**	- Human chorionic gonadotropin measures, maternal (or paternal) report of pregnancy history (interview or questionnaire), medical records (based on maternal report), hospitalization records
Consideration of confounding	- Age, gravidity, maternal smoking (consider if these are related to exposure)
Relevant exposure time window(s)	- Up to 3 months preceding conception, conception cycle, and gestational period
Respiratory (noncancer) – pulmonary function ***Measures***	- - Standard protocol
Consideration of confounding	- Age, sex, height, smoking
Relevant exposure time window(s)	- Up to 6 months preceding pulmonary function measures

Cancer **Measures**	- Accuracy and validity of mortality cause of death data (or incidence data, if available)
Consideration of confounding	- Lung cancer: smoking
Relevant exposure time window(s)	- 5–20 years before death

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2. PRELIMINARY EVIDENCE TABLES

2.1. Data Extraction for Preliminary Epidemiology Evidence Tables

The evidence tables present data from studies related to a specific health effect. 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 a method for presenting and evaluating the suitability of the data for the analysis of hazard potential and utility of the data for exposure-response evaluation. For each study listed, key information on the study design, including characteristics that inform study quality, and study results pertinent to evaluating the health effects of hexavalent chromium exposure are summarized in preliminary evidence tables.

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. Gastrointestinal Effects

Table 2-1. Evidence pertaining to gastrointestinal (GI) effects following exposure to hexavalent chromium

Reference and Study Design	Results
Birk et al. (2006) (Germany) cohort study ***Population***: Exposed: male chromate prodcution workers from two plants; worked at least 12 months after each plant converted to a no-lime process (n = 901); Leverkusen n = 593, began work in 1958 or later, mean duration 9 yrs; Uerdingen (n = 308, began work in 1964 or later, mean duration 11 yrs Referent: external analysis (compared with regional rates); also included analysis by exposure level ***Outcome:*** cause on death certificate based on ICD9 ***Exposure Assessment:*** Cumulative exposure using job exposure matrix developed based on work histories and urinary Cr measurements (most collected from routine medical examinations; (n=7000 from 1958–1998 in Leverkusen and n = 5400 from 1964–1995 in Uerdingen). Personal air samples (n = 252 from 1985–1998 in Leverkusen and n = 215 from 1986–1994 in Uerdingen) and area air samples (n = 3422 from 1973–1998) in Leverkusen and n = 1161 from 1978–1995 in Uerdingen) were available for part of the study period. Exposure mean: varied over time (general decline from 1960s through 1990s). Mean concentration in air: 8.83 and 8.04 µg Cr/m^3 in Leverkusen and Uerdingen, respectively. Range of concentration in urine: from 15–50 µg/L up to 1970 to 1–<10 µg/L in 1987–1998 in Leverkusen; from 5–30 µg/L up to 1970 to 1–<10 µg/L in 1987–1996 in Uerdingen. *Mean Length of Follow-Up:* 16 yrs for Leverkusen plant; 19 yrs for Uerdingen plant Smoking data available for more than 90% of cohort	**Reported Endpoint:** diseases of the digestive system; ICD9 Exp. Group — cases — SMR — 95% CI chromate workers — 6 — 0.52 — 0.19–1.13 Stat Method: SMR calculated using German national rates
Hayes et al. (1979) (United States) cohort (retrospective) study ***Population:*** Exposed: male chromium chemical production workers hired as hourly employees between 1945 and 1974 (n = 1803); employed greater than 90 days Referent: compared to age, race, and cause-specific rates for Baltimore City males for the appropriate time periods About 11.5% lost to follow-up ***Outcome:*** cause on death certificate based on ICD8 codes 520–577 ***Exposure Assessment:*** average air concentrations are available in Braver et al. (1985); new milling and roasting plant constructed in 1950 led to reduction in exposures; analysis did not differentiate between periods of employment	**Reported Endpoint:** deaths due to diseases of the digestive system; ICD8 (520-577) Exp. Group — cases — SMR — 95% CI workers — 23 — 0.64 — 0.40–0.95 Stat Method: SMRs using city referent rates

Reference and Study Design	Results
old plant (1945–1949; n = 555): 795 µg/m^3 CrO_3; 413 µg/m^3 Cr VI old plant (1950–1959; n = 354): 143 µg/m^3 CrO_3; 74 µg/m^3 Cr VI new plant (1950–1959; n = 219 plus unknown n for 1957): 60 µg/m^3 CrO3; 31 µg/m3 Cr VI	
Luippold et al. (2005) **(United States)** cohort (retrospective) study ***Population:*** Exposed: male and female chromate production employees exposed to low-level hexavalent chromium at two plants (Plant 1 = North Carolina; Plant 2 = Texas) (n = 617); average duration of employment was 12.4 years at Plant 1 and 7.8 years for Plant 2; age at first exposure was similar for both plants (28.9 years and 31.3 years for Plants 1 and 2, respectively); mean time since first exposure: 20 years for Plant 1 and 10 years for Plant 2 Referent: compared with national and state-specific mortality reference rates; results only provided using state-specific rates ***Outcome:*** cause on death certificates (pre-1979) and in the National Death Index-Plus (post-1979) based on ICD9 codes 520–579 ***Exposure Assessment*:** job-exposure matrices created based on personal air-monitoring measurements and plant personnel records 5230 personal air samples 1974–1988 in Plant 1; 1200 personal air samples 1980–1998 in Plant 2; annual geometric means range 0.36–4.36 µg/m^3 Cr VI *Length of Follow-Up:* follow-up for 60% of Plant 1 employees was >20 years; maximum follow-up for Plant 2 employees was 18 years; end of the study follow-up period was December 31, 1998	**Reported Endpoint:** deaths due to diseases of the digestive system; ICD8 (520-577) Exp. Group — cases — SMR — 95% CI chromate workers — 1 — 0.43 — 0.01–2.41 Stat Method: SMRs using state referent rates

SMR: standard mortality rate; 95% CI: 95% confidence interval

2.3. Hepatic Effects

Table 2-2. Evidence pertaining to hepatic effects following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Birk et al. (2006) (Germany) cohort study ***Population***: Exposed: male chromate prodcution workers from two plants; worked at least 12 months after each plant converted to a no-lime process (n = 901); Leverkusen n = 593, began work in 1958 or later, mean duration 9 yrs; Uerdingen (n = 308, began work in 1964 or later, mean duration 11 years Referent: external analysis (compared with regional rates); also included analysis by exposure level ***Outcome:*** cause on death certificate based on ICD9 ***Exposure Assessment:*** Cumulative exposure using job exposure matrix developed based on work histories and urinary Cr measurements (most collected from routine medical examinations; (n = 7000 from 1958–1998 in Leverkusen and n = 5400 from 1964–1995 in Uerdingen). Personal air samples (n = 252 from 1985–1998 in Leverkusen and n = 215 from 1986–1994 in Uerdingen) and area air samples (n = 3422 from 1973–1998) in Leverkusen and n = 1161 from 1978–1995 in Uerdingen) were avaiable for part of the study period. Exposure mean: varied over time (general decline from 1960s through 1990s). Mean concentration in air: 8.83 and 8.04 µg Cr/m^3 in Leverkusen and Uerdingen, respectively. Range of concentration in urine: from 15–50 µg/L up to 1970 to 1– <10 µg/L in 1987–1998 in Leverkusen; from 5–30 µg/L up to 1970 to 1– <10 µg/L in 1987–1996 in Uerdingen. *Mean Length of Follow-Up:* 16 yrs for Leverkusen plant; 19 yrs for Uerdingen plant Smoking data available for more than 90% of cohort	**Reported Endpoint:** cirrhosis of the liver; ICD9 Exp. Group / cases / SMR / CI chromate workers / 3 / 0.4 / 0.08–1.16 Stat Method: SMR calculated using German national rates
Moulin et al. (1993a) **(France)** cohort (retrospective) study ***Population****:* Exposed: male welders (n = 2721) with at least 1 year of employment (mean year of birth 1940; mean duration of employment 19.5 years) and an internal comparison group of manual workers (n = 6683) employed in 13 factories in France; smoking habits of 87% of total study population known; not statistically different between welders and nonwelders (both about 53%) Referent*:* compared with national death rates for the male population *Loss To Follow-Up:* 122 (4.5%) welders and 221 (3.3%) nonwelders lost to follow-up	**Reported Endpoint:** liver cirrhosis deaths; ICD8 (571) ***welders by duration of employment*** Exp. Group / cases / SMR / p-value <10 years / 1 / 0.64 / NS 10–19 years / 2 / 0.58 / NS ≥20 years / 17 / 2.03 / <0.05 ***welders by time since first employment*** Exp. Group / cases / SMR / p-value <10 years / 1 / 0.86 / NS 10–19 years / 2 / 0.58 / NS ≥20 years / 17 / 1.94 / <0.05

Reference and Study Design	Results by Endpoint
Outcome: cause determined from French national file of causes of death managed by the French National Institute for Medical Research and Health using ICD8 code 571; records of hospitals and of general practitioners also used ***Exposure Assessment:*** based on duration of employment and time since first employment; data collected from personnel registers of 13 factories *Length of follow-up:* approximately 11–13 years	Stat Method: SMRs using national referent rates
Moulin et al. (1993b) (France) cohort (retrospective) study ***Population:*** Exposed: stainless steel producing workers (n = 4227); males with at least 3 years of employment between 1 January 1968 and 31 December 1984 at UGINE SA plant, died in France, and with complete data Referent: compared to national death rates for the male population; males 59 workers lost to follow-up ***Outcome:*** cause on death certificate based on ICD8 code 571 ***Exposure Assessment:*** based on job histories in different workshops in the plant from company records *Length of Follow-Up:* ≤17 years	**Reported Endpoint:** liver cirrhosis deaths; ICD8 (571) Exp. Group: production workforce excluding office and administration; cases: 55; SMR: 1.74; 95% CI: 1.31–2.26 Stat Method: SMRs using national referent rates
Moulin et al. (1990) (France) cohort (retrospective) study ***Population***: Exposed: male ferrochromium and stainless steel plant workers (n = 1717) employed at least 1 year between January 1, 1952, and December 31, 1982 (when production of ferrochromium was occurring); smoking habits of 67% of cohort members known from medical records; of these, 67.2% of exposed and 70.4% of nonexposed were current smokers Referent: compared with French general population (n = 552) About 32 workers lost to follow-up ***Outcome:*** cause ascertained from general practitioners or from hospital records using ICD8 code 571 ***Exposure Assessment:*** exposure based on individual job histories at the factory; data available as "exposed" or "nonexposed" with "exposed" meaning to have been employed for at least 1 year in the workshops producing ferrochromium or in the workshops producing stainless steel *Length of follow-up*: follow-up for mortality occurred from the date of first employment to December 31, 1982	**Reported Endpoint:** liver cirrhosis deaths; ICD8 (571) Exp. Group: nonexposed workers; cases: 2; SMR: 0.52; 95% CI: 0.06–1.88 Exp. Group: exposed workers; cases: 6; SMR: 0.77; 95% CI: 0.28–1.68 Stat Method: SMRs using national death rates

Reference and Study Design	Results by Endpoint
Saraswathy and Usharani (2007) (India) cross-sectional study ***Population:*** Exposed: chrome platers from a chrome plating unit (n = 130); males and females (98% male) from Coimbatore, Tamilnadu, India; continuously employed in the factory (8 hours/day/week) <= 8 years; average age = 33.4 years Referent: residents from the same area as workers and not known to be exposed to chromium or other metals at work or residents who live in the vicinity of the factory (n = 130) used as reference group; non-white males (100% male); average age = 31 years ***Outcome:*** liver enzymes measured in blood ***Exposure Assessment:*** based on employment as a chrome plater in a factory and duration of exposure (i.e., 8–15 or 16–25 years of exposure); no measurements of chromium reported	**Reported Endpoint:** alanine aminotransferase [ALT] (IU/L) Exp. Group / n / mean / SD / p-value reference / 130 / 22 / 1.69 / n/a exposed 8–15 years / 73 / 34.34 / 2.5 / <0.01 exposed 16–25 years / 57 / 43.28 / 1.72 / <0.01 **Reported Endpoint:** alkaline phosphatase [ALP] (IU/L) Exp. Group / n / mean / SD / p-value reference / 130 / 60.84 / 5.67 / n/a exposed 8–15 years / 73 / 70.15 / 6.24 / <0.01 exposed 16–25 years / 57 / 83.72 / 7.63 / <0.01 **Reported Endpoint:** aspartate aminotransferase [AST] (IU/L) Exp. Group / n / mean / SD / p-value reference / 130 / 19.18 / 2.14 / n/a exposed 8–15 years / 73 / 32.92 / 3.71 / <0.01 exposed 16–25 years / 57 / 38.62 / 4.04 / <0.01 Stat Method: t-test

Reference and Study Design	Results by Endpoint
Khan et al. (2013) (Pakistan) cross-sectional study ***Population:*** Exposed: male tannery workers (n = 120) from Sialkot, Pakistan; working for more than 5 years; selected randomly by employer records after informed consent; excluded any worker with chronic illness including diabetes mellitus, hepatitis, renal failure, contact dermatitis or with any orthodontic/orthopedic implant; average age = 33 years Referent: male residents from the same area (n = 120) used as reference group; methods of recruitment not reported ***Outcome:*** liver enzymes measured in blood ***Exposure Assessment****:* blood and urine median (interquartile range) Exposed: blood 569 (377–726) nmol/L urine 131 (46–313) nmol/L (r = 0.741, p < 0.01) Referent: blood 318 (245–397) nmol/L urine 13 (3–26) nmol/L	**Reported Endpoint:** alanine aminotransferase [ALT] (U/L) Exp. Group / n / mean / SD / p-value unexposed workers: 120 / 27.63 / 11.26 / n/a exposed workers: 120 / 33.82 / 12.23 / 0.001 **Reported Endpoint:** alkaline phosphatase [ALP] (U/L) Exp. Group / n / mean / SD / p-value unexposed workers: 120 / 186 / 38 / n/a exposed workers: 120 / 197 / 65 / 0.222 Stat Method: t-test

n = total in group; n/a: not applicable; SMR: standard mortality rate; SD: standard deviation; 95% CI: 95% confidence interval

2.4. Hematological Effects

Table 2-3. Evidence pertaining to hematological effects following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint			
Khan et al. (2013) (Pakistan) cross-sectional study ***Population:*** Exposed: male tannery workers (n = 120) from Sialkot, Pakistan; median (range) duration of employment: 9 (5–21) years; selected randomly by employer records after informed consent; excluded any worker with chronic illness including diabetes mellitus, hepatitis, renal failure, contact dermatitis or with any orthodontic/ orthopedic implant; average age = 33 years Referent: male residents from the same area (n = 120) used as reference group; methods of recruitment not reported ***Outcome:*** standard complete blood count (CBC) ***Exposure Assessment:*** blood and urine median (interquartile range) Exposed: blood 569 (377–726) nmol/L urine 131 (46–313) nmol/L (r = 0.741, p < 0.01) Referent: blood 318 (245–397) nmol/L urine 13 (3–26) nmol/L	Parameter (mean ± SD)	unexposed workers (n = 120)	exposed workers (n = 120)	p-value
	red blood cells [RBC] (x 10^{12}/L)	5.27±0.42	5.18±0.49	0.1
	hemoglobin [Hb] (g/L)	14.55±1.2	12.52±1.82	0.001
	platelet count (x 10^{9}/L)	290.26±76.27	246.5±64.12	0.001
	Stat Method: t-test			
Song et al. (2012) (China) cross-sectional study ***Population:*** Exposed: chromate production factory workers (n = 100); males and females (74% male) with no past or present medical history of liver disease, renal dysfunction, diabetes, cardiovascular disorder or other chronic diseases; no dietary supplements containing elements or vitamins; no radiation exposure in the past year; and employment in the present job for at least one year; median (range) duration of employment: 13.03 (1–33) years; excluded workers who might be exposed to a little Cr III and iron; average age = 37.9 years Referent: no occupational exposure to chromate or other toxic metals and lived more than 20 kilometers away from the factory in the same city (n = 50); average age = 38.1 years ***Outcome:*** standard complete blood count (CBC)	Parameter (mean ± SD)	unexposed (n = 50)	exposed (n = 100)	p-value
	red blood cells [RBC] (x 10^{12}/L)	4.73±0.43	4.78±0.75	0.596
	hemoglobin [Hb] (g/L)	144.76±12.55	148.77±27.16	0.218
	Stat Method: Mann-Whitney U-test			

Reference and Study Design	Results by Endpoint
***Exposure Assessment**:* 8-hour personal exposure samples collected for all participants; air samples collected at multiple sites median (range) Exposed: air 16.96 (0.31–145.95) µg/m^3 Referent: air 0.06 (0.01–0.34) µg/m^3	

n = total in group; SD: standard deviation

2.5. Immunological Effects

Table 2-4. Evidence pertaining to immunological effects following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Qian et al. (2013) (China) cross-sectional study ***Population:*** Exposed: male chromate production workers (n = 106) aged 25–50 years old with no medical history of allergy, asthma, or allergic rhinitis; no skin infections, fever, or other clinical disease; >=1 year of employment in the factory with >=3 months in the same work location; workers split into two groups: Group 1 (50 workers) used to examine cytokine production; Group 2 (56 workers) used to analyze humoral immunity; same activity pattern and occupational hazards among groups; smoking status and alcohol intake information collected mean ± SD years working for Group 1: 17.4 ± 7.7; Group 2 mean not provided Referent: nonexposed males living approximately 20 km from the factory (n = 50); average age = 39.4 ± 8.5 years Significantly more workers in Group 1 smoked and consumed alcohol compared with referents; Group 2 and referents were similar. ***Outcome:*** cytokines and levels of immunoglobulin and complement measured in serum ***Exposure Assessment:*** air samples from six representative areas in each workshop; blood samples collected from workers at the end of 5 consecutive working days and from reference group after completion of the questionnaire; urine sample collected from all subjects and normalized to creatinine median (quartile) Group 1: air (mean ± SD) 14.38±18.08 µg/m^3 blood 14.8 (13.9) µg/L urine 10.86 (8.79) µg/g creatinine Group 2: air (mean ± SD) 28.55±29.70 µg/m^3 blood 16.2 (15.1) µg/L	***blood chromium concentration, µg/L***

Parameter	reference (n = 50)	exposed[a,b]	p-value
serum IgG (g/l) (mean ± SD)	12.41±2.05	10.94±2.45[b]	0.026
serum IgA (g/l) (mean ± SD)	2.82±1.15	2.35±0.88[b]	0.043
serum IgM (g/l) (mean ± SD)	0.97±0.43	1.17±0.49[b]	0.246
serum IgE (g/l) (median, quartile)	81.87 (237.08)	55.19[b] (157.41)	0.610
serum C3 (g/l) (mean ± SD)	0.91±0.13	1.20±0.24[b]	0.001
serum C4 (g/l) (mean ± SD)	0.23±0.05	0.32±0.07[b]	0.001
serum IL-2 (pg/ml) (mean ± SD)	1.25±0.18	1.24±0.11[a]	0.811
serum IL-4 (pg/ml) (mean ± SD)	1.42±0.29	1.37±0.20[a]	0.311
serum TNF-gamma (pg/ml) (median, quartile)	1.50 (0.33)	1.60[a] (0.32)	0.880
serum IL-6 (pg/ml) (median, quartile)	2.45 (1.15)	2.05[a] (0.73)	0.021
serum IL-10 (pg/ml) (mean ± SD)	1.82±0.34	1.68±0.38[a]	0.045
serum IFN-gamma (pg/ml) (mean ± SD)	3.46±0.91	3.06±0.73[a]	0.032
serum IL-17A (pg/ml) (mean ± SD)	7.56±2.90	6.08±1.92[a]	0.004
serum IFN-gamma/IL-4 (mean ± SD)	3.48±0.92	3.13±0.58[a]	0.026

[a] Group 1 (n = 50)
[b] Group 2 (n = 56)
Stat Method: two sample t-test or Mann-Whitney U test and chi-square test

blood chromium concentration, µg/L

Parameter	corr coeff (n=156)	p-value

Reference and Study Design	Results by Endpoint
urine 16.28 (12.35) µg/g creatinine Referent: blood 1.74 (1.29) µg/L urine 0.92 (0.51) µg/g creatinine	serum IgG (g/l) -0.325 0.002 serum IgA (g/l) -0.231 0.031 serum C3 (g/l) 0.352 0.001 serum C4 (g/l) 0.276 0.01 serum IFN-gamma (pg/ml) -0.245 0.045 serum IL-17A (pg/ml) -0.244 0.016 ***urine chromium concentration, µg/g*** serum IL-10 (pg/ml) -0.25 0.04 Stat Method: Pearson and Spearman correlations; blood or urine levels used as continuous variable for correlation coefficient calculation
Boscolo et al. (1997) (Italy) cross-sectional study ***Population:*** Exposed: male plastic factory workers aged 34.8 ± 6.1 years old (n = 15); 9 smokers; occupational exposure period of 3.9 ± 1.9 years (range: 14 months–11 years) Referent: residents living in the same area with similar age and smoking habits as workers; not occupationally exposed to toxic agents (n = 15) ***Outcome:*** lymphocyte subpopulations and immunoglobulins measured in blood ***Exposure Assessment:*** pre-shift serum and urine chromium levels measured median (25th–75th percentiles) Exposed: serum 0.26 (0.19–0.50) µg/L urine 0.45 (0.28–0.88) µg/L or 0.20 (0.14–0.43) µg/g creatinine Referent: serum 0.22 (0.07–0.44) µg/L urine 0.17 (0.13–0.42) µg/L or 0.12 (0.10–0.17) µg/g creatinine ambient air chromate concentration range = 0.1–5.7 µg/m^3	Exp. Group Parameter (median, 25th–75th percentiles) / reference (n = 15) / exposed (n = 15) / p-value IgA (mg/dl) 277 (186–292) 193 (182–282) NS IgG (mg/dl) 1151 (942–1276) 1240 (991–1296) NS IgM (mg/dl) 79 (58–111) 118 (75–140) NS CD5+-CD19+ (10^3/ul) 35 (26–52) 51 (27–55) NS CD5--CD19+ (10^3/ul) 258 (248–408) 133 (117–209) <0.001 total CD19+ (10^3/ul) 330 (260–460) 180 (150–280) <0.001 CD3+ (10^3/µl) 1890 (1680–2170) 1630 (1035–1995) NS CD3--CD25+ (10^3/µl) 165 (128–230) 116 (89–134) <0.05 CD3--HLADR+ (10^3/µl) 475 (368–585) 398 (237–488) <0.05 CD4+-CD45RO- (10^3/µl) 530 (430–560) 350 (255–460) <0.01 CD4--CD45RO+ (10^3/µl) 590 (500–710) 470 (355–650) NS total CD25+ (10^3/µl) 540 (360–600) 360 (265–452) NS total CD4+ (10^3/µl) 1140 (970–1240) 870 (585–l 135) <0.05 total CD8+ (10^3/µl) 810 (570–870) 710 (435–795) NS

Reference and Study Design	Results by Endpoint			
	total HLA-DR+ (10^3/µl)	657 (518–820)	488 (394–689)	NS
	CD16+-56+ (10^3/µl)	490 (290–730)	460 (300–610	NS
	lymphocytes (10^3/µl)	2730 (2300–3090)	2340 (1490–2915)	NS
	total leukocytes (10^3/µL)	6776 (5680–8190)	6764 (5940–7180)	NS
	Stat Method: Mann-Whitney test; Bravais-Pearson correlation coefficient was used to test for trend, but trends were assessed in reference group separate from exposed subjects			
Verschoor et al. (1988) (Netherlands) cross-sectional study ***Population:*** Exposed: chrome-plating workers (aged 39 ± 12 years; employed 8 ± 6 years), stainless steel welders (aged 41 ± 9 years; employed 16 ± 8 years), and boilermakers (aged 38 ± 10 years; employed 8 ± 6 years) (total n = 75) Referent: employees (aged 35 ± 12 years) in a truck factory located in the same area as the two chrome-plating companies, cutters working in the same company as the stainless steel welders, or employees from a construction factory located in the neighborhood of the stainless steel welders (total n = 63) Welder and referent subgroups did not differ from each other with respect to smoking habits. ***Outcome:*** serum immunoglobulin G measured in blood ***Exposure Assessment:*** end-of-shift serum chromium and urine chromium measured; chrome-plating workers and stainless steel welders exposed to water-soluble Cr VI; boilermakers exposed to metallic Cr geometric mean (range) Chrome platers: serum 0.6 (0.2–1.3) µg/L urine 9 (1–34) µg/g creatinine Welders: serum 0.2 (0.04–2.9) µg/L urine 3 (1–62) µg/g creatinine Boilermakers: serum 0.2 (0.07–0.7) µg/L	**Reported Endpoint:** serum immunoglobulin G (IgG) (g/l)			
	Exp. Group	n	mean	SD	p-value
	reference	63	11.6	2.4	n/a
	chrome platers	21	11.6	3.2	NS
	welders	38	11.1	2.6	NS
	boilermakers	16	11.1	2.8	NS
	Stat Method: ANOVA; correlation analysis using serum chromium				

<table>
<tr><th>Reference and Study Design</th><th>Results by Endpoint</th></tr>
<tr><td>urine 1 (0.3–1.5) µg/g creatinine
Referent:
serum 0.2 (0.1–0.9) µg/L
urine 0.4 (0.1–2) µg/g creatinine</td><td></td></tr>
<tr><td rowspan="4">Mignini et al. (2009) (Italy)
cross-sectional study
Population: Exposed: male shoe, hide, and leather industry workers aged 39.7 ± 4.3 years old (n = 40); average exposure period (±SD) within shoe industry and in tanneries 7.4 ± 3.7 years; smokers excluded
Referent: nonsmoking staff of the same age range as the exposed subjects (n = 44)
Outcome: lymphocyte subpopulations and cytokine levels measured in blood
Exposure Assessment: levels of chromium measured in the air, serum, and urine; exposed group separated into “greater” and “less” exposure groups based on urine levels; approximate mean levels in urine based on visual inspection of the figures:
greater exposed: 0.6 µg/L
less exposed: 0.4 µg/L
referent: 0.15 µg/L</td><td>Reported Endpoints: neutrophils, macrophages, lymphocytes, lymphocyte subpopulations (CD4+, CD8+, CD19+, CD16+/CD56+, CD4/CD8)</td></tr>
<tr><td>Authors stated there was no difference between exposed and reference groups for neutrophils, macrophages, lymphocytes, or lymphocyte subpopulations (CD4+, CD8+, CD19+, CD16+/CD56+, and CD4/CD8). (Reported in figures only.)
Stat Method: Duncan Multiple Range, Newman-Keuls, or Mann-Whitney test</td></tr>
<tr><td>Reported Endpoints: peripheral blood mononucleatic cells, IL-12, lymphocyte proliferation, IL-6, IL-2</td></tr>
<tr><td>Authors stated the high-exposure group showed decreased peripheral blood mononucleatic cells and IL-12 and increased lymphocyte proliferation, IL-6, and IL-2. (reported in figures only)
Stat Method: Duncan Multiple Range, Newman-Keuls, or Mann-Whitney test</td></tr>
<tr><td rowspan="2">Tanigawa et al. (1998) (Japan)
cross-sectional study
Population: Exposed: male workers (retired or currently employed) in manufacturing of chromic acid, sodium dichromate, and potassium dichromate at a chemical plant, aged 41–65 (mean 57) years old (n = 19; 7 current smokers); chromate workers exposed for 7–39 (mean 19) years; exposure terminated at 1–39 (mean 18) years before the study
Referent: nonexposed male volunteers including 13 current smokers, aged 50–65 years (mean 57 years), who worked at the same factory (n = 33)
Outcome: lymphocyte subpopulations measured in blood
Exposure Assessment: based on job description stratified by smoking status</td><td>Reported Endpoint: T cells</td></tr>
<tr><td>
<table>
<tr><th></th><th colspan="2">Exp. Group</th><th></th></tr>
<tr><th>Parameter (mean ± SD)</th><th>nonexposed workers; nonsmokers (n = 20)</th><th>chromate workers; nonsmokers (n = 12)</th><th>p-value</th></tr>
<tr><td>CD3+ T lymphocytes (cells/mm^3)</td><td>1840±650</td><td>1150±640</td><td><0.01</td></tr>
<tr><td>CD4+ T lymphocytes (cells/mm^3)</td><td>1250±450</td><td>870±510</td><td><0.05</td></tr>
<tr><td>CD8+ T lymphocytes (cells/mm^3)</td><td>670±480</td><td>330±200</td><td><0.01</td></tr>
<tr><th></th><th>nonexposed workers; smokers (n = 13)</th><th>chromate workers; smokers (n = 7)</th><th>p-value</th></tr>
<tr><td>CD3+ T lymphocytes (cells/mm^3)</td><td>2110±530</td><td>1140±380</td><td><0.001</td></tr>
<tr><td>CD4+ T lymphocytes (cells/mm^3)</td><td>1660±570</td><td>790±260</td><td><0.01</td></tr>
</table>
</td></tr>
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<table>
<tr><th>Reference and Study Design</th><th>Results by Endpoint</th></tr>
<tr><td></td><td>CD8+ T lymphocytes (cells/mm^3) 540±280 470±250 NS
Stat Method: Student’s t test or Welch's t test</td></tr>
<tr><td rowspan="2"><a>Kuo and Wu (2002) (Taiwan)
cross-sectional study
Population: Exposed: male and female workers in five chromium electroplating plants in central Taiwan (n = 10); post-treatment workers (n = 17); for entire study population, average age 37 years old; work duration 72.9 months; 42% smokers
Referent: male and female administrative workers not exposed to chromium or any other metals (n = 19)
Outcome: immunological parameters measured in blood
Exposure Assessment: personal sampler affixed to workers' collars for the duration of one shift; urinary chromium measured at end of shift
High:
urine >6.41 µg/g creatinine
Moderate:
urine 1.14–6.40 µg/g creatinine
Referent:
urine <1.13 µg/g creatinine</td><td>airborne Cr concentration, mg/m^3
Parameter | corr coeff (n = 46) | p-value
B-cells (%) | 0.05 | NS
T-cells (%) | -0.008 | NS
T4 (%) (anti-Leu4 CD3-FITC + anti-Leu3a CD4-PerCP) | -0.06 | NS
T4/T8 ratio | -0.01 | NS
T8 (%) (anti-Leu3a CD4-PerCP + anti-Leu2a CD8-FITC) | -0.08 | NS
IL-6 (ng/ml) | -0.004 | NS
IL-8 (ng/ml) | 0.13 | NS
TNF-alpha (ng/ml) | -0.12 | NS
Stat Method: Pearson correlation</td></tr>
<tr><td>urinary chromium level, µg/g creatinine
Reported Endpoint:
Parameter (adjBeta±SE) | low (ref, n = 19) | moderate (n = 17) | p-value | high (n = 10) | p-value
B-cells (%) | 0 | -2.87±1.41 | <0.05 | -4.29±2.23 | <0.1
T-cells (%) | 0 | -7.81±8.55 | NS | -8.82±4.93 | <0.1
T4 (%) (anti-Leu4 CD3-FITC + anti-Leu3a CD4-PerCP) | 0 | -0.03±2.54 | NS | -0.23±4 | NS
T4/T8 ratio | 0 | 0.07±0.19 | NS | 0.53±0.3 | <0.1
T8 (%) (anti-Leu3a CD4-PerCP + anti-Leu2a CD8-FITC) | 0 | -1.78±2.28 | NS | -6.49±3.59 | NS
IL-6 (ng/ml) | 0 | 0.38±0.26 | NS | 0.69±0.26 | <0.01
IL-8 (ng/ml) | 0 | 16.24±19.5 | NS | 38.74±20.1 | <0.05
TNF-alpha (ng/ml) | 0 | -0.63±1.3 | NS | -0.85±1.34 | NS
Stat Method: linear regression model; adjusted for age, gender and smoking</td></tr>
</table>

Reference and Study Design	Results by Endpoint
Khan et al. (2013) (Pakistan) cross-sectional study ***Population:*** Exposed: male tannery workers (n = 120) from Sialkot, Pakistan; median (range) duration of employment: 9 (5–21) years; average age 33 years old; selected randomly by employer records after informed consent; excluded any worker with chronic illness including diabetes mellitus, hepatitis, renal failure, contact dermatitis or with any orthodontic/ orthopedic implant; smoking status information not indicated Referent: male residents from the same area (n = 120); methods of recruitment not reported ***Outcome:*** WBC count measured in blood ***Exposure Assessment:*** blood and urine median (interquartile range) Exposed: blood 569 (377–726) nmol/L urine 131 (46–313) nmol/L (r = 0.741, p < 0.01) Referent: blood 318 (245–397) nmol/L urine 13 (3–26) nmol/L	**Reported Endpoint:** white blood cells [WBC] (10^9/L) Exp. Group | n | mean | SD | p-value unexposed workers | 120 | 7.56 | 1.25 | n/a exposed workers | 120 | 8.79 | 1.82 | 0.001 Stat Method: t-test
Wang et al. (2012) (China) cross-sectional study ***Population:*** Exposed: male chromate production plant workers who weigh or pack chromate aged 38.66 ± 6.07 years; exposed to sodium dichromate for at least 6 months (n = 86); mean (range) work duration time: 12.01 ± 0.84 (1–33) years Referents: healthy residents from housekeeping company (including salesman, meter checker, repairman, etc.) living in same city without occupational exposure to chromate or other chemicals (n = 45) used as reference group; matched to exposed by socioeconomic and demographic status such as age, smoking, drinking; average age 39.64±10.3 years ***Outcome:*** WBC count measured in blood ***Exposure Assessment:*** post-shift urine samples collected from exposed workers after 5 consecutive work days; analysis performed 3 hours after sample collection Reference:	**Reported Endpoint:** white blood cell count [WBC] (10^9/L) Exp. Group | n | mean | SD | p-value reference | 45 | 6.17 | 1.32 | n/a chromate-exposed workers | 86 | 6.96 | 1.72 | 0.025 Stat Method: Mann-Whitney test

Reference and Study Design	Results by Endpoint
urine 1.53+/-2.09 µg/g creatinine Exposed: urine 18.68+/-14.60 µg/g creatinine	

adjBeta: adjusted Beta; NS: not significant; n/a: not applicable; SE: standard error; SD: standard deviation

2.6. Reproductive and Developmental Effects

Table 2-5. Evidence pertaining to reproductive and developmental effects following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Hormones	
Li et al. (2001) (China) cross-sectional study ***Population:*** Exposed: male electroplating factory workers working at electroplating factory for 1–15 yr (n = 21) Referent: compared with workers from the same factory without exposure to any harmful chemicals (n = 22) ***Outcome***: hormones measured in serum ***Exposure Assessment:*** chromium measured in serum and seminal fluid (µmol/mL) Exposed: serum: 1.4 +/- 0.01 × 10^{-3} (n = 21) seminal fluid: 7.55 +/- 0.06 × 10-3 (n = 18) Referent: serum: 1.26 +/- 0.02 × 10^{-3} (n = 13) seminal fluid: 6.38 +/- 1.06 × 10^{-3} (n = 4)	**Reported Endpoint:** hormone levels Exp. Group Parameter: follicle stimulating hormone (FSH) (mean ± SE, x 10^{-3} IU/mL) — reference (n = 21): 2.41±0.08; exposed (n = 20): 7.34±0.34; p-value: <0.01 Parameter: luteinizing hormone (LH) (mean ± SE, x 10^{-3} IU/mL) — reference (n = 21): 6.85±0.3; exposed (n = 20): 6.33±0.16; p-value: NS Stat Method: not reported
Bonde and Ernst (1992) (Denmark) cross-sectional study ***Population:*** Exposed: male tungsten inert gas stainless steel welders and manual metal arc and/or metal active gas mild steel welders (n = 60); smoking most prevalent among the highest exposed (73.6%) Referent: compared with non-welding metal workers and electricians (n = 47) ***Outcome***: hormones measured in serum ***Exposure Assessment***: pre-shift blood samples obtained from 86 subjects (5 plants only); post-work shift spot urine samples collected and those with urinary chromium levels at/below the median (<1.07 nmol/mmol creatinine) comprised reference group that contained 100% of electricians, 16% of stainless steel welders, 46% of mild steel welders, and 48% of non-welding metal workers high: >1.78 nmol/mmol creatinine	**Reported Endpoint:** hormone levels ***pre-shift blood chromium concentration, nmol/L*** Parameter: follicle stimulating hormone [FSH] (IU/L) — n: 107; adjBeta: -0.02; p-value: NS Parameter: luteinizing hormone [LH] (IU/L) — n: 107; adjBeta: -0.05; p-value: NS Parameter: testosterone (nmol/L) — n: 107; adjBeta: -0.001; p-value: NS Stat Method: linear regression; chromium entered in model as a continuous variable; adjustment factors included age, alcohol drinking, race/ethnicity, smoking status, shift work, use of Finnish bath, fertility problems, history of urogenital disorder, fever, abstinence period, occupation ***urinary chromium concentration, nmol/mmol creatinine*** Exp. Group Parameter — >1.78 (n = 23); 1.07–1.78 (n = 24); <1.07 (n = 60); p-value

Reference and Study Design	Results by Endpoint				
medium: 1.07–1.78 nmol/mmol creatinine low: <1.07 nmol/mmol creatinine	follicle stimulating hormone [FSH] (mean ± SD, IU/L)	4.5±2.2	5.0±2.6	4.7±2.9	NS
	luteinizing hormone [LH] (mean ± SD, IU/L)	6.7±2.8	6.8±2.4	6.8±3.0	NS
	testosterone (mean ± SD, nmol/L)	16.4±5.6	18.7±7.3	21.0±7.8	NS
	Stat Method: linear regression; chromium entered in model as a continuous variable				
Hjollund et al. (1998) (Denmark) cohort (prospective) study ***Population:*** Exposed: male welders 20–35 years old who were first-pregnancy planners (couples without earlier reproductive experience who intended to discontinue contraception in order to become pregnant) recruited 1992–1994 from members of the union of metal workers and 3 other trade unions (n = 126); enrolled couples discontinued birth control and were followed up to 6 menstrual cycles or until a pregnancy was achieved Referent: first-pregnancy planners who were nonmetal workers (n = 200) or metal workers without welding during the past 3 months (n = 68) Among the 3 exposure groups, 23–35% were smokers ***Outcome***: hormones measured in serum ***Exposure Assessment****:* questionnaire on current and previous welding exposure, including type and welding method, average daily duration of welding, and welding with or without application of local exhaust ventilation; at entry, each male provided blood sample and semen sample	**Reported Endpoint:** hormone levels				
			Exp. Group		
	Parameter	reference (n = 200)	non-welder (n = 68)	welder (n = 126)	
	follicle stimulating hormone (FSH) (IU/L) (median, 25th–75th percentile)	3.3 (2.3–4.9)	3.5 (2.4–4.4)	3.2 (2.5–4.3)	
	luteinizing hormone (LH) (median, 25th–75th percentile)	3.3 (2.6–4.5)	3.1 (2.5–4.7)	3.3 (2.6–4.6)	
	testosterone/SHBG (units) (median, 25th–75th percentile)	0.48 (0.38–0.59)	0.49 (0.39–0.65)	0.47 (0.37–0.62)	
	Authors stated that hormone measurements were not significantly different in exposed vs. reference groups. Stat Method: analysis of covariance using SAS GLM procedure				

Reference and Study Design	Results by Endpoint
Sperm parameters	
Li et al. (2001) (China) cross-sectional study ***Population:*** Exposed: male electroplating factory workers working at electroplating factory for 1–15 yr (n = 21) Referent: compared with workers from the same factory without exposure to any harmful chemicals (n = 22) ***Outcome***: sperm parameters (sample collected after 5 days abstinence) ***Exposure Assessment****:* chromium measured in serum and seminal fluid (µmol/mL) Exposed: serum: 1.4 +/- 0.01 × 10^{-3} (n = 21) seminal fluid: 7.55 +/- 0.06 × 10-3 (n = 18) Referent: serum: 1.26 +/- 0.02 × 10^{-3} (n = 13) seminal fluid: 6.38 +/- 1.06 × 10^{-3} (n = 4)	**Reported Endpoint:** sperm parameters Exp. Group Parameter | reference (n = 22) | exposed (n = 21) | p-value sperm counts (mean ± SE, 10^6/ml) | 88.96±3.4 | 47.05±2.13 | <0.05 sperm motility (mean ± SE, %) | 81.92±0.41 | 69.71±0.93 | <0.05 liquefaction time (mean ± SE, min) | 30.9±0.86 | 32.81±0.76 | NS Stat Method: not reported
Bonde and Ernst (1992) (Denmark) cross-sectional study ***Population:*** Exposed: male tungsten inert gas stainless steel welders and manual metal arc and/or metal active gas mild steel welders (n = 60); smoking most prevalent among the highest exposed (73.6%) Referent: compared with non-welding metal workers and electricians (n = 47) ***Outcome***: sperm parameters (3 samples at 1-month intervals between samples; collected after 3 days abstinence); parameters of repeated samples from each individual were averaged ***Exposure Assessment***: pre-shift blood samples obtained from 86 subjects (5 plants only); post-work shift spot urine samples collected and those with urinary chromium levels at/below the median (<1.07 nmol/mmol creatinine) comprised reference group that contained 100% of electricians, 16% of stainless steel welders, 46% of mild steel welders, and 48% of non-welding metal workers high: >1.78 nmol/mmol creatinine	**Reported Endpoint:** sperm parameters ***pre-shift blood chromium concentration, nmol/L*** Parameter | n | adjBeta | p-value sperm concentration (million/mL) | 107 | 0.25 | NS proportion of motile sperms (%) | 107 | 0.04 | NS sperm penetration rate (cm/hr) | 107 | 0.02 | NS proportion of normal sperm forms (%) | 107 | 0.07 | NS Stat Method: linear regression; chromium entered in model as a continuous variable; adjustment factors included age, alcohol drinking, race/ethnicity, smoking status, shift work, use of Finnish bath, fertility problems, history of urogenital disorder, fever, abstinence period, occupation ***urinary chromium concentration, nmol/mmol creatinine*** Exp. Group Parameter (mean ± SD) | >1.78 (n = 23) | 1.07-1.78 (n = 24) | <1.07 (n = 60) | p-value total sperm count (million/ejaculation) | 150.7±90.7 | 179.5±103.1 | 156.2±100.9 | NS sperm concentration (million/mL) | 50.7±20.9 | 62.8±21.7 | 54.5±26.9 | NS

Reference and Study Design	Results by Endpoint			
medium: 1.07–1.78 nmol/mmol creatinine low: <1.07 nmol/mmol creatinine	proportion of motile sperms (%)	51.6±16.4	54.8±11.9	55.2±14.6 NS
	sperm penetration rate (cm/hr)	3.69±0.79	3.61±0.68	3.75±0.56 NS
	proportion of normal sperm forms (%)	56.8±20.5	61.0±17.1	65.8±17.8 NS
	Stat Method: linear regression; chromium entered in model as a continuous variable			
Danadevi et al. (2003) (India) cross-sectional study ***Population:*** Exposed: male welders aged 21–41 years old employed in a welding plant and exposed to welding fumes for 2–21 years (n = 57) Referent: compared with subjects matched for age, lifestyle, and economic status who were not exposed to known harmful chemicals (n = 57) Forty-five (40.7%) men in the study population were smokers ***Outcome***: sperm parameters (2 samples at weekly intervals between samples; collected after 3 days abstinence) ***Exposure Assessment:*** 28 welders and 27 referents randomly selected for blood analysis; blood sampled on the morning of the 4th day of the workweek mean ± SD Exposed: blood 131.0 ± 52.6 µg/L Referent: blood 17.4 ± 8.9 µg/L	**Reported Endpoint:** sperm parameters			
		Exp. Group		
	Parameter (mean ± SD)	reference (n = 57)	welders (n = 57)	p-value
	sperm count (x 10^6/mL)	62.8 ± 43.7	14.5 ± 24.0	<0.001
	rapid linear progressive motility (%)	63.5 ± 5.3	32.2 ± 15.3	<0.001
	nonspecific aggregation (%)	14.0 ± 12.0	49.0 ± 22.0	<0.001
	sperm vitality (%)	80.4 ± 6.8	67.6 ± 22.8	<0.001
	normal morphology (%)	69.0 ± 8.0	37.0 ± 14.3	<0.001
	head defects (%)	16.4 ± 5.6	38.3 ± 9.7	<0.001
	mid-piece defects (%)	9.8 ± 3.8	19.5 ± 9.2	<0.001
	tail defects (%)	4.8 ± 0.8	5.2 ± 4.9	NS
	Additional analysis evaluated the relationship between blood chromium and semen parameters in the control group and welders using simple regression analysis. There was significant positive correlation between percentage of tail defects and blood chromium in male welders; significant negative correlation occurred between blood chromium in male welders and sperm count, sperm motility, including other measures of motility not shown, and sperm vitality; smoking did not show an effect on semen parameters in welders or referents.			
	Stat Method: Mann-Whitney U test			
Hjollund et al. (1998) (Denmark) cohort (prospective) study ***Population:*** Exposed: male welders 20–35 years old who were first-pregnancy planners (couples without earlier reproductive experience who intended to discontinue contraception in order to become pregnant) recruited 1992–1994 from members of the union of metal workers and 3 other trade unions (n = 126); enrolled couples discontinued birth control and were followed	**Reported Endpoint:** sperm parameters			
			Exp. Group	
	Parameter	reference (n = 200)	non-welder (n = 68)	welder (n = 126)
	sperm count per ejaculate (10^6) (median, 25th and 75th percentiles)	136 (55–252)	148 (75–241)	144 (77–300)
	sperm density (10^6/mL) (median, 25th and 75th percentiles)	50 (24–80.5)	52.5 (27–99)	56.0 (27–98)
	sperm density <20x10^6/mL (% of subjects)	21	17.7	15.1

Reference and Study Design	Results by Endpoint			
up to 6 menstrual cycles or until a pregnancy was achieved	motile sperm (%) (median, 25th and 75th percentiles)	62 (53–69)	65 (55–74)	67 (56–72)
Referent: first-pregnancy planners who were nonmetal workers (n = 200) or metal workers without welding during the past 3 months (n = 68)	straight line velocity (VSL) (µm/s) (median, 25th and 75th percentiles)	24.8 (18–32)	25.9 (18–31)	24.6 (19–29)
Among the 3 exposure groups, 23–35% were smokers	curvilinear velocity (VCL) (µm/s) (median, 25th and 75th percentiles)	74.1 (62– 82)	70.7 (61–81)	68.9 (57–77)
Outcome: sperm parameters; monthly samples obtained during follow-up (maximum of 6 menstrual cycles)	normal morphology (%) (median, 25th and 75th percentiles)	40.0 (34–45)	40.5 (34–45)	42.5 (34–48)
Exposure Assessment*:* questionnaire on current and previous welding exposure, including type and welding method, average daily duration of welding, and welding with or without application of local exhaust ventilation; at entry, each male provided blood sample and semen sample	normal morphology <30% (% of subjects)	19.0	13.9	10.5
	Authors stated that sperm parameters were not significantly different in exposed vs. reference groups. Stat Method: analysis of covariance using SAS GLM procedure			
Other reproductive and developmental endpoints				
Hjollund et al. (1995) **(Denmark)** cohort (retrospective) study ***Population:*** Exposed: married metal workers in steel manufacturing companies (n = 1483 pregnancies; maternal mean age of the 2 exposed groups about 28 years old); worked for a minimum of 1 year from 1964–1984 Referent: married subjects reporting no welding used as reference group (1037 pregnancies; maternal mean age: 28.8 ± 5.3 years old) Paternal smoking similar among groups (~59–63%) ***Outcome***: spontaneous abortions among spouses (identified through Danish population register with dates of marriage and divorce) obtained through hospital discharge records (Danish In-patient Hospital Register), 1977–1987 ***Exposure Assessment****:* questionnaire filled out in 1986 recording first and last year worked in a particular type of welding	**Reported Endpoint:** spontaneous abortion; ICD8			
	Exp. Group	cases	OR	95% CI
	reference	94	1	n/a
	mild-steel welding	54	0.96	0.68–1.4
	stainless steel welding	62	0.78	0.55–1.1
	Stat Method: logistic regression			
Hjollund et al. (2000) **(Denmark)** cohort (prospective) study ***Population:*** Exposed: male first-pregnancy planners (couples without earlier reproductive experience who intended to	**Reported Endpoint:** spontaneous abortion/miscarriage			
	Exp. Group	cases	adjRR	95% CI
	no welding (reference)	48	1	n/a
	mild-steel welding	13	1	0.5–2.1

Reference and Study Design	Results by Endpoint
discontinue contraception in order to become pregnant) recruited 1992–1994 from members of the union of metal workers and 3 other trade unions (77 pregnancies); ; enrolled couples discontinued birth control and were followed up to 6 menstrual cycles or until a pregnancy was achieved Referent: subjects reporting no welding (203 pregnancies) ***Outcome***: early loss based on human chorionic gonadotrophic hormone analysis in 10 daily urine samples, with an elevation (>1.0 IU/l) followed by decline; clinical loss based on June 1996 interview or questionnaire about pregnancy outcome for all clinically-diagnosed pregnancies ***Exposure Assessment****:* questionnaire on current and previous welding exposure, including type (stainless steel, mild steel, or other metal) and welding method, average daily duration of welding, and welding with or without application of local exhaust ventilation	stainless steel welding 10 3.5 1.3–9.1 Stat Method: Cox regression; adjusted for center, female age, female body mass index, menstrual cycle length, male and female smoking, caffeine and alcohol consumption, reproductive disease
Hjollund et al. (2005) (Denmark) cohort (retrospective) study ***Population:*** Exposed: IVF-treated women in a couple with male metal workers (n = 319 [91 stainless steel welders, 128 mild steel welders, 100 non-welding metalworkers]); 181 male metal workers with historical stainless steel welding (n = 61, <1 yr; n = 57, 1–5 yr; n = 63, 6+ yr); information for subject recruitment available from the Danish In Vitro Fertilization Register (DIVF) covering all IVF treatments after 1993 Referent: nonexposed pregnancies (n = 2925 with or without outcome) Smoking information obtained through questionnaire ***Outcome***: information on pregnancy survival until clinical detection collected from the DIVF register; outcome information collected from national health registers ***Exposure Assessment****:* questionnaires used to identify metal welders, exposure duration, and welding type	**Reported Endpoint:** spontaneous abortion/miscarriage; ICD10 ***historical stainless steel welding*** Exp. Group / cases / adjRR / 95% CI nonexposed reference pregnancies 830 1 n/a <1 year 16 0.93 0.48–1.79 1-5 years 15 0.94 0.55–1.6 6+ years 13 0.68 0.38–1.25 Exp. Group / cases / adjRR / 95% CI nonmetal workers 830 1 n/a metal workers–no welding 32 1.17 0.82–1.67 metal workers–mild steel welding 32 0.95 0.66–1.36 metal workers–stainless steel welding 16 0.59 0.36–0.98 Stat Method: Cox regression; adjusted for center, male and female smoking, male and female coffee consumption, male and female alcohol consumption, male and female age, number of transferred embryos

Reference and Study Design	Results by Endpoint
Bonde et al. (1992) (Denmark) cohort (retrospective) study ***Population:*** Exposed: male production workers employed at Danish stainless steel (n = 1317; mean age: 29.5 ± 4.8 years old) or mild steel (n = 924; mean age: 29.6 ± 4.8 years old) manufacturing companies for a minimum of 1 year between April 1964 and December 1984 who fathered children 1973–1986 considered at risk based on paternal welding exposure Referent: compared with members of company cohort, excluding metal workers, who fathered children considered not at risk based on paternal welding exposure (n = 1328; mean age: 30.3 ± 5.3 years old) Paternal smoking similar among groups (~64–69%) ***Outcome***: history of spontaneous abortion collected by midwives for women with a pregnancy ending in live birth after 1977; other pregnancy outcomes for all pregnancies in relevant time period collected from Danish Medical Birth Register with linkage to in-patient register (for congenital malformations) and death certificates (for neonatal mortality) ***Exposure Assessment****:* self-questionnaire reporting first and last year worked for each welding type and welding methods used *Length of Follow-Up:* 0–20 years	**Reported Endpoint:** spontaneous abortion/miscarriage Exp. Group / cases / adjOR / 95% CI not at risk (reference) / 23 / 1 / n/a at risk from mild steel welding / 12 / 1.1 / 0.5–2.4 at risk from stainless steel welding / 38 / 2.0 / 1.1–3.5 Stat Method: logistic regression; adjusted for maternal age, birthplace, marital status, and paternal smoking and drinking habits **Reported Endpoint:** preterm birth/delivery (>3 weeks preterm) Exp. Group / cases / OR / 95% CI not at risk (reference) / 52 / 1 / n/a at risk from mild steel welding / 26 / 0.71 / 0.44–1.45 at risk from stainless steel welding / 67 / 1.32 / 0.91–1.91 Stat Method: logistic regression **Reported Endpoint:** birth weight <= 2500 g Exp. Group / cases / OR / 95% CI not at risk (reference) / 84 / 1 / n/a at risk from stainless steel welding / 83 / 1.01 / 0.74–1.38 at risk from mild steel welding / 52 / 0.89 / 0.63–1.28 Stat Method: logistic regression **Reported Endpoint:** all malformations; ICD8: 740-759 Exp. Group / cases / adjOR / 95% CI not at risk (reference) / 87 / 1 / n/a at risk from stainless steel welding / 75 / 0.81 / 0.62–1.06 at risk from mild steel welding / 37 / 0.57 / 0.41–0.80 Stat Method: Poisson regression, the influence of some confounders assessed using logistic regression models; adjusted for age of parents, maternal parity, degree of specialization of hospital department, paternal alcoholic beverage consumption and smoking habits, occupational status of the mother, living area **Reported Endpoint:** neonatal mortality Exp. Group / cases / OR / 95% CI not at risk (reference) / 11 / 1 / n/a at risk from stainless steel welding / 11 / 0.99 / 0.43–2.30

Reference and Study Design	Results by Endpoint			
	at risk from mild steel welding	2	0.26	0.06–1.18
	Stat Method: logistic regression			

cases = number of cases calculated from information provided by study authors
adjBeta: adjusted Beta; adjOR: adjusted odds ratio; adjRR: adjusted relative risk; NS: not significant; n = total in group; n/a: not applicable; OR: odds ratio; SE: standard error; SD: standard deviation; 95% CI: 95% confidence interval

2.7. Noncancer Respiratory Effects – Pulmonary Function

Table 2-6. Evidence pertaining to noncancer respiratory effects (pulmonary function) following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Lung: function	
Huvinen et al. (2002b) (Finland) cohort (prospective) study ***Population:*** Exposed: workers in the furnace department of the ferrochromium plant and steel melting shop (n = 104; mean age 48 ± 6.9 years old) Referent: compared with workers from the cold rolling mill whose exposure to chromium or dust in general was extremely low (n = 81; mean age 45.6 ± 7 years old) *Loss To Follow-Up:* 5 subjects lost to follow-up because they left the company (2) or died from cardiac infarction (3) ***Outcome:*** diffusing capacity measured by experienced lab technicians ***Exposure Assessment:*** subjects categorized by job classification; personal air samples from 1987 (n = 72) and 1999 (n = 10) collected 1987: median = 0.0005 mg/m^3, maximum = 0.0066 mg/m^3 1999: median = 0.0003 mg/m^3, maximum = 0.0007 mg/m^3 stationary samples provided similar medians	**Reported Endpoint:** diffusing capacity of the lung for carbon monoxide (T_{LCO}) (mean percentage of predicted values) Exp. Group / n / mean / SD / p-value unexposed never smokers: 27 / 112.1 / 11.7 / n/a Cr VI exposed never smokers: 41 / 112.1 / 13.9 / NS unexposed ever smokers: 52 / 102.1 / 11.8 / n/a Cr VI exposed ever smokers: 63 / 109 / 17.5 / <0.05 Stat Method: Student's t-test
Lung: spirometry	
Kuo et al. (1997) (Taiwan) cross-sectional study ***Population:*** Exposed: male and female Taiwanese chromium electroplating factory workers from 9 factories (n = 155); workers were from 3 factories that used chromium (mean age 36.3 years old), 6 that used nickel-chromium (mean age 39.6 years old) Referent: compared with workers from 2 zinc electroplating factory workers (n = 34; mean age 36.9 years old) ***Outcome:*** respiratory function test using machine operated by worker	**Reported Endpoint:** forced expiratory volume in 1 sec [FEV1] (mL) Exp. Group / n / reg. coeff / p-value zinc workers: 34 / n/a / n/a nickel-chromium workers: 129 / -311.5 / <0.05 chromium workers: 26 / -368 / <0.05 **Reported Endpoint:** forced vital capacity [FVC] (mL) Exp. Group / n / reg. coeff / p-value zinc workers: 34 / 1 / n/a nickel-chromium workers: 129 / -404.2 / <0.01 chromium workers: 26 / -556.4 / <0.01 **Reported Endpoint:** maximum expiratory flow rate [MEFR] (L/sec)

Reference and Study Design	Results by Endpoint			
Exposure Assessment: end of shift urine samples; average urinary chromium concentrations (µg/g creatinine): 3.7 (zinc workers), 7.3 (nickel-chromium workers), and 41 (chromium workers)	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	0.37	NS
	chromium workers	26	0.38	NS
	Reported Endpoint: peak expiratory flow in 1 second [PEF] (L/sec)			
	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	1.47	NS
	chromium workers	26	0.21	NS
	Reported Endpoint: peak expiratory flow in 25 seconds [PEF25] (L/sec)			
	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	0.17	NS
	chromium workers	26	0.13	NS
	Reported Endpoint: peak expiratory flow in 50 seconds [PEF50] (L/sec)			
	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	0.1	NS
	chromium workers	26	0.15	NS
	Reported Endpoint: peak expiratory flow in 75 seconds [PEF75] (L/sec)			
	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	0.01	NS
	chromium workers	26	0.03	NS
	Reported Endpoint: vital capacity [VC] (mL)			
	Exp. Group	n	reg. coeff	p-value
	zinc workers	34	1	n/a
	nickel-chromium workers	129	-296.2	<0.05
	chromium workers	26	-462.9	<0.01
	Stat Method: Multiple regression comparing lung function of chromium, nickel, and zinc workers (Cr workers' result minus Zn workers' result or Ni-Cr workers' result minus Zn workers' result)			

Reference and Study Design	Results by Endpoint
Lindberg and Hedenstierna (1983) (Sweden) cross-sectional study ***Population:*** Exposed: male and female employees in chrome plating industry (n = 104); employed in the chrome plating industry at 1 of 13 companies; working on the day of study; 40 nonsmokers and 64 smokers Referent: male auto mechanics (excluding painters or welders) (n = 119) and office employees (n = 19) used as reference group for lung function and nose and throat measurements, respectively (n = 138) ; 52 nonsmokers and 67 smokers ***Outcome***: spirometry; means reported for low, mixed, and high for Monday and Thursday am and used as a reference ***Exposure Assessment****:* personal air samples for 84 participants on 13 different days, personal air samples for 11 participants over a week, and 5 stationary air samples over 19 days; median exposure time was 4.5 years low exposure: <2 µg Cr VI/m^3 mixed exposure: <2 µg Cr VI/m^3 and other acids and metallic salts high exposure: ≥2 µg Cr VI/m^3	**Reported Endpoint:** CV% Exp. Group / n / mean / SD / p-value ***nonsmokers*** reference / 52 / 11.65 / 6.13 / n/a exposed / 17 / 15.2 / 8.1 / NS ***smokers*** reference / 67 / 12.43 / 5.52 / n/a exposed / 24 / 17.1 / 7.9 / NS Stat Method: multiple linear regression **Reported Endpoint:** FEF_{25-75} (L/sec) Exp. Group / n / mean / SD / p-value ***nonsmokers*** reference / 52 / 4.16 / 1.44 / n/a exposed / 26 / 4.71 / 1.6 / NS ***smokers*** reference / 67 / 4.36 / 1.33 / n/a exposed / 48 / 4.45 / 1.36 / NS Stat Method: multiple linear regression **Reported Endpoint:** FEF_{25-75} (L/sec) on Thursday afternoon Exp. Group / n / mean / SD / p-value low / 10 / 4.54 / 1.45 / NS mixed / 15 / 4.64 / 1.26 / NS high / 6 / 4.59 / 1.53 / <0.05 FEF_{25-75} observed on Monday and Thursday morning were reference values; authors stated FEF_{25-75} significantly decreased on Thursday afternoon compared with Monday morning and Thursday morning in high exposure group. Stat Method: multiple linear regression **Reported Endpoint:** FEV1.0 (L) Exp. Group / n / mean / SD / p-value ***nonsmokers*** reference / 52 / 4.08 / 0.85 / n/a exposed / 26 / 4.54 / 0.92 / NS ***smokers*** reference / 67 / 4.38 / 0.92 / n/a exposed / 48 / 4.31 / 0.85 / NS Stat Method: multiple linear regression **Reported Endpoint:** $FEV_{1.0}$ (L) on Thursday afternoon Exp. Group / n / mean / SD / p-value low / 10 / 4.43 / 0.97 / NS mixed / 15 / 4.06 / 0.95 / NS

Reference and Study Design	Results by Endpoint				
	high	6	4.92	1.29	<0.05
	$FEV_{1.0}$ observed on Monday and Thursday morning were reference values; authors stated $FEV_{1.0}$ significantly decreased on Thursday afternoon compared with Monday morning and Thursday morning in high exposure group. Stat Method: multiple linear regression				
	Reported Endpoint: FVC (L)				
	Exp. Group	n	mean	SD	p-value
	nonsmokers				
	reference	52	5.2	1	n/a
	exposed	26	5.61	0.99	NS
	smokers				
	reference	67	5.66	1.02	n/a
	exposed	48	5.27	0.9	NS
	Stat Method: multiple linear regression				
	Reported Endpoint: FVC (L) on Thursday afternoon				
	Exp. Group	n	mean	SD	p-value
	low	10	5.35	1.24	NS
	mixed	15	4.73	1.22	<0.01
	high	6	5.75	1.58	<0.01
	FVC observed on Monday and Thursday morning were reference values; authors stated FVC significantly decreased on Thursday afternoon compared with Monday morning and Thursday morning in high and mixed exposure groups. Stat Method: multiple linear regression				
	Reported Endpoint: phase III, % N_2/L				
	Exp. Group	n	mean	SD	p-value
	nonsmokers				
	reference	52	1.49	1.33	n/a
	exposed	17	1.09	0.57	NS
	smokers				
	reference	67	1.34	0.54	n/a
	exposed	24	1.63	0.97	NS
	Stat Method: multiple linear regression				
Huvinen et al. (2002b) (Finland)	**Reported Endpoint:** FEV% ($FEV_{1.0}$/FVC x 100)				
cohort (prospective) study	Exp. Group	n	mean	SD	p-value
Population: Exposed: workers in the furnace department of the ferrochromium plant and steel melting shop (n = 104; mean age 48 ± 6.9 years old)	unexposed never smokers	27	99.8	5.8	n/a
	Cr VI exposed never smokers	41	97.9	7.2	NS
Referent: compared with workers from the cold rolling mill whose exposure to	unexposed ever smokers	52	95.2	8.7	n/a

Reference and Study Design	Results by Endpoint				
chromium or dust in general was extremely low (n = 81; mean age 45.6 ± 7 years old) *Loss To Follow-Up:* 5 subjects lost to follow-up because they left the company (2) or died from cardiac infarction (3) ***Outcome:*** spirometry by experienced lab technicians ***Exposure Assessment:*** subjects categorized by job classification; personal air samples from 1987 (n = 72) and 1999 (n = 10) collected 1987: median = 0.0005 mg/m^3, maximum = 0.0066 mg/m^3 1999: median = 0.0003 mg/m^3, maximum = 0.0007 mg/m^3 stationary samples provided similar medians	Cr VI exposed ever smokers	63	97.8	7.8	NS
	Reported Endpoint: forced expiratory volume in 1 second ($FEV_{1.0}$)				
	Exp. Group	n	mean	SD	p-value
	unexposed never smokers	27	92.3	10.5	n/a
	Cr VI exposed never smokers	41	91.9	11.3	NS
	unexposed ever smokers	52	88.5	13.6	n/a
	Cr VI exposed ever smokers	63	87.9	14.1	NS
	Reported Endpoint: forced vital capacity (FVC) (L)				
	Exp. Group	n	mean	SD	p-value
	unexposed never smokers	27	92.4	8.5	n/a
	Cr VI exposed never smokers	41	94.2	12	NS
	unexposed ever smokers	52	92.9	11.5	n/a
	Cr VI exposed ever smokers	63	89.6	11.5	NS
	Stat Method: Student's t-test				
Bovet et al. (1977) (Switzerland) cross-sectional study ***Population:*** Exposed: male chromium electroplating workers (n = 44) employed in one of 17 chromium electroplating plants; the three exposure groups did not significantly differ by age, exposure time, or smoking status ***Outcome:*** wedge bellows spirotest using Kory et al., 1961 or Bates et al., 1962 standards ***Exposure Assessment:*** based on urinary measurements taken at end of morning or end of afternoon: low exposure: ≤6.0 µg/g creatinine medium exposure: 6.1–15 µg/g creatinine high exposure: 15.1 µg/g creatinine	**Reported Endpoint:** forced expiratory flow 25%-75% (FEF_{25-75}) (% of the standards of Bates)				
	urinary chromium concentration				
	Exp. Group	n	mean	SD	
	low (≤6.0)	26	106.98	27.15	
	medium (6.1–15)	12	90.73	22.00	
	high (≥15.1)	6	78.23	19.28	
	Reported Endpoint: forced expiratory volume in one second (FeV_1) (% of the standards of Kory)				
	Exp. Group	n	mean	SD	
	low (≤6.0)	26	95.64	10.63	
	medium (6.1–15)	12	92.73	13.72	
	high (≥15.1)	6	81.93	14.87	
	Reported Endpoint: vital capacity (% of the standards of Kory)				
	Exp. Group	n	mean	SD	
	low (≤6.0)	26	95.77	9.96	
	medium (6.1–15)	12	97.98	13.19	
	high (≥15.1)	6	89.85	14.22	
	Stat Method: not reported				

Reference and Study Design	Results by Endpoint			
		n	F value	p-value
	Parameter			
	forced expiratory flow 25%-75% (FEF_{25-75}) (% of the standards of Bates)	44	3.90	<0.03
	forced expiratory volume in one second (FeV_1) (% of the standards of Kory)	44	3.45	<0.05
	vital capacity (% of the standards of Kory)	44	1.04	0.36
	Authors noted that there was a significant effect of chromium on FeV_1 and FEF_{25-75}. Stat Method: univariate ANOVA			

NS: not significant; n/a: not applicable; SD: standard deviation; reg coeff: regression coefficient

2.8. Noncancer Respiratory Effects – Nasal Pathology and Histopathology

Table 2-7. Evidence pertaining to noncancer respiratory effects (nasal pathology and histopathology) following exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Clinical observation	
Huvinen et al. (2002b) (Finland) cohort (prospective) study ***Population:*** Exposed: workers in the furnace department of the ferrochromium plant and steel melting shop (n = 104; mean ± SD age 48 ± 6.9 years old) Referent: compared with workers from the cold rolling mill whose exposure to chromium or dust in general was extremely low (n = 81; mean ± SD age 45.6 ± 7 years old) *Loss To Follow-Up:* 5 subjects lost to follow-up because they left the company (2) or died from cardiac infarction (3) ***Outcome:*** self-reported (questionnaire) ***Exposure Assessment:*** subjects categorized by job classification; personal air samples from 1987 (n = 72) and 1999 (n = 10) collected 1987: median = 0.0005 mg/m^3, maximum = 0.0066 mg/m^3 1999: median = 0.0003 mg/m^3, maximum = 0.0007 mg/m^3 stationary samples provided similar medians	**Reported Endpoint:** rhinitis >3/12 months Exp. Group: Cr VI exposed group; percent difference[†]: 0.4; 95% CI: -13.3–14.1 Stat Method: Fisher's exact test
Lung: nonneoplastic lesions	
Huvinen et al. (1996) (Finland) cross-sectional study ***Population:*** Exposed: male stainless steel production workers (n = 109; mean ± SD age 43.3 ± 6.9 years old); minimum of 8 years of employment in the same department Referent: compared with male cold rolling mill workers (n = 95; mean ± SD age 40.7 ± 7.1 years old) ***Outcome:*** lesions determined by chest radiography	**Reported Endpoint:** lung: nonneoplastic lesions Exp. Group: reference (n = 95); Cr VI exposed (n = 109) bilateral pleural plaques (% of total): 0; 4.6; NS changes in visceral pleura (% of total): 1.1; 0.9; NS small opacities (% of total): 12.8; 12; NS unilateral pleural plaques (% of total): 3.2; 4.6; NS

Reference and Study Design	Results by Endpoint
Exposure Assessment: subjects grouped into 4 categories according to exposure to different chromium compounds; personal and stationary air samples collected during 1987 exposure study; Cr VI at low concentrations throughout the steel smelting shop; it exceeded the detection limit in only some personal samples; generally below detection in the cold rolling mill mean Cr VI concentration in urine for 44 workers: 0.03 µmol/L (1993) and 0.04 µmol/L (1987)	Stat Method: chi-square test
Nasal cavity: gross pathology	
Huvinen et al. (2002a) (Finland) cross-sectional study ***Population:*** Exposed: male stainless steel production workers (n = 29); never smokers with a minimum of 14 years employment in the same department Referent: compared with workers from the cold rolling mill (n = 39) whose exposure to chromium or dust in general was extremely low (total dust content = 0.3–0.5 mg/m^3) ***Outcome:*** questionnaire for nasal symptoms; physical exam including anterior rhinoscopy and rigid nasoendoscopy ***Exposure Assessment:*** subjects divided into 4 groups based on type of chromium exposure; Cr VI group comprised 29 workers from the steel melting shop (median Cr VI air concentration = 0.5 µg/m^3)	**Reported Endpoint:** nasal epithelium Exp. Group referent (n = 39) / steel melting shop (n = 29) Parameter [RR (95% CI)] atrophic nasal epithelium: 1 / 2.7 (0.36–20.2) infected nasal epithelium: 1 / 1.5 (0.64–3.7) livid/endemic nasal epithelium: 1 / 3.7 (1.3–10.6) total atypical nasal epithelium: 1 / 2.4 (1.4–4.1) Stat Method: likelihood-based risk ratio
Nasal cavity: nonneoplastic lesions	
Lindberg and Hedenstierna (1983) (Sweden) cross-sectional study ***Population:*** Exposed: male and female employees in chrome plating industry (n = 104); employed in the chrome plating industry at 1 of 13 companies; working on the day of study; 40 nonsmokers and 64 smokers Referent: male auto mechanics (excluding painters or welders) (n = 119) and office employees (n = 19) used as reference group for lung function and nose and throat	**Reported Endpoint:** atrophy ***8-hr mean air concentration Cr VI µg/m^3*** Exp. Group / n / cases / p-value <= 1.9 / 19 / 4 / NR 2–20 / 24 / 8 / <0.05 ***highest air concentration Cr VI µg/m^3*** Exp. Group / n / cases / p-value 0.2–1.2 / 10 / 1 / n/a 2.5–11 / 12 / 8 / NR 20–46 / 14 / 0 / NR **Reported Endpoint:** perforation only ***8-hr mean air concentration Cr VI µg/m^3***

Reference and Study Design	Results by Endpoint
measurements, respectively (n = 138) ; 52 nonsmokers and 67 smokers ***Outcome***: visual inspections conducted prior to interviews ***Exposure Assessment****:* personal air samples for 84 participants on 13 different days, personal air samples for 11 participants over a week, and 5 stationary air samples over 19 days; median exposure time was 4.5 years low exposure: <2 µg Cr VI/m^3 mixed exposure: <2 µg Cr VI+/m^3 and other acids and metallic salts high exposure: ≥2 µg Cr VI/m^3	Exp. Group / n / cases / p-value <= 1.9 / 19 / 0 / NR 2–20 / 24 / 3 / NR ***highest air concentration Cr VI µg/m^3*** Exp. Group / n / cases / p-value 0.2–1.2 / 10 / 0 / n/a 2.5–11 / 12 / 0 / NR 20–46 / 14 / 3 / NR
	Reported Endpoint: subjective irritation
	8-hr mean air concentration Cr VI µg/m^3 Exp. Group / n / cases / p-value <= 1.9 / 19 / 4 / NR 2–20 / 24 / 11 / NR ***highest air concentration Cr VI µg/m^3*** Exp. Group / n / cases / p-value 0.2–1.2 / 10 / 0 / n/a 2.5–11 / 12 / 8 / NR 20–46 / 14 / 4 / NR
	Reported Endpoint: ulceration
	8-hr mean air concentration Cr VI µg/m^3 Exp. Group / n / cases / p-value <= 1.9 / 19 / 0 / NR 2–20 / 24 / 8 / <0.01 ***highest air concentration Cr VI µg/m^3*** Exp. Group / n / cases / p-value 0.2–1.2 / 10 / 0 / n/a 2.5–11 / 12 / 0 / NR 20–46 / 14 / 7 / NR Stat Method: chi-square test with Yate's correction. Number of ulceration cases at the highest exposure value compared with controls was not discussed separately from the data reported as 8-hr mean value of exposure.
Lin et al. (1994) (Taiwan, Province of China) cross-sectional study ***Population:*** Exposed: male and female chromium electroplating workers from 7 chromium electroplating factories (n = 79; aged 15–64 years old) Referent: compared with male and female workers from 3 aluminum electroplating factories (n = 40; aged 14–65 years old)	**Reported Endpoint:** nasal septum abnormality

Exp. Group

Parameter (%)	Al workers (n = 40)	Cr office workers and drivers (n = 19)	Cr other process fields (n = 29)	Cr tank workers (n = 31)	p-value for trend
nasal septum perforation	0	11	10	35	<0.001

Reference and Study Design	Results by Endpoint
Outcome: condition based on otolaryngologist exam ***Exposure Assessment:*** based on job category; air and urine samples analyzed for Cr *geometric mean air concentrations:* Al electroplating factory workers (n = 15): 0.1 µg/m^3 Cr electroplating office, outdoor workers (n = 14): 2.4 µg/m^3 Cr electroplating workers in other process fields (n = 25): 11.2 µg/m^3 Cr electroplating workers near electroplating tanks (n = 23): 89.7 µg/m^3 *mean +/- SD urine levels:* Al electroplating factory workers (n = 40): 0.13 +/- 0.09 µg/g creatinine Cr electroplating office, outdoor workers (n = 19): 1.9 +/- 1.7 µg/g creatinine Cr electroplating workers in other process fields (n = 29): 3.5 +/- 1.6 µg/g creatinine Cr electroplating workers near electroplating tanks (n = 30): 11.9 +/- 8.7 µg/g creatinine	nasal septum scar formation 0 0 3 10 0.043 nasal septum ulcer 0 16 48 68 <0.001 Stat Method: Mantel extension test for trend
Kitamura et al. (2003) (Korea) cross-sectional study ***Population:*** Exposed: male chromium plating workers aged 19–53 years old (n = 27) with signs and symptoms of olfactory irritation, but without nasal septum perforation or ulcer Referent: compared with healthy male clerks working at the same factory (n = 34) ***Outcome:*** rhinoscopy examination by otolaryngologist ***Exposure Assessment:*** based on job title; blood and urine Cr levels measured plating workers blood Cr: 1.29 (0.16–3.69) µg/dL; urinary Cr: 2.88 (0.01–8.37) µg/g creatinine referent blood Cr: 0.55 (0.04–1.95) µg/dL; urinary Cr: 2.26 (0.01–10.18) µg/g creatinine air concentrations in plating factories	**Reported Endpoint:** inflammation of nasal mucosa Exp. Group Parameter (%) — reference (n = 34) — Cr plating workers (n = 26) — p-value inflammation of nasal mucosa — 65 — 73 — NS obstruction or adhesion of the olfactory cleft — 6 — 46 — <0.01 Stat Method: chi-squared test

Reference and Study Design	Results by Endpoint
Cr VI: 0.013, 0.033, 0.0054, and 0.0047 mg/m^3 Cr III: 0.059, 0.021, 0.0063, and 0.0047 mg/m^3	
Kuo et al. (1997) (Taiwan) cross-sectional study ***Population:*** Exposed: male and female Taiwanese chromium electroplating factory workers from 9 factories (n = 155); workers were from 3 factories that used chromium (mean age 36.3 years old), 6 that used nickel-chromium (mean age 39.6 years old) Referent: compared with workers from 2 zinc electroplating factory workers (n = 34; mean age 36.9 years old) ***Outcome:*** condition based on otolaryngologist exam ***Exposure Assessment:*** end of shift urine samples; average urinary chromium concentrations (µg/g creatinine): 3.7 (zinc workers), 7.3 (nickel-chromium workers), and 41 (chromium workers)	**Reported Endpoint:** nasal obstruction Exp. Group; n; Prev (%); p-value zinc workers; 34; 0; nickel-chromium workers; 129; 17.8; 0.01 chromium workers; 26; 15.4; 0.01 **Reported Endpoint:** nasal septum perforation Exp. Group; n; Prev (%); p-value zinc workers; 34; 0; n/a nickel-chromium workers; 129; 1.6; NS chromium workers; 26; 30.8; <0.01 **Reported Endpoint:** nasal septum ulcer Exp. Group; n; Prev (%); p-value zinc workers; 34; 0; n/a nickel-chromium workers; 129; 5.4; NS chromium workers; 26; 38.5; <0.01 **Reported Endpoint:** paranasal sinusitis Exp. Group; n; Prev (%); p-value zinc workers; 34; 0; n/a nickel-chromium workers; 129; 0.8; 1.00 chromium workers; 26; 0; 1.00 Stat Method: chi-squared test or analysis of variance; Mantel extension test for trend
Royle (1975) (United Kingdom) cross-sectional study ***Population:*** Exposed: male and female chromium platers (n = 997; mean age 42.9); exposed to chromic acid >=3 months; employed at 1 of 54 plating plants whose principal industry was chromium plating Referent: compared with male and female manual workers in the same area (n = 1117; mean age 43.6) ***Outcome:*** self-reported (questionnaire) ***Exposure Assessment:*** questionnaire used to record number of years a worker was exposed to chromic acid during chromium plating; air and dust analyses recorded in 42 of 54 plants (1969–1970); Cr air levels generally <0.03 mg/m^3; dust levels generally between 0.3 and 97.0 mg/g	**Reported Endpoint**: nasal effects ***years CrO_3 exposure*** Exp. Group Parameter (%); <1 (n = 234); 1-5 (n = 394); >5 (n = 369); p-value for trend nasal ulcers; 6; 13.1; 16.8; 0.001 nose bleeding; 14.5; 19; 16; NS nasal perforations; 0.5; 3.6; 8.7; 0.001 Stat Method: not reported

Reference and Study Design	Results by Endpoint
PHS (1953) (United States) cohort (retrospective) study ***Population:*** Exposed: male workers in 6 plants directly involved in the manufacture of chromates and bichromates from chromite ore (n = 897) Referent: none ***Outcome:*** information obtained from medical records ***Exposure Assessment:*** exposure based on time worked in industry	**Reported Endpoint:** perforation of nasal septum ***time worked in industry*** Exp. Group — n — Prev (%) <6 months — 41 — 2.4 6 months–3 years — 117 — 39.3 3-10 years — 370 — 55.4 >10 years — 369 — 69.6 Stat Method: not reported
Gibb et al. (2000b) (United States) cohort (retrospective) study ***Population:*** Exposed: male workers in a chromate production plant in Baltimore, MD (n = 2307); first employed between August 1, 1950 and December 31, 1974 Referent: none ***Outcome:*** physician findings reported in clinic and first records ***Exposure Assessment:*** airborne Cr VI measurements taken 1950–1985 based on job title to provide worker exposure estimates; short-term airborne dust samples collected in workers' breathing zones 1950–1964; mid-1960s–1985, 24-hour measurements from fixed-site monitors and observations of time spent near each monitor used; 1977–1985, full-shift personal samples collected based on job title; plant closed 1985 *Length of Follow-Up:* 18 years	**Reported Endpoint:** ulcerated nasal septum ***ambient airborne chromium*** Parameter — cases — adjRR — p-value 0.1 mg CrO_3/m^3 increase — 1451 — 1.2 — 0.0001 Authors stated that ambient airborne hexavalent chromium exposure was significantly associated with occurrence of ulcerated nasal septum. Stat Method: Cox proportional hazards model adjusted for calendar year at hire and age at hire
Cohen et al. (1974) (United States) cross-sectional study ***Population:*** Exposed: white male and female electroplate workers aged 18–63 years old in the nickel-chrome department (n = 37) Referent: compared with randomly-chosen workers employed in other areas of the plant not significantly exposed to chromic acid (n = 15) ***Outcome:*** self-reported (questionnaire) ***Exposure Assessment:*** air samples collected from the breathing zones of several exposed workers in the nickel-chrome	**Reported Endpoint:** nasal ulceration Parameter (%) — non-exposed (n = 15) — exposed (n = 37) nasal mucosa (grade 0) — 93 — 5 shallow erosion of septal mucosa (grade 1) — 0 — 22 ulceration and crusting of septal mucosa (grade 2) — 0 — 32 avascular, scarified areas of septal mucosa without erosion or ulceration (grade 3) — 0 — 30 perforation of septal mucosa (grade 4) — 7 — 11

Reference and Study Design	Results by Endpoint
department and referents; mean Cr VI = 0.0029 (ND–0.0091) and 0.0003 (0.0001–0.0004) in nickel-chrome plating area and referent areas, respectively	Stat Method: Fisher's exact test (results not provided)

cases = number of cases calculated from information provided by study authors

[†] difference in percent of respiratory symptoms between referents and Cr VI exposed subjects

adjRR: adjusted relative risk; NS: not significant; NR: not reported; n/a: not applicable; SD: standard deviation; RR: relative risk; 95% CI: 95% confidence interval

2.9. Lung Cancer

Table 2-8. Evidence pertaining to lung cancer following inhalation exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Studies of Baltimore chromate production plant (after improvements to production facilities)	
Gibb et al. (2000a) (United States) cohort study ***Population:*** Exposed: male chromate production workers in Baltimore, MD (n = 2357); first employed between August 1, 1950, and December 31, 1974, after improvements made to chromium production processes. Mean duration 3.1 years; median 5 months. Referent: external analysis (compared with Maryland state rates); internal analysis across exposure levels ***Outcome***: National Death Index (1979–1992); Social Security data 1977–1978; information through 1977 obtained from Hayes et al. (1979); cause on death certificate based on ICD8 ***Exposure Assessment****:* Cumulative exposure using job exposure matrix developed based on work histories and approximately 70,000 routinely collected exposure measurements taken beginning in 1950; measurement protocols changed over time: short term (10–20 minutes) breathing zone samples used high volume air sampling pump and impinger from 1950 to 1961; fixed site samples (24 1-hour samples per day) from 154 areas and estimation of time spent in specific areas used beginning in the 1960s; reduced to 27 areas and 8 3-hour samples in 1979; full-shift personal samples beginning in 1977; dust samples collected about 3 years after plant closed at or near 26 of the 27 fixed sites; air analyzed for trivalent/hexavalent ratio. Also includes information on smoking status at beginning of employment for 93% of cohort. Five-year lag used for all models. *Mean Length of Follow-Up:* 30 years Related studies: earlier analyses of related cohorts: Hayes et al. (1979) and Braver et al. (1985); subsequent analyses of exposure-response: OSHA (2006); Park and Stayner (2006); and Park et al. (2004).	**Reported Endpoint:** lung cancer mortality; ICD8 ***cumulative Cr exposure (mg CrO_3/m^3-yrs)*** Exp. Group: each 10-fold increase; cases: 122; RR: 1.38; p-value: 0.0001 Stat Method: Cox proportional hazard models using age as the time variable and adjusting for smoking status. ***cumulative Cr exposure quartiles (mg CrO_3/m^3-yrs)*** 0-0.00149: 26; 1; (referent) 0.0015-0.0089: 28; 1.83; NR 0.009-0.0769: 30; 2.48; NR 0.077-5.25: 38; 3.32; NR Stat Method: Cox proportional hazard models using age as the time variable, median value in each exposure quartile, and adjusting for smoking status. Additional analyses indicated associations with hexavalent chromium (RR 1.55 per 10-fold increase) but not with trivalent chromium (RR 0.17 per 10-fold increase). OSHA (2006) includes additional modeling of these data using: different numbers of exposure categories (e.g., 5, 6, 10); Baltimore city rather than Maryland state reference rates; different lag periods; estimates of cumulative smoking (pack-years). Park and Stayner (2006) examined evidence of non-linearity using these data: the potential value of two-stage modeling was evaluated and found to provide little improvement in model fit; additional modeling of departure from linearity using a one-stage model and second-degree fractional polynomials; and other measures to examine intensity thresholds and effects of different assumptions regarding exposure half-life. Park et al. (2004) used these data to estimate excess lifetime risk of lung cancer. At the (then) OSHA permissible exposure limit (PEL) of 0.10 mg/m^3, the excess lifetime risk was 255 (95% CI 109–416) per 1,000.

Reference and Study Design	Results by Endpoint
Studies of Ohio chromate production plant	
Proctor et al. (2004) (United States) cohort study ***Population:*** Exposed: male chromate production workers in Painesville, OH, who worked at least 12 months beginning in January 1940 or later (n = 482); mean duration not reported; 45% <5 years in exposed job Referent: external analysis (compared with Ohio state rates); internal analysis across exposure levels ***Outcome***: National Death Index; cause on death certificate based on ICD9 code 162 ***Exposure Assessment****:* Cumulative exposure and highest average monthly exposure using job exposure matrix developed based on work histories and approximately 800 area air samples collected from 23 surveys conducted in 1943–1981. Also includes information on smoking status at beginning of employment for 35% of cohort Five-year lag used for all models. *Mean Length of Follow-Up:* 30 years Related studies: Proctor et al. (2003) (additional exposure assessment details); Crump et al. (2003); Luippold et al. (2003); Mancuso (1997, 1975) (previous studies of an earlier cohort: workers hired 1931–1937, with exposure based on 1949 industrial hygiene survey)	**Reported Endpoint:** lung cancer mortality; ICD9 (162) ***cumulative hexavalent chromium exposure (mg/m^3- yrs)*** Exp. Group / cases / SMR / p-value 0-0.19 / 3 / 0.67 / n/a 0.2-0.48 / 8 / 1.8 / NS 0.49-1.04 / 4 / 0.91 / NS 1.05-2.69 / 16 / 3.7 / <0.05 2.7-23 / 20 / 4.6 / <0.05 Stat Method: SMRs using state referent rates ***highest monthly hexavalent chromium exposure (mg/m^3)*** Exp. Group / cases / SMR / p-value <0.052 / 4 / 1 / n/a 0.053-0.16 / 4 / 1.7 / NS 0.209-0.212 / 9 / 1.9 / <0.05 0.27-0.42 / 5 / 1.9 / <0.05 0.47-0.57 / 20 / 2.9 / <0.05 0.58-4.1 / 9 / 6.9 / <0.05 Stat Method: SMRs using state referent rates Crump et al. (2003) includes additional modeling of these data (e.g., using relative risk and additive risk models with additional exposure categories for cumulative exposure).
Studies of modern production facilities	
Birk et al. (2006) (Germany) cohort study ***Population***: Exposed: male chromate prodcution workers from two plants; worked at least 12 months after each plant converted to a no-lime process (n = 901); Leverkusen n = 593, began work in 1958 or later, mean duration 9 yrs; Uerdingen (n = 308, began work in 1964 or later, mean duration 11 years Referent: external analysis (compared with regional rates); also included analysis by exposure level ***Outcome:*** cause on death certificate based on ICD9 ***Exposure Assessment***: Cumulative exposure using job exposure matrix developed based on work	**Reported Endpoint:** lung cancer mortality; ICD9 (162) Exp. Group / n / SMR / 95% CI chromate workers / 22 / 1.48 / 0.93–2.25 Stat Method: SMR calculated using German national rates ***cumulative Cr in urine (µg/L-yr)*** Exp. Group / n / OR / 95% CI ≥200 / 8 / 6.9 / 2.6–18.2 ≥200 (adjusting for peak exposure) / 8 / 3.7 / 1.2–11.2 Peak exposure (one or more measure ≥40 µg/L, adjusting for cumulative exposure) / NR / 3.4 / 0.9–12.1 Authors state risk unchanged after controlling for smoking. Stat Method: logistic regression

<table>
<tr><th>Reference and Study Design</th><th>Results by Endpoint</th></tr>
<tr><td>histories and urinary Cr measurements (most collected from routine medical examinations; (n = 7000 from 1958–1998 in Leverkusen and n = 5400 from 1 964–1995 in Uerdingen). Personal air sam ples (n =252 from 1985–1998 in Leverkusen and n =215 from 1986–1994 in Uerdingen) and area air samples (n = 3422 from 1973–1998) in Leverkusen and n= 1161 from 1978–1995 in Uerdingen) were avaiable for part of the study period.</td><td></td></tr>
<tr><td>Exposure mean: varied over time (general decline from 1960s through 1990s). Mean concentration in air: 8.83 and 8.04 µg Cr/m^3 in Leverkusen and Uerdingen, respectively. Range of concentration in urine: from 15–50 µg/L up to 1970 to 1–<10 µg/L in 1987–1998 in Leverkusen; from 5–30 µg/L up to 1970 to 1–<10 µg/L in 1987–1996 in Uerdingen.

Mean Length of Follow-Up: 16 years for Leverkusen plant; 19 years for Uerdingen plant

Smoking data available for more than 90% of cohort

Related studies: Korallus et al. (1993) (earlier study of both plants); Industrial Health Foundation (2002) [see table entry below; this report provides more extensive details regarding the study population, exposure measures, and analysis than found in Birk et al. (2006)]</td><td>***cumulative Cr in urine (µg/L-yr) 10-year lag***

<table>
<tr><th>Exp. Group</th><th>n</th><th>SMR</th><th>95% CI</th></tr>
<tr><td>0–39.9</td><td>6</td><td>0.93</td><td>0.34–2.01</td></tr>
<tr><td>40–99.9</td><td>3</td><td>0.78</td><td>0.16–2.28</td></tr>
<tr><td>100–199.9</td><td>5</td><td>1.31</td><td>0.43–3.07</td></tr>
<tr><td>≥200</td><td>8</td><td>2.05</td><td>0.88–4.04</td></tr>
</table>
Similar results seen with 0- and 10-year lags.

Stat Method: SMRs calculated using North Rhine-Westphalia referent population rates</td></tr>
<tr><td>Luippold et al. (2005) (United States)

cohort study

Population: Exposed: male and female chromate production workers from two plants (n = 617), worked at least 12 months: Castle Hayne, NC (n = 430, began work 1971 or later, mean duration 12 years) and Corpus Christi, TX (n = 187, began work 1980 or later, mean duration 8 years)

Referent: external analysis (compared with state rates)

Outcome: cause on death certificates (pre-1979) and in National Death Index-Plus (post-1979) based on ICD9 code 162

Exposure Assessment: Cumulative exposure using job exposure matrix developed based on work histories and personal air-monitoring measurements (n = 5461 from 1974–1992 and 1995–1998 in the North Carolina plant; n = 1249 from 1980–1982, 1986–1988, and 1990–1998 in the Texas plant). Additional area samples available for other years in the study period.</td><td>Reported Endpoint: lung cancer mortality; ICD9 (162)

<table>
<tr><td>occupation</td></tr>
</table>
<table>
<tr><th>Exp. Group</th><th>cases</th><th>SMR</th><th>95% CI</th></tr>
<tr><td>chromate workers</td><td>3</td><td>0.84</td><td>0.17–2.44</td></tr>
</table>
Stat Method: SMRs using state referent rates</td></tr>
</table>

Reference and Study Design	Results by Endpoint
exposure range: 0.36–4.36 µg/m^3 *Mean Length of Follow-Up:* 20 years for North Carolina plant; 10 years for Texas plant Smoking data available for 89% of cohort Related studies: Pastides et al. (1994) (North Carolina plant; earlier – 10 year mean follow-up); Industrial Health Foundation (2002) [see table entry below; this report provides more extensive details regarding the study population, exposure measures, and analysis than found in Luippold et al. (2005)]	
Industrial Health Foundation (2002) (United States; Germany) cohort study [This is the original analysis of the 4 plants that were subsequently published as separate papers by Birk et al. (2006) and Luippold et al. (2005) for two plants in Germany and two plants in the United States, respectively. Details from this report pertaining to the cohorts, exposure measures, and analysis are provided in the table entries above for Birk et al. (2006) and Luippold et al. (2005).] ***Population:*** Exposed: chromate production workers in four plants (two in Germany, n = 901 and two in United States (n = 617) (total n = 1518); worked 1 year or more in plants using low- or no-lime chromium production processes Referent: external analysis (compared German national rates and U.S. state rates); internal analysis across exposure levels ***Outcome***: cause on death certificate (ICD not reported) ***Exposure Assessment:*** Cumulative and peak exposure measures developed based on work histories and job exposure matrix based on urinary Cr measures (German plants) and personal air monitoring levels (U.S. plants); for internal analysis combining all plants, air exposure levels for the U.S. plants were converted to urinary exposure levels using a published conversion factor (0.77); this value was somewhat smaller than the conversion factor derived from limited parallel data from the German plants (0.85 for Leverkusen plant and 0.92 for Uerdingen)	**Reported Endpoint:** lung cancer mortality; ICD9 (162) ***cumulative Cr exposure (µg/L-yr)*** Exp. Group / cases / SMR / 95% CI <40 / 9 / 0.89 / 0.41–1.7 40–99.9 / 3 / 0.78 / 0.16–2.3 100–<200 / 5 / 1.31 / 0.43-3.1 ≥200 / 8 / 2.05 / 0.88–4.0 Stat Method: SMRs calculated using North Rhine-Westphalia and state referent population rates Exp. Group / cases / adjOR / 95% CI <40 / 3 / 1.0 / (referent) 40–<200 / 9 / 2.0 / 0.6–6.9 ≥200 / 9 / 8.0 / 2.4–27.1 Stat Method: logistic regression; adjusted for smoking and limited to age at first exposure ≥35 yrs (only 1 death among those exposed before age 35) Exp. Group / adjOR / 95% CI High cumulative (>200 µg/L-yrs) / 3.8 / 1.2–11.5 Ever peak (≥40 µg/L) / 3.1 / 0.9–11.3 Stat Method: logistic regression; adjusted for smoking and limited to German cohort (22 of the 25 deaths occurred in Germany; Germany had higher cumulative exposures; and individual data allowed assessment of "peak" exposure)

Reference and Study Design	Results by Endpoint
Mean Length of Follow-Up: 16 years for Leverkusen plant; 19 years for Uerdingen plant; 20 years for North Carolina plant; 10 years for Texas plant Smoking data available for 93% of German workers and 89% of U.S. workers	
Davies et al. (1991) (United Kingdom) cohort study ***Population****: Exposed:* male chromate production workers at three facilities, two of which implemented process and hygiene improvements at factories (allowing comparison of "prechange" and "postchange" workers) (n = 2607); worked at least 1 full year with some of the work occurring between January 1, 1950, and June 30, 1976 Referent*:* local and national death rates adjusted for social class and area differences ***Outcome***: cause on death certificate based on ICD9 codes 162 and 239.1 ***Exposure Assessment****:* based on job history, duration of service, start of employment, and implementation of process and hygiene improvements that started in 1955; no exposure estimates provided *Mean Length of Follow-Up:* not reported	**Reported Endpoint:** lung cancer mortality; ICD9 (162 and 239.1) Exp. Group / cases / SMR / p-value Rutherglen prechange (starting dates 1945–1958): 41 / 1.60 / <0.001 Rutherglen postchange (starting dates 1959–1966): 8 / 0.97 / NS Eaglescliffe prechange (starting dates 1945–1960): 52 / 1.95 / <0.001 Eaglescliffe postchange (starting dates 1961–1976): 6 / 1.09 / NS Stat Method: SMRs using area mortality data, adjusted for class and area; Poisson distribution used to test statistical significance (results also provided using national rates, but with little difference) Authors noted several cases of lung cancer among postchange workers at young ages (<50 years) and seven additional lung cancers among postchange workers in Eaglescliffe identified after the end of the follow-up period (Dec 1, 1988).
Studies of stainless steel welders	
Gerin et al. (1993) (9 European countries) cohort study ***Population:*** Exposed: male stainless steel workers in IARC multicenter historical cohort study from 135 companies in 9 European countries (n = 11,092) Referent: compared with expected deaths ***Outcome:*** method not reported ***Exposure Assessment****:* Cumulative dose estimated based on each subject's exposure history constructed including dates of starting and stopping employment; the base metal welded and the welding process; changes in exposure over time; and information on the history of the welding practice over time by company (based on	**Reported Endpoint:** lung cancer mortality ***cumulative hexavalent Cr exposure in ever stainless steel welders (mg-years/m^3)*** Exp. Group / cases / SMR / 95% CI <0.05: 0 / 0 / 0–12.7 0.05–0.5: 7 / 1.30 / 0.52–2.68 0.5–1.5: 9 / 1.93 / 0.88–3.66 1.5+: 5 / 1.41 / 0.46–3.29 Stat Method: SMRs using expected relative risks ***cumulative hexavalent Cr exposure in predominantly stainless steel welders (mg-years/m^3)*** Exp. Group / cases / SMR / 95% CI <0.05: 0 / 0 / 0–28.4 0.05–0.5: 3 / 2.08 / 0.43–6.09

Reference and Study Design	Results by Endpoint			
average concentrations of welding fumes for each welding situation)	0.5–1.5	4	2.00	0.55–5.12
	1.5+	5	1.48	0.48–3.45
	Stat Method: SMRs using expected relative risks			

adjOR: adjusted odds ratio; NR: not reported; NS: not significant; n/a: not applicable; SMR: standard mortality rate; RR: relative risk; 95% CI: 95% confidence interval

2.10. Cancers Associated with Oral Exposure

Table 2-9. Evidence pertaining to cancer following oral exposure to hexavalent chromium

Reference and Study Design	Results by Endpoint
Stomach: neoplastic lesions	
Several papers based on mortality data for a population in northeastern China **Zhang and Li (1997)[a]; (1987)** **Beaumont et al. (2008)** **Kerger et al. (2009)** ecological studies ***Population:*** Exposed: males and females from 5 agricultural villages 1–5 miles east of ferrochromium alloy plant near JinZhou city in the LiaoNing Province. Groundwater contaminated by Cr VI up to 20 mg/L (n ~ 10,000) between 1960 and 1978; reporting of a yellowing of the water by local residents in 1964 is what led to the investigation and identification of this contamination by the local health department. Referent: Original study by Zhang and Li (1987) and Beaumont et al. (2008) : comparison was area including the industrial town of TangHeZi and 3 agricultural villages near TangHeZi with no groundwater hexavalent chromium pollution. Kerger et al. (2009) presented results using TangHeZi only, and using the other villages excluding TangHeZi from the referent group. ***Outcome:*** cause on death records ***Exposure Assessment:*** comprehensive well survey (21–170 wells per village tested) in 1965; periodic testing through 1979 [a] Zhang and Li (1997) was retracted in 2006 by *Journal of Occupational and Environmental Medicine* because "financial and intellectual input to the paper by outside parties was not disclosed" (Brandt-Rauf, 2006).	**Reported Endpoint:** stomach cancer deaths Reference and Comparison Group — RR — 95% CI Beaumont et al. (2008) (four areas) — 1.82 — 1.11–2.91 Beaumont et al. (2008) (LiaoNing Province) — 1.69 — 1.12–2.44 Kerger et al. (2009) (agricultural villages, excludes TangHeZi) — 1.22 — 0.74–2.01 Kerger et al. (2009) (TangHeZi, excludes agricultural villages) — 2.07 — 1.25–3.44 [Other differences in the analytic approach and results among these studies will be presented in greater detail in the draft Toxicological Review.]
Linos et al. (2011) (Greece) ecological study ***Population:*** Exposed: male and female adult residents of industrial area of Greece (Oinofita region) who were registered as permanent residents of Oinofita in the municipality records (n = 5842); legally registered citizens of the municipality at any time during the follow-up period (1/1/1999–31/12/2009)	**Reported Endpoint:** stomach cancer deaths; ICD9 (151) Exp. Group — cases — SMR — 95% CI — p-value total — 6 — 1.21 — 0.44–2.63 — 0.755 male — 4 — 1.16 — 0.32–2.96 — 0.909 female — 2 — 1.33 — 0.16–4.81 — 0.886 Stat Method: SMRs using Voiotia mortality statistics

Reference and Study Design	Results by Endpoint
Referent: compared with mortality statistics of the entire Voiotia prefecture (similar geographical, population density, socioeconomic, and ethnic origin characteristics) ***Outcome:*** cause on death certificate based on ICD9 code 151 ***Exposure Assessment:*** measurements of Cr VI in groundwater from Oinofita municipality November 2007–February 2008: levels above 10 µg/L in 35 out of 87 samples with maximum of 156 µg/L September 2008–December 2008: 41–53 µg/L in 3 samples of public drinking water July 2007–July 2010: 13 measurements above 10 µg/L with maximum of 51 µg/L (other potential contaminants not measured)	
Oral, liver, and other GI tract and urinary tract cancers	
Linos et al. (2011) (Greece) ecological study ***Population:*** Exposed: male and female adult residents of industrial area of Greece (Oinofita region) who were registered as permanent residents of Oinofita in the municipality records (n = 5842); legally registered citizens of the municipality at any time during the follow-up period (1/1/1999–31/12/2009) Referent: compared with mortality statistics of the entire Voiotia prefecture (similar geographical, population density, socioeconomic, and ethnic origin characteristics) ***Outcome:*** cause on death certificate based on ICD9 code 151 ***Exposure Assessment:*** measurements of Cr VI in groundwater from Oinofita municipality November 2007–February 2008: levels above 10 µg/L in 35 out of 87 samples with maximum of 156 µg/L September 2008–December 2008: 41–53 µg/L in 3 samples of public drinking water July 2007–July 2010: 13 measurements above 10 µg/L with maximum of 51 µg/L (other potential contaminants not measured)	**Reported Endpoint**: lip, oral cavity and pharynx cancer deaths; ICD9 (140-149) Exp. Group / cases / SMR / 95% CI / p-value total / 3 / 3.44 / 0.71–10.1 / 0.117 male / 3 / 4.69 / 0.97–13.7 / 0.055 female / 0 / n/a / n/a / n/a **Reported Endpoint**: colon cancer deaths; ICD9 (153) Exp. Group / cases / SMR / 95% CI / p-value total / 6 / 0.84 / 0.31–1.82 / 0.844 male / 1 / 0.28 / 0.01–1.54 / 0.249 female / 5 / 1.40 / 0.45–3.26 / 0.578 **Reported Endpoint**: liver primary cancer deaths; ICD9 (155.0) Exp. Group / cases / SMR / 95% CI / p-value total / 6 / 11.0 / 4.05–24.0 / <0.001 male / 4 / 8.12 / 2.21–20.8 / 0.003 female / 2 / 39.5 / 4.79–143 / 0.002 **Reported Endpoint**: pancreas cancer deaths; ICD9 (157) Exp. Group / Exp. Group / Exp. Group / Exp. Group / Exp. Group total / 6 / 0.85 / 0.31–1.85 / 0.882 male / 4 / 0.88 / 0.24–2.25 / 1.000 female / 2 / 0.80 / 0.10–2.88 / 1.000 **Reported Endpoint**: bladder cancer deaths; ICD9 (188) Exp. Group / cases / SMR / 95% CI / p-value total / 3 / 0.82 / 0.17–2.40 / 1.000 male / 2 / 0.65 / 0.08–2.36 / 0.821

Reference and Study Design	Results by Endpoint				
	female	1	1.68	0.04–9.38	0.896
	Reported Endpoint: kidney and other genitourinary organ deaths; ICD9 (184, 187, 189)				
	Exp. Group	cases	SMR	95% CI	p-value
	total	6	2.04	0.75–4.43	0.158
	male	1	0.63	0.02–3.51	1.000
	female	5	3.68	1.19–8.58	0.025
	Stat Method: SMRs using Voiotia mortality statistics				

adjBeta: adjusted Beta; n/a: not applicable; SMR: standard mortality rate; RR: relative risk; 95% CI: 95% confidence interval

3. PRELIMINARY TOXICOKINETIC STUDY INFORMATION

Studies relevant to the absorption, distribution, metabolism, or excretion (ADME) of hexavalent chromium identified through the literature search for this chemical are summarized in Tables 3-1 to 3-5. These tables summarize key study design features; they do not include an extraction of detailed study information or results, and as such, do not represent evidence tables. The purpose of these tabulations is to elicit early discussions with stakeholders and the public on potential issues related to these studies, and to provide an opportunity for identifying other relevant studies not captured in the literature search.

Table 3-1 presents a summary of studies that contain primary in vivo toxicokinetic data in rats, mice, and humans following hexavalent chromium exposure. These tables indicate whether studies contained concurrent data for trivalent chromium exposure, as these data are informative in directly assessing differences between hexavalent and trivalent chromium kinetics. Table 3-1 also indicates whether a study has been used quantitatively or qualitatively in the development of physiologically-based pharmacokinetic (PBPK) models.

Table 3-2 presents a summary of studies that contain in vitro or ex vivo data related to absorption and/or reduction in the GI tract or blood. These studies primarily focus on quantitative analysis of kinetics.

Table 3-3 presents a summary of studies related to the distribution and reduction of hexavalent chromium in a variety of systems. These studies differ from those in Table 3-2 in that the experiments primarily focused on mechanisms by modifying the enzymes or transport carriers in the systems tested. Tables 3-1 to 3-3 include only those studies pertaining primarily to hexavalent chromium *toxicokinetics*, and do not include studies that primarily address hexavalent chromium *toxicity*.

Table 3-4 presents a summary of studies related to human biomonitoring of hexavalent chromium in industrial or volunteer populations that focus primarily on data on biomarkers of exposure as opposed to human health effects.

Table 3-5 identifies papers that present PBPK models for hexavalent chromium. Figure 3-1 illustrates how toxicokinetic data from multiple sources are utilized in PBPK models, and how these models may be applied in dose-response assessment.

Table 3-1. Preliminary categorization of in vivo hexavalent chromium toxicokinetic studies

Reference	Species	Tissue matrices and notes	Cr III control[a]	PBPK use[b]
Intravenous (IV) injection				
Cavalleri et al. (1985)	Rat	Bile, whole blood, and plasma. 2 hour time course data.	N	Y
Cikrt and Bencko (1979)	Rat	Total body burden, urine, feces, liver, kidneys, plasma, and GI tract wall. 24 hour time course data.	Y	Y
Danielsson et al. (1982)	Mouse	Fetus, placenta, liver, kidney, serum. Injection to pregnant mice at day 13 or 16 of gestation. Spot sample 1 hour after injection.	Y	N
Liu et al. (1994) Liu et al. (1996)	Mouse	Blood, liver, heart, spleen, kidney, and lung. Kinetics of pentavalent chromium (Cr V) following Cr VI reduction. 60 minute time course data.	N	N
Norseth et al. (1982)	Rat	Bile and liver. 2 hour time course data.	Y	N
Merritt et al. (1989)	Hamster	Urine, plasma, RBC, kidney, spleen, liver, and lung. Monthly or weekly injections. 5 week post exposure time course data	N	N
Richelmi et al. (1984)	Rat	Blood. In vivo Cr VI measurement of reduction and capacity. Spot sample at 1 minute post exposure.	N	Y
Intraperitoneal (IP) injection				
Afolaranmi and Grant (2013)	Rat	Liver, kidney, heart, brain, lung, spleen, testes, blood, urine, and feces. Effect of ascorbic acid. Spot sample 24 hours post exposure.	N	N
Balakin et al. (1981)	Rat	Liver, whole body (excluding liver), wall of cecum, chime of cecum, urine, and feces. Spot sample 30 minutes post exposure. This is a chelation study that included a Cr VI-only group.	Y	N
Bryson and Goodall (1983)	Mouse	Total body burden, urine, and feces. 21-day time course data.	Y	N
Bulikowski et al. (1999)	Rat	Skin. Injections over 30 days. Micronutrient interaction study with Cr VI-only groups.	N	N
Döker et al. (2010)	Mouse	Liver, kidney, brain, lung, heart, and testis. Effect on other essential metals analyzed. Spot sample at 12 hours post exposure.	N	N
Manzo et al. (1983)	Rat	Bile, plasma, liver, urine, feces, stomach, small intestine, and large intestine. Detection in GI tissues post exposure. 2 hour time course data.	Y	Y
Ogawa et al. (1976)	Mouse	Urine, feces, whole body. Spot sample data at 48 hours post exposure.	Y	N
Sankaramanivel et al. (2006)	Rat	Bone (vertebrae, femur, and calvaria). IP injections once per day for 5 days.	N	N

Reference	Species	Tissue matrices and notes	Cr III control[a]	PBPK use[b]
Suzuki (1988b)	Rat	Plasma, whole blood. 60 minute time course data.	N	N
Ueno et al. (1995)	Mouse	Liver. Total Cr and pentavalent (Cr V). 12-hour time course data.	N	N
Subcutaneous injection				
Pereira et al. (1999)	Mouse	Liver, kidney, and spleen. Multiple injections (once per week for varying number of weeks). Spot sample at 1 week after last exposure.	N	N
Yamaguchi et al. (1983)	Rat	Urine, feces, lung, liver, kidney, brain, heart, spleen, testis, muscle, hair, blood. 30-day time course data.	Y	N
Oral				
Collins et al. (2010) (National Toxicology Program studies)	Rat, Mouse	Urine, feces, erythrocytes, plasma, liver, kidney, glandular stomach, and forestomach (2-year study). Blood, kidney, and femur (21-day study only). No mouse urinary data for chronic Cr III study. Chronic Cr III/Cr VI data at multiple sacrifice times (after 2-day washout period). Time course (2-day) gavage data (urine/feces only) for Cr III only.	Y	Y
Iranmanesh et al. (2013)	Rat	Liver, kidney, intestine, spleen, and testicle. Drinking water exposure for 60 days. Spot sample after 7-day washout period. This is a chelation study that included a Cr VI-only group.	N	N
Finley et al. (1997) Kerger et al. (1997) Kerger et al. (1996) Paustenbach et al. (1996)	Human	Human toxicokinetic volunteer studies. Urine, plasma, and RBC. Multiple exposure scenarios (i.e., single and repeated doses). Time course data over multiple days before, during and after exposure.	Y	Y
Kirman et al. (2012)	Rat, Mouse	Oral cavity, stomach, duodenum, jejunum, ileum, plasma, red blood cell (RBC), and liver. Spot sample at end of 90-day exposure period.	N	Y
Saxena et al. (1990)	Rat, Mouse	Oral (drinking water) study in pregnant rodents. Maternal blood, placenta, and fetus.	N	N
Sutherland et al. (2000)	Rat	Bone, kidney, liver, and testes. Exposure for 44 weeks, with spot samples 4–6 days post-exposure (no time course data).	N	N
Thomann et al. (1994)	Rat	Blood, liver, kidney, spleen, bone, and total carcass. 6 week exposure followed by 140 days post exposure. Time course data of pre and post exposure periods.	N	Y
Intratracheal				
Bragt and van Dura (1983)	Rat	Urine, feces, blood, heart, lungs, spleen, kidneys, liver, pancreas, testes, and bone marrow (femur). 50-day post exposure time course data for whole body retention and blood. 10-day time course data for urine and feces. Spot sample data for other tissues at 50 days post exposure. 3 different Cr VI formulations.	N	Y

Reference	Species	Tissue matrices and notes	Cr III control[a]	PBPK use[b]
Edel and Sabbioni (1985)	Rat	Lung, trachea, kidney, liver, spleen, pancreas, epididymus, testes, brain, heart, thymus, femur, skin, fat, muscle, stomach, small intestine, large intestine, blood, plasma, RBC, lung lavage, urine, and feces. Spot sample in tissues at 24 hours post exposure. 7-day time course data of excretion.	Y	Y
Perrault et al. (1995)	Sheep	Bronchoalveolar lavages (BAL), lung. Exposure and analysis of particulate forms. 30-day time course data for BAL; spot sample for lung at day 30.	Y	N
Gao et al. (1993)	Rat	Blood, plasma, urine, and lymphocytes. 72-hour time course data.	Y	N
Vanoirbeek et al. (2003)	Rat	Lung, liver, plasma, RBC, urine. Spot tissue samples at 2 and 7 days post exposure. 7-day time course data of urinary excretion.	Y	N
Wiegand et al. (1987) Wiegand et al. (1984a)	Rabbit	Blood, plasma, RBC, liver, kidneys, urine, lung, and trachea. 4-hour post exposure time course data.	Y	N
Inhalation				
Cohen et al. (1997)	Rat	Lung (and lung fluids/subcompartments), liver, kidney, and spleen. Exposure for 5 hours/day, 5 days a week. Spot samples at 2 or 4 weeks (24 hours post exposure)	N	N
Kalliomäki et al. (1983) Kalliomäki et al. (1983)	Rat	Blood, liver, kidneys, stomach, spleen and lung. Welding arc fumes (with chromium concentration measurement). Exposures vary in hours per day or number of days exposed. Spot samples at 24 hours post exposure. 106-day time course data for elimination study.	N	N
Suzuki et al. (1984)	Rat	Lung, whole blood, plasma, RBC, kidney, spleen, heart, liver, and testis. Aerosolized Cr III and Cr VI. Exposure for 2 or 6 hours. 7-day time course data.	Y	N
Multiple routes				
Coogan et al. (1991)	Rat	RBC, WBC. Oral and IV injection. Spot samples at 1 hour, 24 hours, and 7 days post exposure.	N	N
Fébel et al. (2001)	Rat	Oral and intrajejunal injection. Urine, feces, jejunum, liver, portae, hepatica, and cava caudalis. Spot sample data (at 60 minutes for intrajejunal injection, and 3 days for oral exposure).	Y	N
Kargacin et al. (1993)	Rat, Mouse	Oral and IP injection. Single and repeated exposures. Liver, kidney, spleen, femur, lung, heart, muscle, and blood. Spot sample data at 4 and 8 weeks for chronic drinking water, 4 and 14 days for repeated IP injections. Spot 24/72 hour data for single IP exposures.	N	Y
Mutti et al. (1979)	Rat	Subcutaneous injection, oral exposure. Urine, spleen, liver, renal cortex, renal medulla, lung, and bone. 48 hour (single	N	Y

Reference	Species	Tissue matrices and notes	Cr III control[a]	PBPK use[b]
		exposure) and 12 week (repeated exposure) time course data.		
Miyai (1980) Miyai et al. (1980)	Rat, Mouse	Inhalation, intratracheal. Lung, plasma, RBC, spleen, kidney, duodenum, testes, urine, and feces. Long-term (30+ day) time course data.	Y	N
Sayato et al. (1980)	Rat	Oral gavage and IV injection. Blood, brain, skull, thyroid, lung, heart, liver, spleen, pancreas, kidney, adrenal, stomach, intestine, bone, muscle, testis, urine, and feces. 30-day time course data of feces/urine and body retention. 5-day time course data for tissues.	Y	Y
Susa et al. (1988)	Mouse	Liver, kidney, spleen, testes, urine and feces. Spot sample 24 hours post exposure. 3-day time course data for urine and feces. This is a chelation study that included Cr VI-only groups.	N	N

[a]Notes (yes/no) if study also collected data for Cr III kinetics.
[b]Notes (yes/no) whether data from a study were used qualitatively or quantitatively in a published PBPK model.

Table 3-2. Preliminary categorization of in vitro and ex vivo hexavalent chromium studies primarily focused on toxicokinetics in the GI tract and blood

Reference	Species	Test system	Notes	PBPK use[a]
Gastric systems				
De Flora et al. (1987)	Human	Gastric juice	Hourly gastric juice samples via nasogastric tube. Cr VI reduction capacity estimated for fed and fasted humans. Circadian effects also observed.	Y
De Flora et al. (1997)	Human	Intestinal bacteria, gastric juice	Reduction and mutagenic activity of Cr VI analyzed at 60 min. Reducing capacities derived for intestine and other tissues (blood, RBC, lung fluids/bacteria, saliva).	Y
Gammelgaard et al. (1999)	Rat	Artificial gastric juice; small intestine	1st order reduction rate half-life derived; permeability parameters through rat jejunum derived.	N
Kirman et al. (2013)	Human	Gastric juice (fasted)	2nd-order reduction kinetics for human gastric juice derived. pH-dependent model derived.	Y
Proctor et al. (2012)	Rat, Mouse	Gastric juice and contents	2nd-order reduction kinetics derived. Reduction capacities estimated for both species.	Y
Shrivastava et al. (2003)	Rat	Crypt, mid and upper villus, intestinal loop	Cr VI reduction in various tissue types. Capacity and time needed to reduce Cr VI analyzed.	N
Skowronski et al. (2001)	N/A	Artificial gastric juice	Oral bioaccessibility study. Examined Cr VI reduction in a simulated soil matrix/gastric juice environment.	N
Reduction and/or uptake in RBCs				
Aaseth et al. (1982)	Human	RBC	Reduction rate of Cr VI in RBC, and trapping of reduced Cr III observed.	Y
Afolaranmi et al. (2010)	Human	Plasma, RBC, whole blood	Distribution into different blood components (RBC and plasma) observed.	N
Alexander and Aaseth (1995)	Human, Rat	Human RBC, rat liver cells	Cellular uptake and reduction analyzed. Effect of pH and anion carrier inhibitors observed.	N
Beyersmann et al. (1984)	Human	RBC	RBC permeability and reduction analyzed.	N
Branca et al. (1989)	Human	Human RBC	Reduction of Cr VI in RBC observed.	N
Coogan et al. (1991)	Human, Rat	RBC, WBC, whole blood	Uptake kinetics, and distribution in cells examined.	N
Corbett et al. (1998)	Human	Plasma, blood	Reduction in plasma quantified in fed/fasted individuals.	Y
Kortenkamp et al. (1987)	Human	RBC	Cellular uptake rates analyzed.	N
Richelmi et al. (1984)	Rat	RBC, plasma	Reduction of Cr VI in RBC and plasma observed.	Y

Reference	Species	Test system	Notes	PBPK use[a]
Wiegand et al. (1985)	Human, Rat	RBC	Uptake into RBC analyzed.	Y

[a]Notes (yes/no) whether data from a study were used qualitatively or quantitatively in a published PBPK model.

Table 3-3. Preliminary categorization of in vitro studies primarily examining distribution and reduction mechanisms

	Human	Rat
Liver	Jannetto et al. (2001) Myers and Myers (1998) Pratt and Myers (1993)	Aiyar et al. (1992) Alexander et al. (1982) Alexander et al. (1986) De Flora et al. (1985) Garcia and Jennette (1981) Gruber and Jennette (1978) Gunaratnam and Grant (2001) Mikalsen et al. (1989) Mikalsen et al. (1991) Ohta et al. (1980) Rossi and Wetterhahn (1989) Rossi et al. (1988) Standeven and Wetterhahn (1991) Ueno et al. (1990) Wiegand et al. (1986)
Lung	Harris et al. (2005) Petrilli et al. (1986) Petruzzelli et al. (1989) Wong et al. (2012)	De Flora et al. (1985) Suzuki (1988a) Suzuki and Fukuda (1990)
RBC	Ottenwälder et al. (1987) Ottenwaelder et al. (1988) Wiegand et al. (1984b) Wiegand and Ottenwaelder (1985)	
Other		Berndt (1976) (kidney) Standeven and Wetterhahn (1991) (kidney) Debetto et al. (1988) (thymocytes) Arslan et al. (1987) (thymocytes)
Miscellaneous systems		
Denniston and Uyeki (1987), Ortega et al. (2005), Sehlmeyer et al. (1990): Chinese hamster ovary Dillon et al. (2002): Chinese hamster lung Krepkiy et al. (2003): Rabbit liver metallothionein O'Brien et al. (1992): Glutathione and other thiols (not specific to a particular tissue or species). Kitagawa et al. (1982): Bovine RBCs.		

Table 3-4. Human biomonitoring and biomarker studies

Reference	Biomarker and industry/exposure notes
Gargas et al. (1994)	Urine / Human volunteer study of ingested chromite ore processing residue in soil
Goldoni et al. (2006)	Exhaled breath / Chrome plating
Lukanova et al. (1996)	Lymphocytes, RBCs, urine / Chrome plating
Muttamara and Leong (2004)	Blood, urine / Chromium alloy factory
Nomiyama et al. (1980)	Urine / Population from geographic areas of known chromium pollution
Pierre et al. (2008)	Urine / Chrome plating
Sjogren et al. (1983) Welinder et al. (1983)	Urine / Stainless steel welding

Table 3-5. Physiologically-based pharmacokinetic models for hexavalent chromium

Reference	Species	Notes
O'Flaherty (1996) O'Flaherty (1993) O'Flaherty et al. (2001) O'Flaherty and Radike (1991)	Rat	Calibrated to data from exposure via IV injection, gavage, inhalation, and drinking water (all data are from studies dated 1985 and earlier). Background Cr III exposure incorporated. Single compartment lumped model for GI kinetics. Model not readily extendable to the mouse.
O'Flaherty et al. (2001)	Human	
Kirman et al. (2012)	Rat, Mouse	Incorporates new data, including those from experiments designed by the authors. Only data for drinking water and dietary routes incorporated. Total concentrations in control groups subtracted from exposure groups to account for background Cr III levels. Multi-compartment GI model, with reduction kinetics based on the model by Proctor et al. (2012).*
Kirman et al. (2013)	Human	

*EPA has developed a revised *ex vivo* reduction model (Schlosser and Sasso, In Press), which follows the same basic principles as Proctor et al. (2012) and Kirman et al. (2013) (i.e., binary reaction with depleting reducing agent), but with a different reaction scheme and pH function. As shown in Figure 3-1, a new reduction model can be incorporated into pre-existing GI tract models.

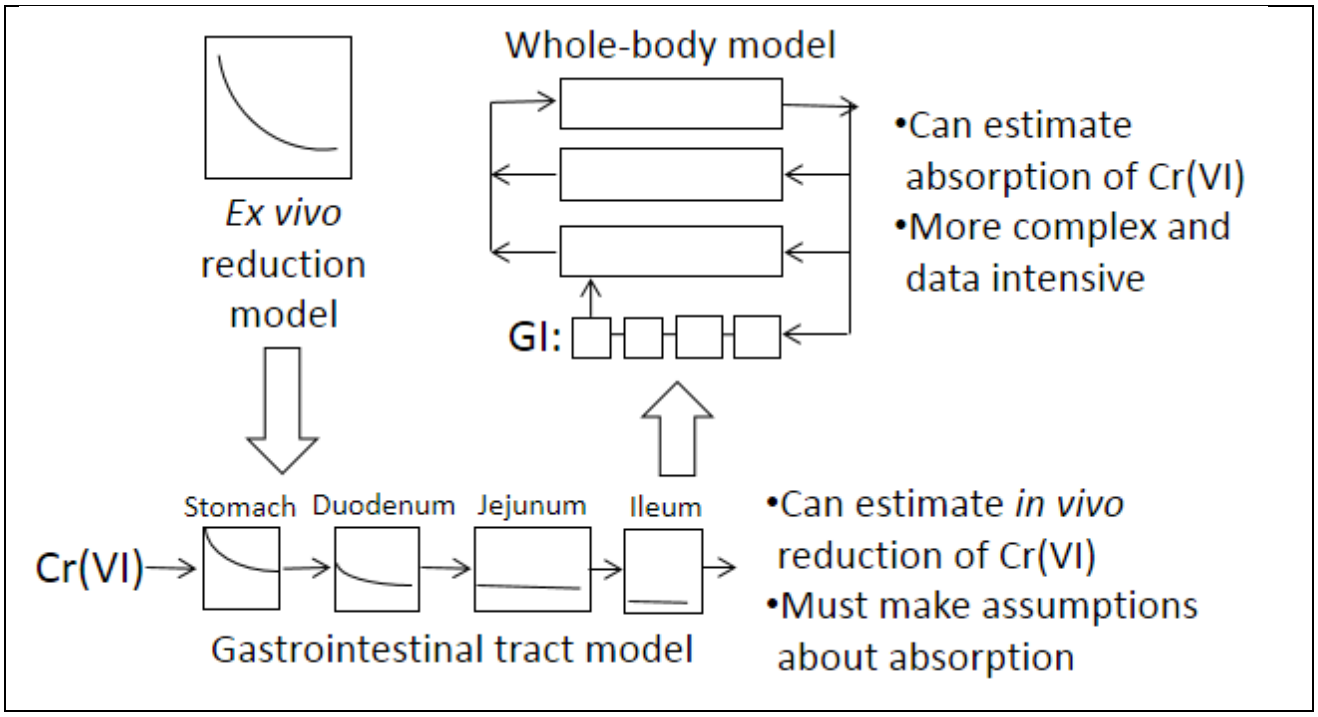

Figure 3-1. Relationship between ex vivo reduction models, in vivo gastric models, and whole-body PBPK models.

These models can be used to estimate the internal dose to the tissues where toxicological responses are observed, and perform animal-human extrapolation[3].

[3] Thompson et al. (2014) used PBPK modeling to estimate the average lifetime daily internal dose (mg hexavalent chromium absorbed per L small intestine segment) for the duodenum, jejunum, and ileum of mice from the NTP 2-year bioassay. Incidence data for all three segments were pooled for internal dose-response modeling. The corresponding human internal dose for interspecies extrapolation was the lifetime daily mg/L hexavalent chromium absorbed in the whole small intestine. The mass of hexavalent chromium escaping stomach reduction (per L small intestine) was considered as an alternative to the human hexavalent chromium absorption dose metric, and requires only the gastrointestinal tract model.

4. PRELIMINARY MECHANISTIC STUDY INFORMATION

The systematic literature search for hexavalent chromium also identified studies evaluating mechanisms of action considered potentially relevant to effects observed following exposure to hexavalent chromium. Studies were included if they evaluated mechanistic events following exposure to: hexavalent chromium; the reductive intermediate oxidation states penta- and tetravalent chromium; trivalent chromium (if relevant to hexavalent chromium effects); or otherwise contained information relevant to the mechanistic understanding of hexavalent chromium toxicity. Reviews or analyses that do not contain original data are not included here, but may be considered in later stages of assessment development.

The diverse array of mechanistic studies presented here includes investigations of the cellular, biochemical, and molecular mechanisms underlying toxicological outcomes. For this preliminary evaluation, information reported in each study was extracted into a database (in the form of an Excel spreadsheet) that will facilitate future evaluation of mechanistic information. This information is being made available to provide an opportunity for stakeholder input, including the identification of relevant studies not captured here.

The information extracted from each study and included in the database corresponds to the column headings in the spreadsheet, and is as follows: link to HERO record (contained within a URL that links to the study abstract in the HERO database), author(s), year, title, source, link to abstract in PubMed (if any), molecular formulation, oxidation state, in vitro/in vivo, species/test system, cell type, endpoint, assay, and mechanistic category. The database supports sorting capabilities, e.g., data can be organized by assay. The database is available through HERO at http://hero.epa.gov/index.cfm?action=reference.details&reference_id=2444793. To access this database, click on the link at the top of the web page and select "download" and then "ok" to view the spreadsheet in Excel. This spreadsheet may also be saved to your desktop by downloading and selecting "save." The resulting inventory of hexavalent chromium mechanistic studies consists of 3,235 discrete measures from 806 studies. Table 4-1 presents a summary of the mechanistic endpoints recorded in the database from each study identified.

The mechanistic categories developed here are not mutually exclusive and are designed to facilitate the analysis of similar studies and experimental observations in a systematic manner. This process will allow the identification of mechanistic events that contribute to mode(s) of action (MOAs) and/or adverse outcome pathways (AOPs) following hexavalent chromium exposure. The mechanistic categories assigned to each mechanistic endpoint reported by an individual study are as follows: 1) mutation, including investigations of gene and chromosomal mutation; 2) DNA

damage, including indicator assays of genetic damage; 3) alterations of DNA repair; 4) oxidative stress; 5) changes in cell death and division (this captures a broad range of assays, but it is useful to consider them together as observations resulting from cell cycle alterations); 6) pathology, which includes morphological evaluations pertaining to the dysfunction of organs, tissues, and cells; 7) epigenetic effects, which are observations of heritable changes in gene function that cannot be explained by changes in the DNA sequence; 8) receptor-mediated and cell signaling effects; 9) immune system effects; 10) cellular and molecular ADME; 11) cellular differentiation and transformation; 12) cellular energetics; and 13) "other," to capture those mechanistic outcomes not easily assigned to a defined category. The ADME category above includes studies conducted to investigate the mechanism of carcinogenicity of hexavalent chromium, specifically, intracellular reduction and the formation of DNA-reactive intermediates and oxygen radicals; as such, these studies would typically not be included in the toxicokinetic studies identified in Section 3.

Information summarized in Table 4-1 and Figure 4-1 and detailed in the mechanistic database can be used to ascertain the breadth and scope of available mechanistic studies. At this preliminary stage, study results are not presented. Additionally, the inclusion of a study in the spreadsheet does not reflect conclusions reached as to mechanistic study quality or relevance. After the epidemiological and experimental studies on each health effect have been synthesized, mechanistic studies will be reviewed and findings synthesized to evaluate potential MOAs and/or AOPs, which can be used to inform hazard identification and dose-response assessment, specifically addressing questions of human relevance, susceptibility, and dose-response relationships.

Table 4-1. Summary of mechanistic endpoints evaluated following exposure to hexavalent chromium

Mechanistic category	Number of mechanistic endpoints								Total mechanistic endppoints/ number of studies
	Mammals								
	Humans		Mice		Rats		Hamsters		
	In vivo	In vitro	In vivo	In vitro	In vivo	In vitro	In vivo	In vitro	
Mutation	14	35	27	11	8	2	0	63	311/144
DNA damage	30	235	18	26	29	19	4	122	769/300
Alterations of DNA repair	2	33	0	1	1	0	0	5	54/28
Oxidative stress	10	175	76	54	215	89	0	10	728/206
Changes in cell death and division	3	303	15	39	52	103	1	114	703/256
Pathology	0	4	23	0	69	4	0	0	110/36
Epigenetic effects	3	40	1	1	1	1	0	2	54/22
Receptor-mediated and cell signaling effects	0	37	1	4	9	3	0	0	60/25
Immune system effects	0	33	4	5	15	1	0	0	63/27
Cellular and molecular ADME	15	36	10	2	52	21	0	23	213/106
Cellular differentiation and transformation	0	10	4	9	1	6	0	26	59/26
Cellular energetics	0	18	0	0	6	17	0	8	58/30
Other	8	7	5	0	6	8	0	0	52/17
								Total Outcomes	3,235/806

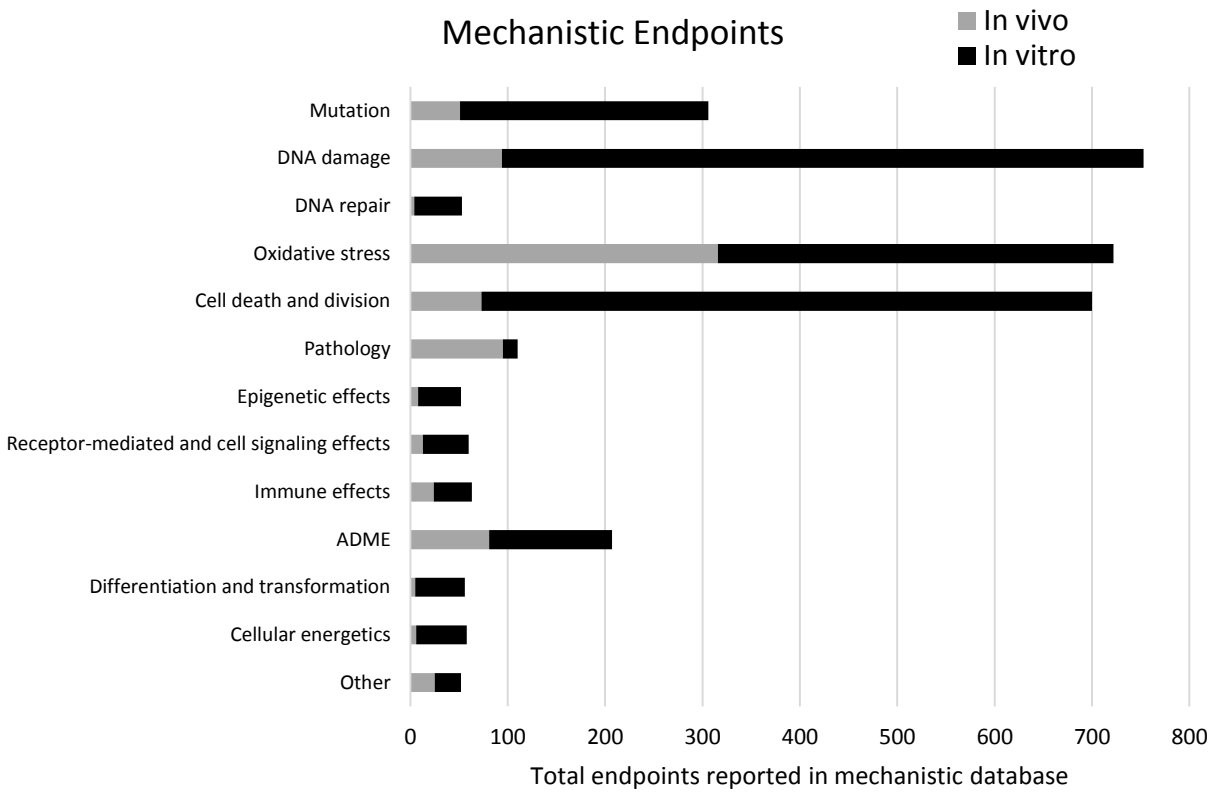

Figure 4-1. Summary of in vivo and in vitro mechanistic endpoints by mechanistic category.

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