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IRIS Toxicological Review of Hexavalent Chromium [Cr(VI)] Supplemental Information

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ABBREVIATIONS

ADAF	age-dependent adjustment factors
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike's information criterion
ALT	alanine aminotransferase
ALP	alkaline phosphatase
Asc	ascorbate
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMI	body mass index
BMR	benchmark response
BMDC	bone marrow-derived stem cell
BW	body weight
CA	chromosomal aberration
CASRN	Chemical Abstracts Service Registry Number
CHO	Chinese hamster ovary (cell line cells)
CPHEA	Center for Public Health and Environmental Assessment
CL	confidence limit
CNS	central nervous system
Cr(III)	trivalent chromium
Cr(IV)	tetravalent chromium
Cr(V)	pentavalent chromium
Cr(VI)	hexavalent chromium
DAF	dosimetric adjustment factor
DLCO	diffusing capacity of carbon monoxide
DNA	deoxyribonucleic acid
ELF	epithelial lining fluid
EPA	Environmental Protection Agency
ER	extra risk
FDA	Food and Drug Administration
FEV1.0	forced expiratory volume of 1 second
FVC	forced vital capacity
GD	gestation day
GGT	γ-glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practices
GSD	geometric standard deviation
GSH	glutathione
GST	glutathione-S-transferase
Hb	hemoglobin
HEC	human equivalent concentration
HED	human equivalent dose
HERO	Health and Environmental Research Online
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LOAEL	lowest-observed-adverse-effect level
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell (corpuscular) volume
MEF	maximal expiratory flow
MMAD	mass median aerodynamic diameter
MN	micronuclei
MOA	mode of action
MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
ORD	Office of Research and Development
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PDC	potassium dichromate
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
$POD_{[HED]}$	human equivalent dose POD
$POD_{[HEC]}$	human equivalent concentration POD
RBC	red blood cell, also known as erythrocyte
RD	relative deviation
RfC	inhalation reference concentration
RfD	oral reference dose
RDDR	regional deposited dose ratio
RNA	ribonucleic acid
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SSD	sodium dichromate dihydrate
PK	pharmacokinetics
TSCATS	Toxic Substances Control Act Test Submissions
TWA	time-weighted average
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_H	human variation uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database deficiencies uncertainty factor
WOS	Web of Science

APPENDIX A. SYSTEMATIC REVIEW PROTOCOL FOR HEXAVALENT CHROMIUM

The systematic review protocol for the IRIS Toxicological Assessment of Hexavalent Chromium, developed in 2019 prior to the current draft (U.S. EPA, 2019b), has been updated to reflect refinements to the systematic review procedures implemented in this draft. The updated version can be found on the IRIS website: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=343950.

APPENDIX B. SUMMARY OF OTHER AGENCY CONCLUSIONS

Table B-1. Noncancer inhalation assessments by other national and international health agencies and associations (in reverse chronological order)

Reference	Value ($\mu g/m^3$)	Time adjustment	Chemical note	Endpoints/Basis
ACGIH (2017)	0.2	8-h TWA	Cr(VI) inhalable particulate matter	Lung cancer; sinonasal cancer; respiratory tract irritation; asthma. Based on Lindberg and Hedenstierna (1983), with support from other studies (including analyses of Baltimore cohort data by Gibb et al. (2000a, b) and Park et al. (2004).
Texas Commission on Environmental Quality (TCEQ) (2014)	0.0043	Lifetime/chronic	Particulate compounds	Excess lung cancer mortality risk of 1×10^{-5}, using risk value derived from Gibb et al. (2000b) and Crump et al. (2003).
	0.066	Lifetime/chronic	Particulate compounds	Respiratory effect (increased relative lung weight after 90 d of exposure) in rats (Glaser et al., 1985).
	0.39	Acute	Particulate compounds	Respiratory effect (increased relative lung weight after 30 d of exposure) in rats (Glaser et al., 1990).
International Programme on Chemical Safety (IPCS) (2013)	0.03	Lifetime/chronic	Cr(VI) salts	Respiratory effects in rats (Glaser et al., 1990).
	0.005	Lifetime/chronic	Chromium trioxide, chromic acid	Upper respiratory effects in humans (Lindberg and Hedenstierna, 1983).
National Institute for Occupational Safety and Health (NIOSH) (2013)	0.2	8-h TWA, 40-h work week	All Cr(VI) compounds	Lung cancer and nonmalignant respiratory effects. Based on analysis of Baltimore cohort data by Park et al. (2004).
Agency for Toxic Substances and Disease Registry (ATSDR) (2012)	0.005	Chronic	Dissolved aerosols and mists	Upper respiratory effects (nasal irritation/ulceration, mucosal atrophy, and decreases in spirometric parameters), based on Lindberg and Hedenstierna (1983).
	N/A	Chronic	Particulates	Insufficient data

Reference	Value ($\mu g/m^3$)	Time adjustment	Chemical note	Endpoints/Basis
	0.005	Intermediate	Dissolved aerosols and mists	Upper respiratory effects (nasal irritation/ulceration, mucosal atrophy, and decreases in spirometric parameters), based on Lindberg and Hedenstierna (1983).
	0.3	Intermediate	Particulates	Respiratory tract (lung) and other effects. Based on quantitative analysis of rat studies (Glaser et al. (1990; 1985)) performed by Malsch et al. (1994).
California EPA (2008)	0.2	Chronic	Soluble compounds	Respiratory effect (bronchoalveolar hyperplasia) in rats (Glaser et al., 1990).
	0.002	Chronic	Chromic trioxide (as chromic acid mist)	Respiratory effects in humans (Lindberg and Hedenstierna, 1983).
Occupational Safety and Health Administration (OSHA) (2006b)	5	8-h TWA	All Cr(VI) compounds	Lung cancer and nasal tissue damage. Based on quantitative analysis of Baltimore cohort data by Gibb et al. (2000a, b) and Luippold et al. (2003).
Dutch National Institute for Public Health and the Environment (RIVM) (2001)	0.0025	Chronic	Inhalable dust	Excess lifetime lung cancer risk of 1×10^{-4}, based on analysis of human occupational studies by the 1987 and 1994 World Health Organization air quality guidelines.[b]
U.S. EPA IRIS (1998)	0.008	Lifetime/chronic	Chromic acid mists/dissolved chromium aerosols	Effects in the nasal cavity. Based on Lindberg and Hedenstierna (1983).
	0.1	Lifetime/chronic	Cr(VI) particulates	Respiratory effects. Based on quantitative analysis of rat studies (Glaser et al., 1990; Glaser et al., 1985) performed by Malsch et al. (1994).

N/A = not applicable; TWA = time-weighted average.

[a]Selected values from states known by U.S. EPA to have derived independent values; most states typically adopt values from U.S. EPA.

[b]Risk value rationale and studies unchanged in WHO (2000).

Table B-2. Cancer inhalation assessments by other national and international health agencies (in reverse chronological order)

Reference	Risk factor $(\mu g/m^3)^{-1}$	Rationale
Texas Commission on Environmental Quality (TCEQ) (2014)	Unit risk factor: 2.28×10^{-3} (particulate compounds)	Linearly extrapolated lung cancer risk based on a weighted average of Gibb et al. (2000b) and Crump et al. (2003) (human occupational cohorts).

International Programme on Chemical Safety (IPCS) (2013)	Occupational exposure risk: 6×10^{-3}	Linearly extrapolated lung cancer risk based on Gibb et al. (2000b).
	Environmental exposure risk: 4×10^{-2}	
International Agency for Research on Cancer (IARC) (2012).	*Carcinogenic to humans* (Group 1)[b]	Lung cancer, based on multiple evidence streams. Positive associations between Cr(VI) exposure and cancer of the nose and nasal sinuses in humans also cited.
National Toxicology Program (NTP) (2011)	Known to be human carcinogen[b]	Cancers of the lung and sinonasal cavity, based on studies in humans.
World Health Organization (2000)	4×10^{-2}	Linearly extrapolated lung cancer risk based on multiple human occupational studies.
U.S. EPA IRIS (1998)	Inhalation unit risk: 1.2×10^{-2}	Linearly extrapolated lung cancer risk based on Mancuso (1997, 1975) (human occupational cohort).
California Department of Health Services (CDHS) (1985)	Inhalation potency: 0.15[c]	Linearly extrapolated lung cancer risk based on Mancuso (1975).

[a]Selected values from states known by U.S. EPA to have derived independent values; most states typically adopt values from U.S. EPA.

[b]Agency does not derive a quantitative risk factor.

[c]As part of an updated evaluation of the science for the public health goal (PHG), California EPA (2011) calculated a slope of 0.16 $(\mu g/m^3)^{-1}$ (with a 95% upper confidence of 0.35) using Gibb et al. (2000b), and a lower bound slope of 0.01 $(\mu g/m^3)^{-1}$ using Luippold et al. (2003).

Table B-3. Oral assessments by other national and international health agencies (in reverse chronological order)

Reference	Risk value or limit	Rationale[b]
Food Safety Commission of Japan (2019)	Tolerable daily intake: 1.1×10^{-3} mg/kg-d	Cancer precursor, mouse small intestine hyperplasia
Health Canada (2016)	Maximum acceptable concentration: 50 µg/L	Cancer precursor, mouse small intestine hyperplasia
Texas Commission on Environmental Quality (TCEQ) (2016)	RfD: 3.1×10^{-3} mg/kg-d	Cancer precursor, mouse small intestine hyperplasia
International Programme on Chemical Safety (IPCS) (2013)	Tolerable daily intake: 9×10^{-4} mg/kg-d	Mouse small intestine noncancer effects
Agency for Toxic Substances and Disease Registry (ATSDR) (2012)	Chronic MRL: 9×10^{-4} mg/kg-d	Mouse small intestine noncancer effects
	Intermediate MRL: 5×10^{-3} mg/kg-d	Hematological effects (rat data at 22 d)
California EPA (2011)	Cancer PHG: 0.02 µg/L	1×10^{-6} cancer risk using OSF of 0.5 $(mg/kg\text{-}d)^{-1}$ (mouse small intestine tumors)
	Noncancer PHG: 2 µg/L	Liver noncancer effects (rats)
California Department of Public Health (2014; 2013)	Proposed MCL: 10 µg/L [see California State Water Board (2022) fact sheet]	Cancer risk [see California EPA (2011)]
New Jersey DEP (2009)	Soil remediation criterion: 1 ppm soil concentration	1×10^{-6} cancer risk using OSF of 0.5 $(mg/kg\text{-}d)^{-1}$ (mouse small intestine tumors)
U.S. EPA/OPP (2008a, b)	OSF: 0.791 $(mg/kg\text{-}d)^{-1}$	Upper-bound cancer risk estimate (mouse small intestine tumors; mutagenic MOA determined)
Assessments based on science or rules published prior to 2008 National Toxicology Program study		
U.S. Food and Drug Administration (2013)	Allowable level in bottled water: 0.1 mg/L (or 100 µg/L) total chromium	Not specified
U.S. Environmental Protection Agency [*Federal Register* (2010)]	MCL: 100 µg/L (total chromium)	Allergic dermatitis[c]
World Health Organization (2003)	50 µg/L	Provisional value (nonspecific)
Dutch National Institute for Public Health and the Environment (RIVM) (2001)	5×10^{-3} mg/kg-d	Provisional noncancer effects, based on no-effect level [rats; MacKenzie et al. (1958)]

Reference	Risk value or limit	Rationale[b]
U.S. EPA/IRIS (1998)	RfD: 3×10^{-3} mg/kg-d	No effect level for noncancer effects [rats; (MacKenzie et al., 1958)]

MCL = maximum contaminant level; MRL = minimal risk level; OSF = oral slope factor; PHG = public health goal.
[a]Selected values from states known by U.S. EPA to have derived independent values; most states typically adopt values from U.S. EPA (based on unspeciated total chromium).
[b]All values based on mouse data from NTP (2008), unless otherwise noted.
[c]Based on rule promulgated in 1991 (National Primary and Secondary Drinking Water Regulations, 56 FR 3526, 1-30-91 and 54 FR 22062, 5-22-89).

In addition to the (mostly) quantitative assessments above, a qualitative assessment was performed by the Dutch National Institute for Public Health and the Environment (RIVM) on irreversible human health hazards from occupational inhalation exposure to Cr(VI) compounds (Den Braver-Sewradj et al., 2021; Hessel et al., 2021; Palmen et al., 2018). Categorization was restricted to irreversible adverse health effects (*likely*, *possible*, *insufficient evidence*, and *unlikely*), and focused primarily on inhalation risk (but recognizing that low incidental oral exposure may occur in occupational settings). Health effects that were determined *likely* in humans were lung cancer, nose and nasal sinus cancer, nasal effects (irritation, ulcerations and perforation of the septum), chronic lung diseases, respiratory allergy, and allergic contact dermatitis. Stomach cancer was categorized as a *possible* human health effect from inhalation. Health effects where there was *insufficient evidence* in humans were immune effects (besides the dermal/respiratory allergies) and reproductive effects (development, fertility, and lactation). Health effects that were determined to be *unlikely* to occur in humans were larynx cancer, intestinal cancer, gastrointestinal effects, hematological effects, hepatic effects, renal effects, neurological, cardiovascular effects, and dental effects.

APPENDIX C. INFORMATION IN SUPPORT OF HAZARD IDENTIFICATION AND DOSE-RESPONSE ANALYSIS

C.1. PHARMACOKINETICS

C.1.1. Absorption

Water soluble Cr(VI) compounds are rapidly absorbed into cells and tissues in the body via phosphate and sulfate anion transport due to the structural similarity of the tetrahedral configuration of the chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) anion to that of phosphate (HPO_4^{2-}) and sulfate (SO_4^{2-}) anions (Alexander and Aaseth, 1995; Wetterhahn et al., 1989), while Cr(III) compounds are absorbed slowly by passive diffusion (Eastmond et al., 2008). In the gastrointestinal (GI) tract following oral ingestion, systemic uptake of Cr(VI) competes with the rapid extracellular reduction to Cr(III) by gastric juices (Proctor et al., 2012; De Flora et al., 1997). Studies listed in Appendix C.1.6 that administered Cr(VI) and Cr(III) to different treatment groups have observed higher urinary, blood, and tissue chromium in the groups exposed to Cr(VI). This was also observed by separate NTP bioassays of Cr(VI) and Cr(III), which found the body burdens of rats and mice exposed to Cr(VI) in drinking water were significantly higher than those exposed to comparable levels of Cr(III) in feed (Collins et al., 2010). Figure C-1 illustrates the difference in chromium concentrations of selected systemic tissues between the Cr(VI) and Cr(III) studies. Despite the estimated daily dose of Cr(III) being threefold higher than that of Cr(VI), chromium tissue concentrations were over tenfold higher for the Cr(VI) group. Because Cr(VI) is more readily absorbed into the GI tract than Cr(III), this is also evidence that systemic absorption of Cr(VI) can occur in rodents following chronic oral exposure, despite reduction of Cr(VI) to Cr(III) by gastric juice (Collins et al., 2010).

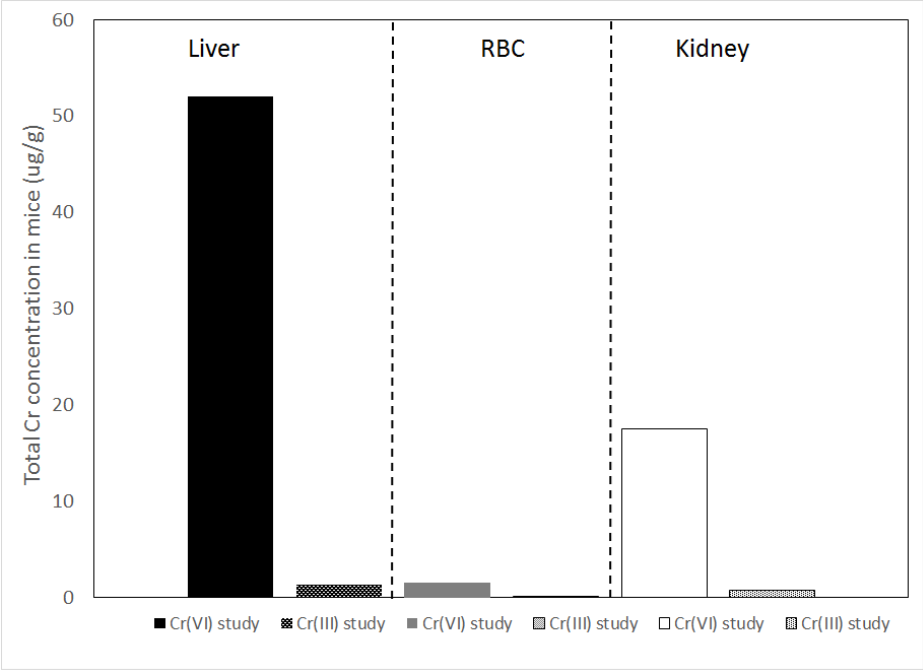

Figure C-1. Comparison of mean tissue concentrations in mice (n = 3) following 182 days of either Cr(VI) or Cr(III) oral exposure. Groups compared are the 516 mg/L SDD group and the 2000 mg/L sodium picolinate group. These correspond to approximately 10 mg/kg-day Cr(VI), and 30 mg/kg-day Cr(III) respectively (average over study period weeks 14–51). These are a subset of data from the NTP studies **Collins et al. (2010)**. Data were collected after a 2-day wash-out period, and therefore concentrations are lower than what would have been measured during ongoing exposure.

Although fewer Cr(VI) pharmacokinetic studies are available for the inhalation route than for the oral route (see Appendix C.1.6), there is evidence that indicates inhaled Cr(VI) is absorbed systemically. The study in rats by Cohen et al. (1997) of inhaled soluble (potassium chromate) and insoluble (barium chromate) Cr(VI) observed absorption of both forms of Cr(VI). Elevated chromium in this study was observed in lung components and systemic tissues (kidney, liver, spleen), with higher levels in groups exposed to the soluble form of Cr(VI). Occupational studies in humans who may have been exposed primarily via inhalation have measured elevated chromium in multiple biomarkers such as red blood cells and urine (Appendix C.1.6). O'Flaherty and Radike (1991) exposed rats to Cr(VI) or Cr(III) at concentrations of 200 µg/m^3 via aerosol inhalation (6 hours/day) and detected elevated chromium in all measured tissues and excreta relative to controls (Table C-6).

C.1.2. Distribution

Upon systemic absorption, Cr(VI) circulates in plasma, where it is absorbed into red blood cells (RBCs), white blood cells, and other systemic tissues. Both the uptake and reduction of Cr(VI) by RBCs has been estimated to be rapid (Devoy et al., 2016). Uptake to RBCs is facilitated by

nonspecific anion transport channels, including the band-3 anion exchanger protein, an anion carrier system of the red blood cell membrane (Buttner et al., 1988; Ottenwaelder et al., 1988; Ottenwälder et al., 1987; Buttner and Beyersmann, 1985). In humans, genetic polymorphisms in the band-3 protein have been shown to be associated with increased accumulation of Cr(VI) in red blood cells (Qu et al., 2008).

Because irreversible binding to hemoglobin occurs, and Cr(III) exhibits a lower rate of transport through cellular membranes than Cr(VI), Cr(III) remains trapped in RBCs over the remaining life of the cells. Supporting evidence is provided by the studies presented in Appendix C.1.6. This property has been exploited for diagnostic purposes whereby hexavalent radiolabeled chromium-51 has been used to label and determine the survival time of RBCs in humans (Gray and Sterling, 1950). Measured in vivo chromium concentration in plasma has been observed to rapidly decrease to background levels after exposure to Cr(VI) has ceased, while in vivo chromium concentration in RBCs decreases more gradually (as chromium-containing RBCs are replaced over time).

Because chromium in the system varies with uptake of Cr(III) [both from diet and from Cr(VI) reduction in the lumen], chromium concentration in RBCs may be normalized by concentration in plasma to evaluate systemic distribution. Although it is noted in Kirman et al. (2012) that the RBC:plasma ratios are generally equal to or less than 1 for low concentrations (and exceed 1 at 60–180 mg/L), evaluating the data for ratios greater than 1 to assess absorption and distribution may not be informative. For example, the RBC:plasma ratios are greater than 1 for some of the control groups for rats and mice analyzed in the NTP (2008) Cr(VI) study (Tables C-2 and C-4). Instead, comparisons against control or Cr(III)-exposed groups are more appropriate. Despite the complications from the 48-hour washout period,[1] a comparison of the NTP (2008) RBC:plasma ratio data for dosed animals against control groups and comparison with groups from the NTP (2007f) Cr(III) study can indicate systemic uptake of Cr(VI). A similar analysis using concentration data for plasma and RBCs in the Kirman et al. (2012) study could not be performed because concentrations are below the method detection limits for the control groups and low concentration groups. For that dataset, RBC:plasma ratios are not informative until Cr(VI) drinking water concentrations ≥20 mg/L in both species, and they cannot be compared to controls.

The RBC:plasma ratio analysis of NTP (2008) data are provided in Figure C-2 and Tables C-1 through C-4. Analysis of the NTP (2007f) Cr(III) data are not presented, but those data indicate RBC:plasma ratios <1 for all Cr(III) dietary exposure groups, with no dose-dependent increase. For rats exposed to Cr(VI) in drinking water, the RBC:plasma ratio increases by approximately 90–225% above controls at 20 mg/L Cr(VI) drinking water concentration. For mice, the ratio increases by approximately 40–100% above controls at 20 mg/L Cr(VI). Because this increase in relative

[1]After two days without Cr(VI) exposure, chromium concentration in the plasma will decrease more rapidly than concentration in RBCs. At the same time, chromium will enter plasma from the tissues, which may counteract some of the washout.

RBC concentration was not observed in rodents exposed to Cr(III), Cr(VI) concentrations at or above 20 mg/L Cr(VI) in drinking water (equivalent to approximately[2] 0.88 mg/kg-day in rats and 1.5 mg/kg-day in mice) likely result in systemic Cr(VI) absorption beyond the liver (where extensive reduction is expected to occur during the first-pass effect). More extensive systemic distribution likely occurs as dose increases, as more Cr(VI) could escape reduction in the stomach, small intestine, and liver.

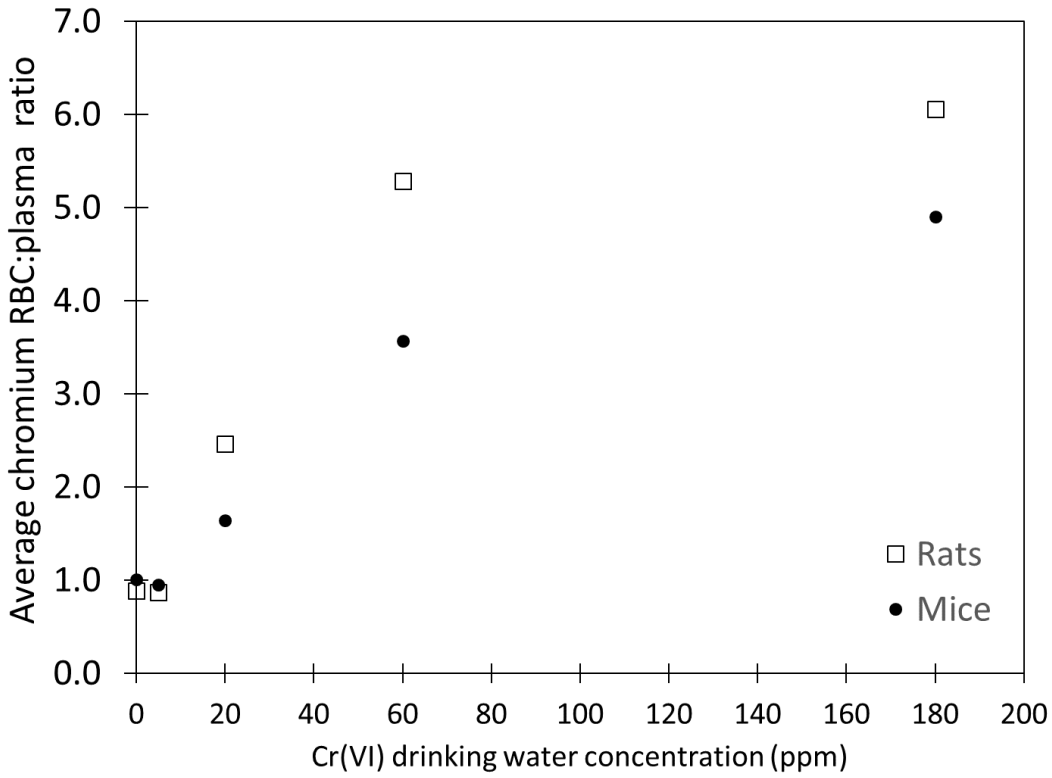

Figure C-2. Ratio of RBC:plasma concentration as a function of Cr(VI) drinking water concentration (1 ppm = 1 mg/L) for male F334 rats and female B6C3F1 mice using data from NTP (2008).

[2]These are time-weighted average daily doses estimated from NTP (2008) drinking water consumption data during the first 53 weeks of exposure.

Table C-1. Concentrations of chromium in erythrocytes and plasma (µg Cr/g) following ingestion of sodium dichromate dihydrate in drinking water (male F334 rats)

Cr(VI) concentrations		0 mg/L	5 mg/L	20 mg/L	60 mg/L	180 mg/L
Erythrocytes	**Day**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**
	6	0.044	0.051	0.126	0.252	0.391
	13	0.051	0.036	0.203	0.504	0.899
	182	0.05	0.054	0.208	0.591	0.997
	371	0.055	0.064	0.16	0.526	0.693
Plasma						
	6	0.052	0.068	0.079	0.087	0.109
	13	0.054	0.048	0.079	0.103	0.146
	182	0.063	0.064	0.081	0.099	0.146
	371	0.054	0.062	0.071	0.11	0.146

Data from NTP (2008). Time-weighted average daily doses for each exposure group are not listed, since they vary with time over the lifespan of the rodent (and will be different at days 6, 13, 182, and 371).

Table C-2. Ratio of erythrocytes:plasma concentrations following ingestion of sodium dichromate dihydrate in drinking water (male F334 rats)

Cr(VI)	0 mg/L	5 mg/L		20 mg/L		60 mg/L		180 mg/L	
Day	**Ratio**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**
6	0.846	0.750	−11.4	1.59	88.5	2.90	242	3.59	324
13	0.944	0.750	−20.6	2.57	172	4.89	418	6.16	552
182	0.794	0.844	6.31	2.57	224	5.97	652	6.83	760
371	1.02	1.03	1.35	2.25	121	4.78	369	4.75	366
TWA:	0.888	0.867	−2.36	2.46	177	5.29	495	6.06	582

TWA = time-weighted average values.

For the chromium picolinate studies (NTP, 2007f), the RBC/plasma ratio did not increase as a function of dose for rats (data not shown).

Table C-3. Concentrations of chromium in erythrocytes and plasma (µg Cr/g) following ingestion of sodium dichromate dihydrate in drinking water (female B6C3F1 mice)

Cr(VI) concentrations		0 mg/L	5 mg/L	20 mg/L	60 mg/L	180 mg/L
Erythrocytes	**Day**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**	**µg Cr/g**
	6	0.04	0.056	0.108	0.26	0.374
	13	0.043	0.042	0.341	0.747	1.19
	182	0.058	0.079	0.194	0.719	1.561
	371	0.036	0.042	0.094	0.34	0.795
Plasma						
	6	0.064	0.075	0.111	0.15	0.213
	13	0.034	0.038	0.133	0.204	0.311
	182	0.051	0.07	0.116	0.167	0.253
	371	0.065	0.086	0.118	0.15	0.209

Data from NTP (2008). Time-weighted average daily doses for each exposure group are not listed, since they vary with time over the lifespan of the rodent (and will be different at days 6, 13, 182, and 371).

Table C-4. Ratio of erythrocytes:plasma concentrations following ingestion of sodium dichromate dihydrate in drinking water (female B6C3F1 mice)

Cr(VI)	0 mg/L	5 mg/L		20 mg/L		60 mg/L		180 mg/L	
Day	**Ratio**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**	**Ratio**	**%↑↓**
6	0.625	0.747	19.5	0.973	55.7	1.73	177	1.76	181
13	1.26	1.11	−12.6	2.56	103	3.66	190	3.83	203
182	1.14	1.13	−0.764	1.67	47.1	4.31	279	6.17	443
371	0.554	0.488	−11.8	0.797	43.8	2.27	309	3.80	587
TWA:	1.01	0.950	−5.53	1.64	63.3	3.57	255	4.90	387

TWA = time-weighted average values.
For the chromium picolinate studies (NTP, 2007f), the RBC/plasma ratio did not increase as a function of dose for mice (data not shown).

Twenty-one-day data from NTP (2007f) in rats, mice, and guinea pigs at 1, 3, 10, 30, 100, and 300 mg/L Cr(VI) in drinking water showed increased chromium tissue concentrations (including in the rat femur) beginning at 10–30 mg/L. Although dose (mg/kg-day) data are not provided, evaluation of other dose data from National Toxicology Program studies for rats and mice

at 21 days indicates that the dose for rats and mice at 10 mg/L Cr(VI) would be greater than 1 mg/kg-day (young growing mice will intake more water on a mg/kg basis).

Studies in rats and mice orally dosed with Cr(VI) have measured total chromium in essentially all tissues, with highest concentrations in kidney, liver, spleen, and bone (Table C-5). Additionally, total chromium concentrations in the small intestine following oral exposure have been measured to be highest in the duodenum (the proximal small intestine) and lowest in the ileum (the distal small intestine) (Figure C-3). This could be an indication that as Cr(VI) in drinking water traverses the small intestine, it is reduced to Cr(III) in the lumen over time.

Table C-5. Chromium in tissues (µg/g wet tissue or µg/mL blood) of mice and rats after ingesting K_2CrO_7 in drinking water (8 mg Cr(VI)/kg-day) for 4 or 8 weeks

Tissue	Controls	4-week exposure	8-week exposure
Mice			
Liver	0.22 ± 0.14	10.92 ± 5.48	13.83 ± 6.06
Kidney	0.24 ± 0.14	3.77 ± 0.99	4.72 ± 0.68
Spleen	0.53 ± 0.38	5.04 ± 1.45	10.09 ± 2.50
Femur	0.90 ± 0.48	7.43 ± 1.03	12.55 ± 2.99
Lung	0.24 ± 0.12	0.99 ± 0.10	1.08 ± 0.26
Heart	0.32 ± 0.15	0.80 ± 0.23	1.02 ± 0.20
Muscle	0.32 ± 0.23	1.12 ± 0.37	0.60 ± 0.25
Blood	0.14 ± 0.05	0.71 ± 0.07	0.42 ± 0.04
Rats			
Liver	0.19 ± 0.14	3.32 ± 0.93	3.59 ± 0.73
Kidney	0.34 ± 0.20	8.62 ± 2.40	9.49 ± 4.38
Spleen	0.43 ± 0.20	3.65 ± 1.87	4.38 ± 0.84
Femur	1.00 ± 0.46	1.85 ± 0.46	1.78 ± 0.99
Lung	0.39 ± 0.43	1.10 ± 0.38	0.67 ± 0.24
Heart	0.38 ± 0.22	0.52 ± 0.12	1.05 ± 0.19
Muscle	0.24 ± 0.14	0.19 ± 0.10	0.17 ± 0.10
Blood	0.19 ± 0.17	0.73 ± 0.15	0.58 ± 0.13

Source: Kargacin et al. (1993).

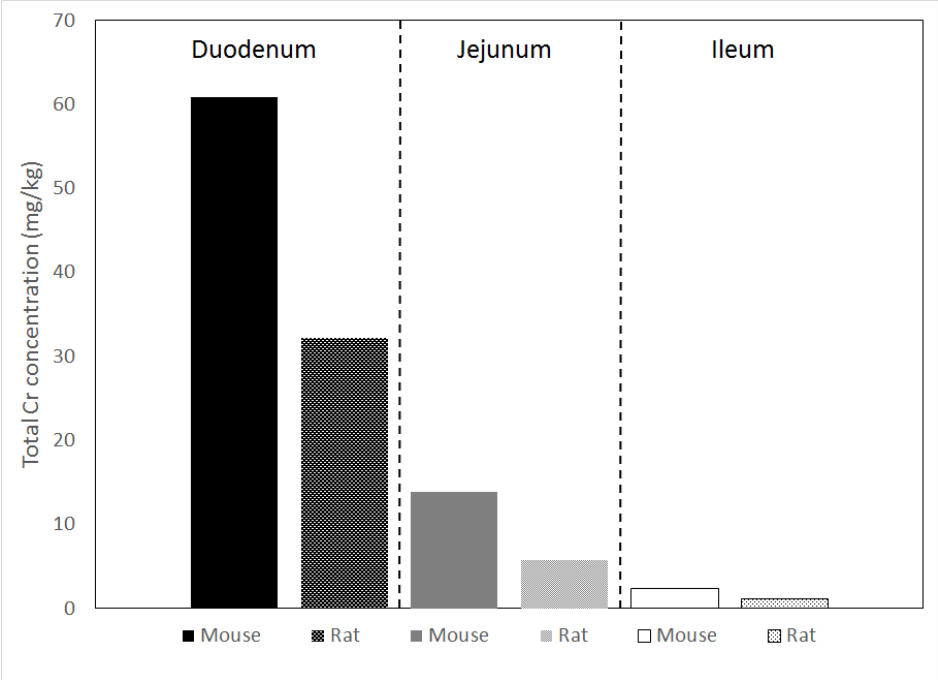

Figure C-3. Mean concentration of total chromium in GI tract tissues of mice and rats following exposure to 180 mg/L Cr(VI) in drinking water for 90 days [approximately 31.9 and 20.5 mg/kg-day Cr(VI) for mice and rats, respectively]. Data from **Kirman et al. (2012)**.

O'Flaherty and Radike (1991) exposed rats to Cr(VI) or Cr(III) at concentrations of 200 µg/m^3 via aerosol inhalation (6 hours/day) or 12.9 mg/L via drinking water ingestion (ad libitum) for 40 days (with an additional 20-day recovery period of no exposure). These concentrations are within the ranges used by some Cr(VI) toxicological studies (NTP (2008) range: 5–180 mg/L Cr(VI) via drinking water; Glaser et al. (1985) range: 25–200 µg/m^3 via inhalation). Measured chromium concentrations in the blood and lungs were higher in rats exposed to Cr(VI) via inhalation, while chromium concentrations in the liver and intestine were higher in rats exposed to Cr(VI) via drinking water. As a result, the severities of toxicological effects induced by Cr(VI) at both portal-of-entry tissues and systemic tissues may differ by exposure route.

For tissues outside the portals of entry and for urine, Cr(VI)-exposed groups exhibited higher chromium levels than Cr(III)-exposed groups (which is consistent with higher systemic absorption of Cr(VI)). For tissues at or near the portals-of-entry (lung for inhalation, intestine for oral ingestion), chromium concentrations were comparable or higher for Cr(III) groups when compared to Cr(VI) groups. This could indicate higher localized clearance of Cr(VI) from portal tissues into blood via absorption. Chromium excretion in feces following oral ingestion of either Cr(VI) or Cr(III) was comparable (fecal chromium can be due to both elimination of systemic chromium and the passing of unabsorbed chromium). All exposure groups (either Cr(VI) or Cr(III)) exhibited higher chromium concentrations than control groups (see Tables C-6 and C-7).

Table C-6. Summary of oral and inhalation data from O'Flaherty and Radike (1991)

Study day	Lung µg Cr/g	Liver µg Cr/g	Intestine µg Cr/g	Kidney µg Cr/g	Muscle µg Cr/g	Blood ng Cr/g	Urine µg Cr/d	Feces mg Cr/d
Inhalation Cr(VI) (200 µg/m³ 6 h/d)								
2	1.95	nd	1.10	nd	nd	42.5	0.520	nd
5	5.10	0.060	1.12	0.217	nd	58.4	0.207	nd
10	7.53	0.062	1.37	0.237	nd	73.8	0.266	0.018
20	13.3	0.066	2.36	0.310	0.047	72.8	0.135	0.048
40	24.3	0.089	3.24	0.580	0.054	75.7	0.047	0.082
60	13.0	0.038	0.820	0.137	0.027	39.8	0.012	nd
Ingestion Cr(VI) (12.9 mg/L ad libitum)								
2	nd	0.209	15.5	0.249	nd	9.00	0.622	0.997
5	nd	0.372	22.7	0.588	nd	11.8	1.79	0.835
10	nd	0.585	14.4	1.60	nd	18.5	2.01	0.949
20	1.17	1.18	29.0	1.71	0.077	48.9	3.08	0.977
40	0.650	1.50	6.80	1.90	0.103	58.3	2.19	1.51
60	0.450	0.509	0.830	0.634	0.070	11.3	0.217	nd
Inhalation Cr(III) (200 µg/m³ 6 h/d)								
2	3.43	nd	3.57	nd	nd	61.5	0.215	0.028
5	8.43	nd	4.19	nd	nd	64.8	0.101	0.035
10	17.1	nd	25.6	nd	nd	23.4	0.084	0.016
20	35.4	nd	39.4	nd	nd	12.0	0.032	0.032
40	63.7	nd	4.80	nd	nd	105.7	0.002	0.074
60	42.9	nd	0.840	nd	nd	89.0	0.001	nd
Ingestion Cr(III) (12.9 mg/L ad libitum)								
2	nd	0.042	18.3	nd	nd	2.48	0.227	0.821
5	nd	trace	17.2	nd	nd	3.11	0.065	0.729
10	nd	0.034	20.6	nd	nd	16.8	0.040	1.20
20	nd	nd	26.8	nd	nd	5.60	0.075	1.07
40	nd	nd	7.15	nd	nd	4.72	0.017	1.12
60	nd	trace	0.830	nd	nd	5.52	nd	nd

Mean values (N = 6); nd = nondetect.

Table C-7. Summary of oral and inhalation control group data from O'Flaherty and Radike (1991)

Study day	Lung µg Cr/g	Liver µg Cr/g	Intestine µg Cr/g	Kidney µg Cr/g	Muscle µg Cr/g	Blood ng Cr/g	Urine µg Cr/d	Feces mg Cr/d
Inhalation control group								
2	nd	0.036	1.13	nd	nd	nd	0.042	nd
5	nd	0.041	0.64	nd	nd	nd	0.001	nd
10	nd	nd	0.83	nd	nd	nd	nd	nd
20	nd	nd	1.08	nd	nd	nd	nd	0.02
40	nd	0.041	1.08	nd	nd	nd	nd	nd
60	nd	0.032	0.84	nd	nd	nd	nd	nd
Ingestion control group								
2	nd	nd	0.65	1.58	trace	1.5	0.017	nd
5	nd	nd	0.83	nd	trace	1.6	nd	0.002
10	nd	nd	0.56	nd	nd	4.2	0.003	nd
20	nd	nd	0.85	nd	trace	3.4	nd	0.013
40	nd	0.035	0.68	nd	trace	6.8	0.01	nd
60	nd	0.032	0.72	nd	0.038	2.5	nd	nd

Mean values (N = 6); nd = nondetect.

C.1.3. Metabolism

Cr(VI) reduces to Cr(III) in the GI tract and in RBCs. Reduction takes place in the GI tract tissue and liver following oral exposure (due to the first-pass effect) and in pulmonary tissues following inhalation exposure. Extracellular reduction in gastric juice and in pulmonary fluids is also possible. Extracellular reduction in the lung is likely to be less effective than reduction in the GI tract, due to higher pH and lower reducing capacity. In blood, plasma reduces Cr(VI) poorly relative to RBCs (Corbett et al., 1998). Intracellular reduction of Cr(VI) (which occurs after Cr(VI) enters the cells of a susceptible tissue) is a potential pathway for metabolic activation. Reactive intermediaries and reactive oxygen species (ROS) are generated as Cr(VI) is intracellularly reduced to Cr(III).

Extracellular reduction in the stomach is expected to impact the systemic uptake of unreduced Cr(VI) and the exposure of the digestive tract epithelium. Stomach reduction may be a major source for interspecies and interindividual differences due to the strong dependence on gastrophysiology and pH. Figure C-4 illustrates the rate of reduction in human gastric juice under different pH conditions. At higher values of pH, Cr(VI) reduction occurs slowly.

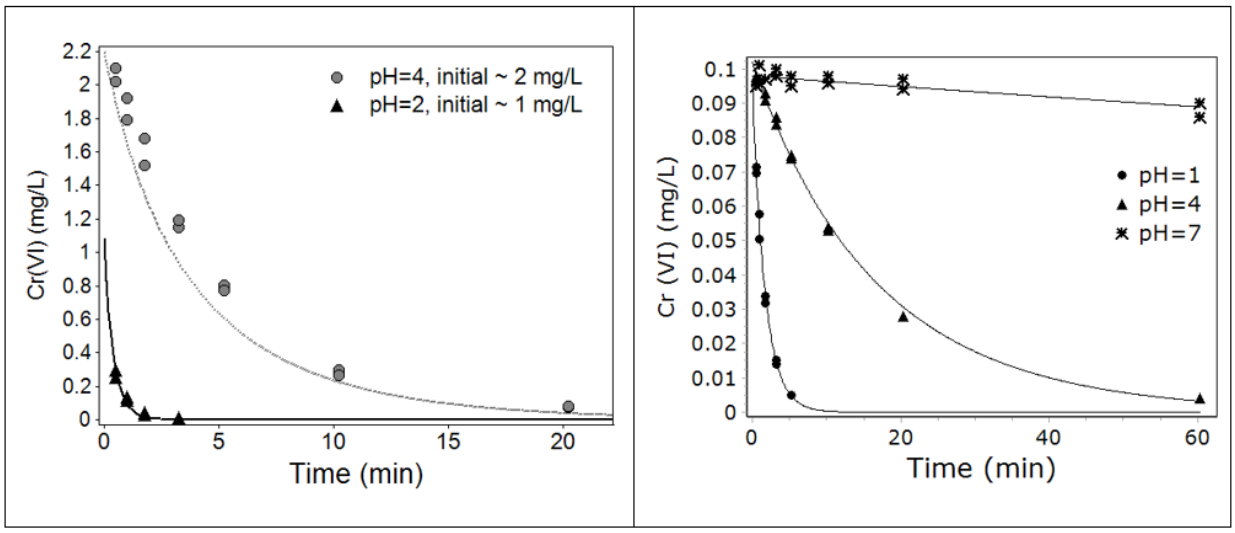

Figure C-4. Reduction of Cr(VI) in samples of human gastric juice (fasted subjects) using data from Proctor et al. (2012). Lines indicate model results by Schlosser and Sasso (2014). (Left) 2:1 dilution of stomach contents, multiple initial Cr(VI) concentrations. (Right) 10:1 dilution of stomach contents, initial Cr(VI) concentration approximately 0.1 mg/L.

The basal values of pH for humans and rodents in the fasted state are approximately 1.3 and 4, respectively (Table C-8). Under these conditions, humans would reduce Cr(VI) more effectively than rodents. This pattern, however, is reversed during the fed state. Human gastric juice pH rises to a peak of about 6, and then decreases to baseline within 2 hours (Mudie et al., 2010). Rodent gastric juice pH decreases during the fed state, but the dynamics are not well characterized.

Table C-8. The pH of the mouse, rat, and human gastrointestinal tract

Section	Female Balb/c mice				Female Wistar rats				Human[a]	
	Fed (n = 8)		Fasted (n = 7)		Fed (n = 5)		Fasted (n = 5)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Fed	Fasted
Stomach	2.98	0.3	4.04	0.2	3.20	1.0	3.90	1.0	4.9	1.3
Duodenum	4.87	0.3	4.74	0.3	5.00	0.3	5.89	0.3	5.4	6.0
Jejunum	4.82	0.2	5.01	0.3	5.10	0.3	6.13	0.3	5.4–6.0	6.2–6.4
Ileum	4.81	0.3	5.24	0.2	5.94	0.4	5.93	0.4	6.6–7.4	
Caecum	4.44	0.2	4.63	0.4	5.90	0.4	6.58	0.4	6.4	
Proximal colon	4.69	0.3	5.02	0.3	5.51	0.5	6.23	0.4	6.8	
Distal colon	4.44	0.3	4.72	0.2	5.77	0.5	5.88	0.5		

Adapted from Mcconnell et al. (2008) and Parrott et al. (2009).
Fed-state pH values for humans represent time-weighted average values during the fed state, and not peak/maximum values occurring during a meal.
Fed-state pH values for rodents were obtained from animals that had not undergone an overnight fast, thus pH does not represent minimum values occurring during a meal.
[a]Standard deviations not available; summary data reviewed in Parrott et al. (2009).

Fed-state reduction kinetics have greater uncertainties, as the gastric juice will be heterogeneous and the pH fluctuation temporary. Secretion of additional gastric juices and enzymes responsible for meal digestion occurs, and various ingested food components may have different effects on reduction rate. Therefore, diet could result in high interindividual variability of fed-state reduction kinetics in the human population. This variability is apparent in ex vivo data by Kirman et al. (2016) (see U.S. EPA (2021b)). In general, gastric juice in the fed state is believed to have a greater capacity[3] for Cr(VI) reduction (because dietary contents such as ascorbate and secreted gastric juices may act as reducing agents). Table C-9 contains a summary of estimated Cr(VI) reducing capacities for various tissues and fluids in mice, rats, and humans. As previously noted in the absorption section, the extent of Cr(VI) reduction by components of the respiratory system is complicated by airway geometries and localized particle deposition.

[3]Reduction capacity is the total amount of Cr(VI) that can be reduced (as $t \rightarrow \infty$) and is a function of how much reducing agent (components capable of reducing Cr(VI)) is contained in gastric juice. This differs from the reduction rate (how fast Cr(VI) can reduce per unit of time), which is a function of stomach pH.

Table C-9. Selected studies of Cr(VI) reduction capacities

Reference	Media (species)	Findings
Estimates of bodily fluid reduction capacity (ex vivo)[a]		
Proctor et al. (2012)	Stomach contents (rat)	Study estimate: 15.7 µg/mL
	Stomach contents (mouse)	Study estimate: 16.6 µg/mL
Kirman et al. (2013)	Gastric fluid (human)	Study estimate: 20 µg/mL [based on a mean of 7 µg/mL (fasted) from this study and a median of 30 µg/mL (fed) from De Flora et al. (1987a)]
Schlosser and Sasso (2014)	Gastric fluid reanalysis (rat, mouse, human)	Reanalysis of data by Proctor et al. (2012) and Kirman et al. (2013). Rat: 4/18 µg/mL (fast/slow pool). Mouse: (3/31 µg/mL fast/slow pool). Human: 10 µg/mL (fasted-state kinetics).
De Flora et al. (2016)	Gastric fluid (human)	Colorimetric method: 10.2 ± 2.39 µg/mL (premeal) and 20.4 ± 2.61 µg/mL (post-meal) Mutagenicity assay: 13.3 ± 1.91 µg/mL (premeal) and 25.6 ± 2.89 µg/mL (post-meal)
Kirman et al. (2016)	Gastric fluid (human)	Fasted state: 2.6 ± 2.8 and 12 ± 18 µg/mL for fast and slow pools, respectively. Fed state: 0.68 ± 0.76 and 27 ± 28 µg/mL for fast and slow pools.
	Gastric fluid reanalysis (rat, mouse, human)	Mouse: 6.1/27 µg/mL (fast/slow pool). Rat: 7.1/73 µg/mL (fast/slow pool).
De Flora et al. (1987a)	Gastric fluid (human)	8.3 ± 4.3 µg/mL (fasting), 31.4 ± 6.7 µg/mL (fed)
Petrilli and De Flora (1982)	Saliva (human)	1.4 ± 0.2 µg/mL
Petrilli et al. (1986)	Epithelial lining fluid (human)	23.7 ± 15.9 µg/mL
Estimates of cellular or organ reduction capacity[a]		
De Flora et al. (1997)	Intestinal bacteria (human fecal)	3.8 ± 1.7 µg/10^9 bacteria (elimination via feces)
	Liver (human)	2.2 ± 0.9 µg/g liver homogenate
	Blood (human)	52.1 ± 5.9 µg/mL intact whole blood
	Red blood cells (human)	63.4 ± 8.1 µg/mL RBC lysate soluble fraction
Petrilli et al. (1986)	Pulmonary alveolar macrophages (human)	4.4 ± 3.9 µg/10^6 PAM S9 fraction
De Flora et al. (1987a)	Peripheral lung parenchyma (human)	200 ± 70 µg/g lung S12 fraction
Capellmann and Bolt (1992)	Plasma (human)	0.48–0.63 nmol/mL [at intubation of 1.5 nmol/mL Cr(VI)]
Upreti et al. (2005)	Intestinal epithelial cells and gut bacteria (rat)	Most Cr(VI) at 10 mg/L completely reduced by bacteria in 6 h. Complete reduction by some cells can take 24 h.

[a]Reduction capacities represent the mass of Cr(VI) that can be reduced by a tissue or fluid, per unit mass or volume of the media.

C.1.4. Excretion

Following oral ingestion, Cr(VI) and its metabolite Cr(III) are primarily eliminated via urinary excretion (Figures C-5 and C-6). Due to poor GI tract absorption of Cr(III), a significant amount of reduced chromium is eliminated in feces without being absorbed. Urinary excretion is also a primary pathway for elimination following inhalation exposure. Intratracheal studies in rodents have observed elevated urinary chromium, and biomonitoring studies in humans in occupations where inhalation exposure could occur have also detected elevated chromium (see Appendix C.1.6). Following chronic, low-dose oral exposure to Cr(VI), most systemic chromium is likely in the trivalent form. Site-specific clearance of Cr(VI) by reduction to Cr(III) in tissues such as the GI tract, liver, and blood is likely to be greater than systemic clearance of Cr(VI) in urine at low doses. Variability in urinary clearance rates of Cr(VI) between individuals and across species likely does not have a significant impact on toxicity under chronic low-dose exposure scenarios (since most, if not all, systemic chromium will have been reduced to Cr(III)).

Intravenous studies have indicated a significant percentage of chromium could be excreted via biliary excretion and fecal elimination; however, these elimination pathways are minor following oral ingestion (due to reduction in the stomach and liver; see Appendix C.1.6). Intravenous injection of Cr(VI) leads to high systemic concentrations that are not observed following oral exposure, and thus some distribution or metabolic mechanisms (i.e., RBC uptake and reduction) may become saturated.

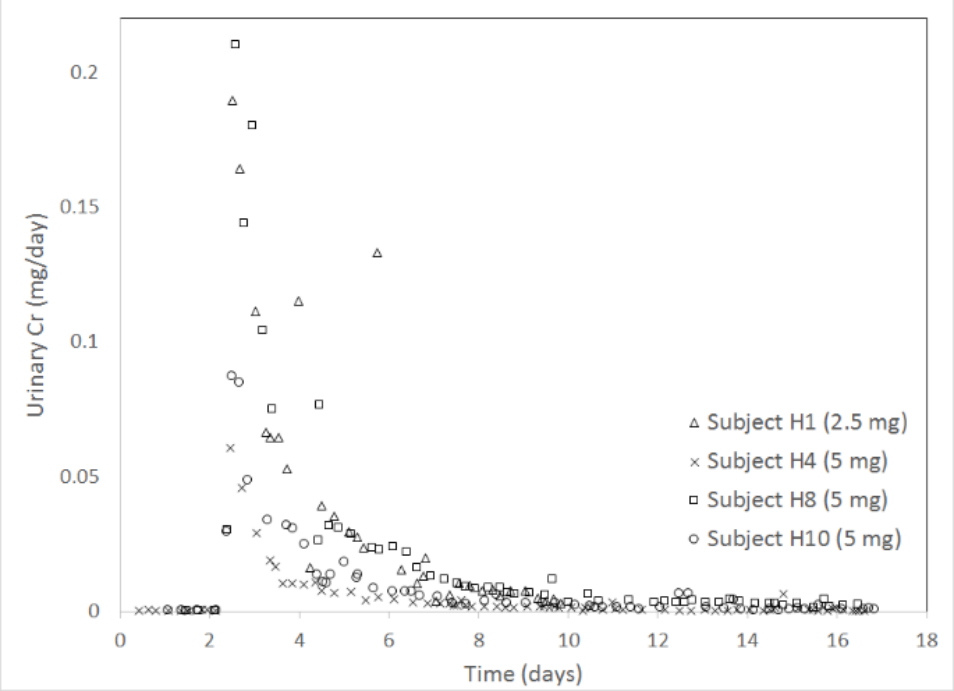

Figure C-5. Urinary rates of excretion by human volunteers administered a glass of drinking water containing 2.5–5.0 mg Cr(VI) at day 2. Data from Kerger et al. (1996).

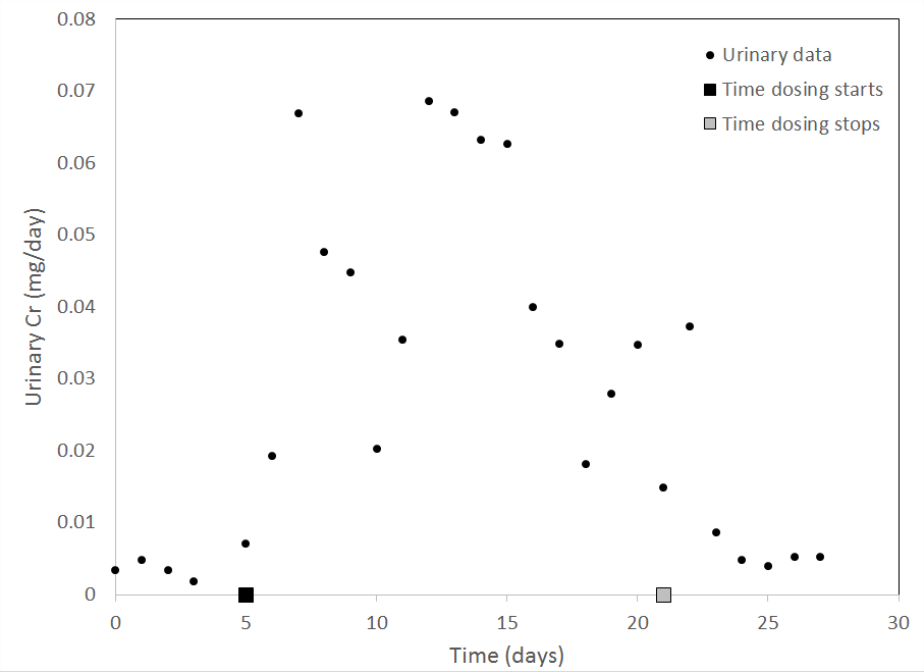

Figure C-6. Urinary excretion rate of a human volunteer ingesting a glass of drinking water with Cr(VI) repeatedly throughout the day (0.8 mg Cr(VI) daily) for 17 days. Data from **Paustenbach et al. (1996)**.

C.1.5. Physiologically Based Pharmacokinetic Models

A description of the available physiologically based pharmacokinetic (PBPK) models for Cr(VI) is available in Section 3.1.2 of the toxicological review. The PBPK model code used in this assessment (in R/MCsim) is available for download in HERO (U.S. EPA, 2022b).

Significant uncertainties exist that may be difficult to fully characterize using PBPK models. The stomach of rodents and humans will dynamically fluctuate between the fed and fasted states. This affects reaction dynamics in multiple ways. As noted in Table C-8, glandular stomach pH is decreased for the rodent during the fed state, while the opposite is true for humans. In addition to pH effects, gastric emptying is delayed in the fed state to digest food, and the volume of contents in the lumen will be increased. Gastric juice induced by food consumption may also have different reducing capacities (and ingested food itself could impact reduction kinetics). MacKenzie et al. (1959) measured absorption in fed and fasted rats following a single oral dose and observed rats in the fasted state exhibited higher tissue and urinary chromium levels than rats in the fed state. This would be consistent with more efficient Cr(VI) reduction in the fed rat than in the fasted rat. Thus, it has been demonstrated that Cr(VI) reduction in the rodent may be affected by fed status in vivo.

In addition to daily pH fluctuations, interindividual and life stage variability of stomach pH in the human population is significant. Hypochlorhydria (low stomach acid) is exhibited by an

unknown fraction of the population,[4] leading to a consistently high stomach pH (Kalantzi et al., 2006; Feldman and Barnett, 1991; Christiansen, 1968). Among adults without hypochlorhydria, 5% of men can exhibit basal pH exceeding 5, and 5% of women can exhibit basal pH exceeding 6.8 (Feldman and Barnett, 1991). That Cr(VI) reduction will be decreased for individuals with high stomach pH is expected, although the reduction rates are uncertain. Gastric juice reduction data were obtained from adults with naturally low stomach pH or stomach pH elevated by proton pump inhibitors. The gastric juice of those with high pH may be chemically or biologically different. Neonates, infants, and young toddlers generally have neutral stomach pH for the first 20–30 months, which then lowers to the normal adult range of 1–2 (Neal-Kluever et al., 2019; Bai et al., 2016).

C.1.5.1. *Application of pharmacokinetic models for dose-response assessment*

A previous PBPK application of the Kirman et al. (2013) model by Thompson et al. (2014) defined the internal dose as the average lifetime daily milligrams Cr(VI) absorbed per liter small intestine segment for the duodenum, jejunum, and ileum individually. This metric was applied to the NTP 2-year bioassay, and dose-response modeling was performed on pooled data (male and female mice, duodenum, jejunum, and ileum). Thompson et al. (2014) excluded jejunum tissue from the analysis of hyperplasia. Because of uncertainties in site-specific absorption for the human, the study authors applied total small intestinal absorption (per L small intestine) as the human dose metric for extrapolation.

Site-specific absorption in the rodent small intestine, however, is uncertain. Ingested drinking water does not evenly distribute in the small intestine lumen, but instead forms multiple discrete pockets of water that vary with time (Mudie et al., 2014). Motility in the intestine is highly variable, and the intestine secretes enzymes that can impact reduction rates. At the microscopic level, data for Cr(VI) indicates uptake might not occur uniformly in GI tract epithelial cells (Thompson et al., 2015a). The well-mixed compartment assumption is likely an inaccurate description of the system, particularly for distal regions of the intestine.

An alternative to the absorption dose metric is pyloric flux. Pyloric flux was defined by Thompson et al. (2014) to be average daily mg Cr(VI) emptied from the stomach to the small intestine, per liter small intestine. This estimate requires only the stomach portion of the gastrointestinal tract PBPK model. Fewer parameters are required to simulate pharmacokinetics in the stomach, and many of these parameters (such as gastric volume and emptying rate) are well characterized in rodents and humans. The full whole-body PBPK model by Kirman et al. (2017) contains approximately 100 PBPK parameters, and many of the fitted chemical-specific parameters have high uncertainty due to the constant presence of background Cr(III) and reduced Cr(III) in all

[4]One estimate is that less than 1% of the adult population might exhibit hypochlorhydria, whereas 10–20% of the elderly population might exhibit this condition (Russell et al., 1993).

Cr(VI) pharmacokinetics studies. The stomach-only model applied in this assessment (Figure C-7) contains approximately 20 parameters.

Furthermore, the data underlying the ex vivo reduction model were generated under batch reaction conditions, which is similar to the stomach compartment. There is added uncertainty when extrapolating ex vivo data to the complex and dynamic intestinal compartments (which may contain different reducing agents). Uncertainties and the possible implications of these and other candidate internal dose metrics are outlined in Table C-10.

For this assessment, a hybrid PBPK-$BW^{3/4}$ scaling approach was used for effects in the small intestine and systemic effects. The hybrid approach applied $BW^{3/4}$ scaling to the mg/kg-day Cr(VI) escaping stomach reduction and entering the small intestine. Because the volume of the small intestine (like other tissues) varies between species by allometry, interspecies scaling by $BW^{3/4}$ is numerically similar to scaling by small intestinal volume.

For effects in the oral mucosa, multiple dose metrics were explored. For example, the concentration of Cr(VI) ingested, scaled by the exposed oral surface areas, can be used as a dose metric. However, without such surface area data for rats, and without an oral cavity pharmacokinetic or pharmacodynamic model, it was not possible to develop these alternative dose metrics. In the absence of an adequately developed theory or information to develop and characterize an oral portal-of-entry dosimetric adjustment factor, application of $BW^{3/4}$ scaling is recommended (U.S. EPA, 2011b, 2005).

Table C-10. Uncertainties and potential impacts of alternative dose metrics for rodent-to-human extrapolation

Dose metric	Added uncertainty	Extrapolation notes
Site-specific absorption Daily mg Cr(VI) absorbed in a small intestine (SI) segment, per L SI segment	• Small intestine lumen not well mixed. • Fluctuations in intestinal motility and secretions not modeled. • Cellular uptake in epithelium not uniformly distributed. • High variability and uncertainty for absorption of Cr(VI)/reduced Cr, perfusion of Cr(III)/ Cr(VI) from systemic plasma, absorption of background Cr(III). • Differences in relative lengths of small intestinal segments between rodents and human preclude direct comparisons.	**Human equivalent dose (HED) estimates:** Similar to pyloric flux, since rapid GI uptake is assumed in all species, and human absorption is still normalized by total SI volume. **Variability assessment:** Difficulty in assessing interindividual variability site-specific absorption fractions. Inconsistent dose metric basis between humans and rodents, since only total Cr(VI) absorption in whole intestine can be estimated by current human PBPK models.
Pyloric flux Daily mg Cr(VI) emptying from the stomach to the SI, per liter SI	• Absorption not modeled (assumes 100% absorption in all species). • Reduction in small intestine neglected.	**HED estimates:** Slightly higher than small intestine absorption dose metric, since this metric assumes 100% absorption for the rodent. **Variability assessment:** Can only assess stomach reduction variability.
Cr(VI) lumen concentration mg Cr(VI) in SI lumen, per liter SI lumen	• Estimates of Cr(VI) concentration in lumen contents not well characterized.	**HED estimates:** Similar to pyloric flux dose metric, since it normalizes the Cr(VI) mass by intestinal lumen volume (which will scale similarly as intestinal tissue volume). **Variability assessment:** Difficult to assess variability.
$BW^{3/4}$-adjusted unreduced Cr(VI) dose Daily mg Cr(VI) emptying from the stomach, per kg BW, multiplied by $(BW_a/BW_h)^{0.25}$	• Does not incorporate volume of gastrointestinal tissue, a site of observed toxicity.	**HED estimates:** 10–20% lower than pyloric flux. Normalizing unreduced Cr(VI) by a $BW^{3/4}$ adjustment has a similar impact on HED as normalizing to intestinal volumes. **Variability assessment:** Can assess only stomach reduction variability.

Dose metric	Added uncertainty	Extrapolation notes
Stomach absorption mg Cr(VI) absorbed in stomach tissue, per liter stomach tissue	• Estimates of Cr(VI) stomach absorption not well characterized. • Intestinal dose metric still applied for rodent.	**HED estimates:** Similar to pyloric flux due to pH dependence. **Variability assessment:** Difficult to assess absorption variability. Would lead to different dose metric basis between humans and rodents.
$BW^{3/4}$ scaling Daily mg/kg Cr(VI) ingested, multiplied by $(BW_a/BW_h)^{0.25}$	• Does not correct for species differences in Cr(VI) reduction.	**HED estimates:** For extrapolations in the low-dose region, would result in lower HEDs than all other approaches. For extrapolations in the high-dose region, would result in slightly lower (~20% lower) HEDs than methods listed above (due to high percentage of dose escaping for human model at high doses). **Variability assessment:** Cannot directly assess inter-individual variability in pharmacokinetics.
Cr(VI) ingested concentration Parts per million (mg/L) Cr(VI) ingested	• Does not correct for species differences in Cr(VI) reduction, tissue uptake, or tissue exposure duration. • May require additional scaling to account for species differences in epithelial surface area and exposure time.	**HED estimates:** Would result in higher HEDs than most other approaches for both oral and intestinal tumors. Feasible only for oral mucosa, prior to mixing/dilution/reduction by gastric and intestinal contents. **Variability assessment:** Cannot directly assess interindividual variability in pharmacokinetics.
$BW^{3/4}$ scaling, adjusted for target tissue volumes Daily mg/kg Cr(VI) ingested, multiplied by: $(BW_a/BW_h)^{0.25} \times V_a/V_h$ (V_a and V_h represent tissue volume as % total body volume)	• Does not correct for species differences in Cr(VI) reduction or tissue uptake. • Must assume steady-state tissue delivery and clearance.	**HED estimates:** Difference from alternative approaches depends on organ site. Would be representative of local tissue dose. Feasible only for oral mucosa, prior to mixing/dilution/reduction by gastric and intestinal contents. **Variability assessment:** Cannot directly assess interindividual variability in pharmacokinetics.

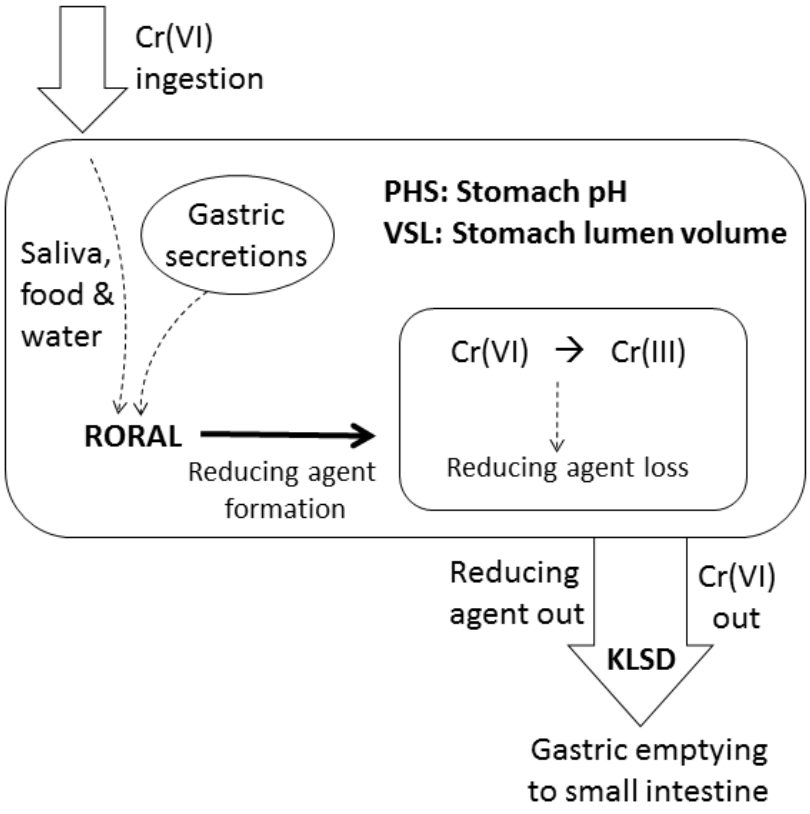

Figure C-7. Schematic of the gastric model and parameters for Cr(VI).
Parameter values and units defined in Tables C-11 (humans), C-13 (mice), and C-16 (rats).

C.1.5.2. *PBPK model assumptions for the human*

Table C-11. Final human physiological parameters for dose-response modeling and rodent-to-human extrapolation

Parameter code variable	Parameter value	Parameter source and notes
BW (kg)	80	Body weight. This value is chosen to maintain consistency for comparison with default approaches (such as $BW^{3/4}$ scaling (U.S. EPA, 2011b, 2005)).
VSLC ($L/kg^{0.75}$)	9.92×10^{-3} (baseline), 2.02×10^{-3} (fasted)	Stomach lumen volume or stomach contents volume (scaled by $BW^{3/4}$). Baseline value (0.24 L for a 70-kg human) is based on ICRP (2006, 2002) reference values for mass of stomach contents (average of adult male and female). Fasted-state value (0.049 L for a 70-kg human, applied in the morning) is based on the mean value measured by Grimm et al. (2018); this is also the default fasted value in GastroPlus (version 9.0) software. Lognormal coefficient of variance of 0.1 applied for Monte Carlo simulations (based on GastroPlus defaults).

Parameter code variable	Parameter value	Parameter source and notes
PHS	1.3 (baseline), 4.9 (fed spike)	Gastric pH. Varies based on fed status (Mudie et al., 2010; Parrott et al., 2009). May be chronically elevated (>4) in some individuals (Kalantzi et al., 2006; Feldman and Barnett, 1991; Christiansen, 1968). Values of 1.3 and 4.9 obtained from Parrott et al. (2009), and decaying exponential function ($e^{-0.9302t}$) following spike during meals estimated by digitizing data from Dressman et al. (1990). For Monte Carlo simulations, the spikes were assumed to begin up to 10 min after the breakfast/lunch/dinner oral doses and up to 30 min before (uniform distribution). Lognormal coefficient of variance of 0.12 applied to baseline for Monte Carlo simulations (based on GastroPlus defaults).
KLSD (h^{-1})	1.39 (baseline), 2.63 (fasted)	Gastric emptying rate (1st order). Based on standard reference value of half-emptying time of noncaloric liquids in adults (30 min) by ICRP (2006, 2002). Fasted-state value based on fasted half-emptying time for water of 15.8 min Mudie et al. (2014). Lognormal coefficient of variance of 0.2 applied for Monte Carlo simulations (based on GastroPlus defaults).
RORAL (L/h)	Calculated (see text) = 0.33 (baseline) = 0.129 (fasted)	Sum of drinking water/food/saliva/GI fluid introduction into gastric compartment. This value is not set but calculated on the basis of steady-state volume of stomach contents and stomach emptying rate (see text). As a comparison, the default Kirman et al. (2017) values for the human are 0.13–0.56 L/h (varying with drinking rate). ICRP (2006, 2002) estimates the average daily generation of saliva and gastric juice in adults to be 0.133 L/h (which is approximately equal to the fasted-state RORAL). Thus, the model assumes, during a baseline 1-h ingestion event, an adult might consume approximately 0.2 L of food and/or drinking water such that the total introduction of contents to the stomach is 0.33 L.
VSIC (fraction)	8.77e−3	Volume of small intestine tissue used for internal dose scaling (fraction of body weight). Used for pyloric flux estimates only. Value for a 70-kg human (~0.62 L) unchanged from Kirman et al. (2012) and Kirman et al. (2017). This is consistent with the ICRP (2006, 2002) value for mass of intestine wall (0.65 kg for adult males, 0.60 kg for adult females).
CRE01 (mg/L)	10.0 (fasted) 20.0 (fed)	Reducing capacity of human gastric juice assuming a single pool of reducing agent according to the model by Schlosser and Sasso (2014). Data from De Flora et al. (2016) were used to derive fasted/fed-state values and to estimate a lognormal distribution for Monte Carlo analyses (lognormal coefficient of variance of 0.5). Model set fed-state values lasting 2 h for the 3 meals (breakfast/lunch/dinner), beginning at the time of the spikes in gastric pH.

For additional kinetic parameters used in the model, see Schlosser and Sasso (2014).
GastroPlus default values used or cited alongside gastric PK parameters because they have been found consistent with values identified by literature screening and also provided estimates of population variability.

The human PBPK model was run assuming the periodic bolus exposure profile for a period of time until the internal dose metric reached steady-state (7 weeks). This was done to prevent an underestimation of the internal dose, which could result from assuming continuous mg/kg-day exposure (less reducing agent depletion occurs if the dose is spread evenly over 24 hours). These drinking water assumptions are consistent with human surveys (U.S. EPA, 2019a; Barraj et al., 2009).

In addition, a change in gastric volume and gastric emptying from baseline was incorporated to account for an early morning fasted state, and a pH spike above baseline was incorporated to account for the fed state. This special fasted state was applied only in the morning, and the parameters only needed to be set shortly (1 hour) before the first ingestion because steady-state in the gastric reducing agent mass balance was achieved quickly. These model assumptions are illustrated in Figure C-8.

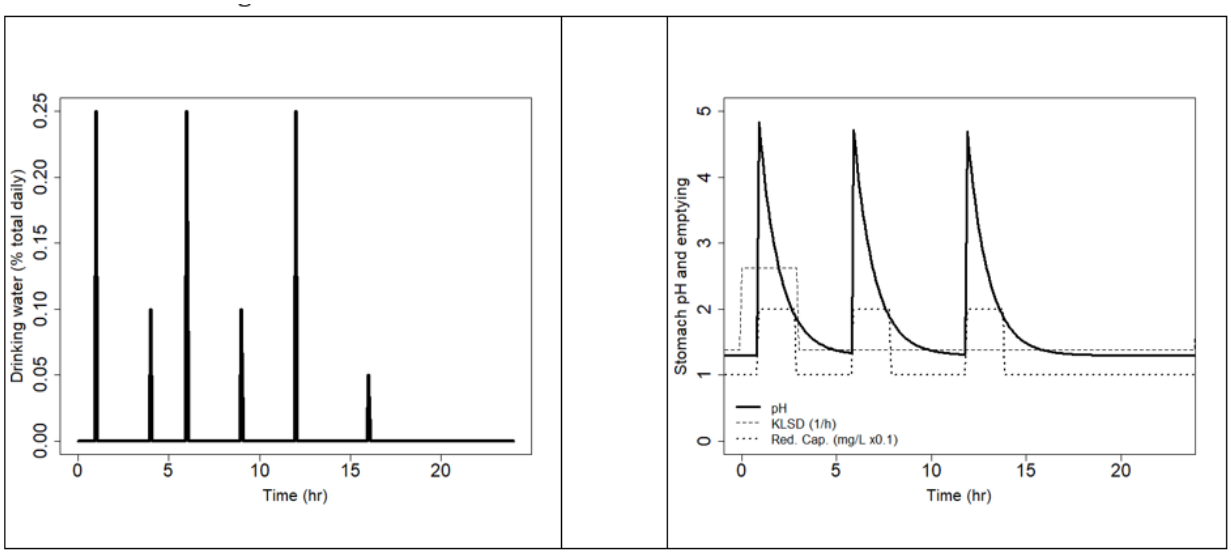

Figure C-8. Time profiles of the average daily oral Cr(VI) dose (left) and gastric pH, reducing capacity (/10), and gastric emptying rate KLSD (right) in the human. Exposure to Cr(VI) was assumed to occur via six discrete drinking water events of varying magnitude, occurring daily. Gastric emptying was elevated for 3 hours in the morning, beginning 1 hour prior to the first daily drinking event to simulate a morning fasted status. Gastric volume was also reduced to the fasted-state value during this time (not shown). Gastric pH was spiked to a value of 4.9 (which decreased exponentially) near the three other large drinking water events (to simulate breakfast, lunch, and dinner fed status). Elevation of the reducing capacity (lasting 2 hours) also occurred at the time of the spikes in pH. For Monte Carlo simulations, a uniform distribution was applied to the timing of the pH and reducing capacity spikes.

Local sensitivity analyses were performed on selected model parameters at a lower dose level and an upper dose level. The sensitivity was characterized by the finite difference method, and the sensitivity coefficients represent the ratios of the relative change in the response variable (internal dose) to the relative change in the independent variable (parameter). For the human model, the sensitivity of the internal dose to kinetic parameters was greater in the low-dose region. This is also illustrated by Figure C-9 for the stomach pH parameter.

Table C-12. Normalized sensitivity coefficients of human gastric model parameters with respect to pyloric flux dose metric

Parameter	Sensitivity coefficient at 0.04 mg/kg-d	Sensitivity coefficient at 0.4 mg/kg-d
CRE01 (reducing capacity of fast binary reaction, mg/L)	−1.2694	−0.7297
KLSD (gastric emptying rate, h^{-1})	0.7661	−0.0129
VSLC (baseline stomach lumen volume, fraction of BW)	−0.2226	−0.5593
VSLCFAST (fasted-state stomach lumen volume, fraction of BW)	−0.3550	−0.1289
K (rate constant for fast binary reaction, L/mg-h)	−1.1920	−0.0409
PHS (baseline)	0.2197	0.0143
PHSF (fed-state spike)[a]	5.1534	0.2461

Note: This model analysis incorporated only two pH spikes (lunch and dinner) and held CRE01 constant (no fed-state increase to 20 mg/L).

[a]To avoid simulation artifacts caused by TSPIKE and ingestion time occurring at same time, the values of TSPIKE were set to 5 minutes prior to water ingestion events.

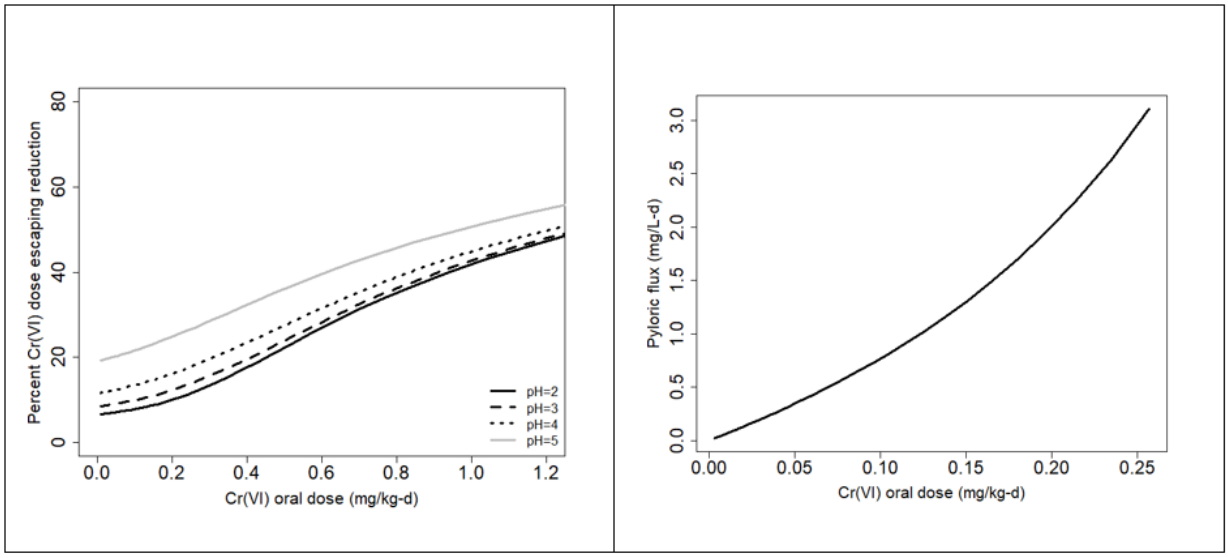

Figure C-9. (a) Percent Cr(VI) escaping stomach reduction (and being emptied to the small intestine) as a function of oral Cr(VI) dose for different values of baseline fasted-state stomach pH (human). (b) Pyloric flux as a function of oral dose for the human. The pH spike was set to begin 10 minutes prior to Cr(VI) ingestion for the three meals in this example (for human equivalent dose calculations, this is a random variable).

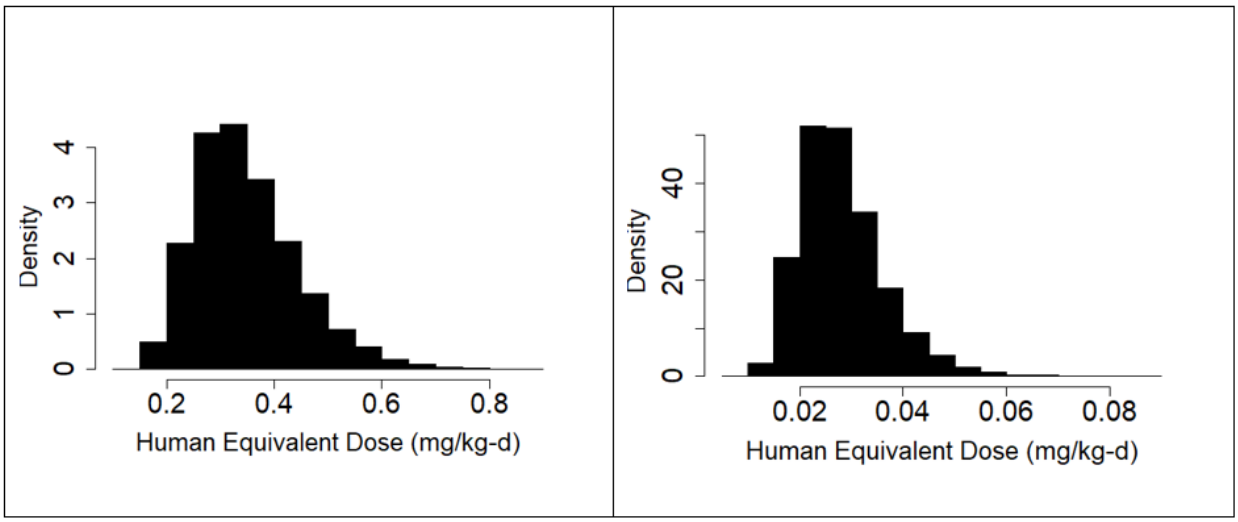

Figure C-10. Monte Carlo analysis (20,000 iterations) of the human equivalent dose at selected values of the internal dose. Model assumes three daily spikes in pH during the three large ingestion events and elevated gastric emptying/reduced gastric volume during early morning ingestion event. All simulations assume lognormal distributions for the baseline and fasted parameters, with coefficient of variance (CV) of 10% for stomach volume, 12% for baseline pH, 50% for fed and fasted reduction capacities, and 20% for stomach emptying. A uniform distribution was applied to the timing of each pH spike to allow for the oral dose to occur up to 30 minutes after the start of a large meal (pH spike), and up to 10 minutes before. All other parameters held constant. (Left) Human equivalent dose (HED) at pyloric flux 4 mg/L-d. (Right) Human equivalent dose (HED) at pyloric flux 0.1 mg/L-day.

To evaluate the potential impact of pharmacokinetic susceptibility on adult populations with high stomach pH, simulations were run using altered assumptions for baseline and fed-state pH (see Table C-13). These simulations included estimating the HED for low-dose and high-dose internal dose PODs. Standard default population simulations assumed a mean baseline pH of 1.3 and a fed spike of 4.9. The PHS = 4 population assumed a mean baseline pH of 4 and a fed spike pH of 4.9. For all simulations, the baseline pH had a lognormal distribution with a coefficient of variance of 0.12.

Although a fed-state pH spike was maintained for the high pH population, some uncertainty exists regarding the daily pH profile in response to meals. The study in healthy elderly subjects by Russell et al. (1993) observed that for individuals with high baseline pH, some exhibited minimal pH change with meals, while others exhibited a decrease in pH with meals.

Table C-13. Human equivalent dose (mg/kg-day) outputs of 20,000 Monte Carlo simulations of varying baseline pH populations using the $BW^{3/4}$-adjusted Cr(VI) dose escaping stomach reduction

Internal dose POD (mg/kg-d)	Model assumption	Mean HED (mg/kg-d)	SD (mg/kg-d)	Lowest 1% HED (mg/kg-d)
0.03	Default	0.328	0.0942	0.171
	PHS = 4	0.220	0.102	0.0596
0.001	Default	0.0320	0.00945	0.0165
	PHS = 4	0.0178	0.0179	0.00204
0.000732	Default	0.0237	0.00708	0.0121
	PHS = 4	0.00943	0.00404	0.00269

At high internal dose (which is most relevant for cancer extrapolation), the mean value for the HED of the pH = 4 population is approximately 33% lower than the HED of the default pH = 1.3 population. At low internal dose (which is most relevant for noncancer extrapolation), the mean value for the HED of the pH = 4 population is approximately 44% lower than the default. The value of the lowest 1% for the default assumption (0.0165 mg/kg-day), however, is still slightly lower than the mean value of the pH = 4 population (0.0178 mg/kg-day), meaning the pharmacokinetic approach is protective for the average of that group.

For values lower than 0.001 mg/kg-day (i.e., 0.000732 mg/kg-day), the mean HED of the pH = 4 population (0.00943 mg/kg-day) is 22% less than the lowest 1% HED of the pH = 1.3 population (0.0121 mg/kg-day). This is because at very low doses, the model is more sensitive to differences in pH. However, all internal-dose PODs for this assessment (which are used to derive human equivalent doses) are higher than 0.001 mg/kg-day. As a result, the pharmacokinetic approach (which uses the lowest 1% value) is protective of the pH = 4 population.

The pharmacokinetics results for all PODs can be compared to $BW^{3/4}$ scaling without pharmacokinetic adjustment for interspecies Cr(VI) reduction (see Appendix D.3). By not accounting for extracellular Cr(VI) reduction in either the rodent (gastric pH = 4.5) or the human (gastric pH = 1.3), the default scaling approach technically applies to the most sensitive population in terms of pharmacokinetics (i.e., a human population in which gastric pH = 4.5 and gastric juice reduction capacity is equivalent to that of the rodent). However, this does not consider the extreme case in which human pH is significantly higher than that assumed for the rodent (pH >> 4.5).

Applying $BW^{3/4}$ adjustment in accordance with (U.S. EPA, 2011b, 2005) and applying an intraspecies uncertainty factor (UF_H) of 3 (rather than 10, because the default approach implicitly accounts for the most sensitive pharmacokinetic population) is protective of the population that has high pharmacokinetic susceptibility. As noted in Appendix D.3, this specifically applies to the low-dose region, for which the model is most sensitive to gastric pH. At high doses, for which the

model is more sensitive to gastric reducing capacity, the lower 1% predictions from Monte Carlo simulations using the pharmacokinetic model are more health protective than $BW^{3/4}$ scaling.

Appendix D.3 contains a table of the RfD derivation using default approaches (no gastric reduction adjustment) and with $UF_H = 3$.

C.1.5.3. *PBPK model assumptions for the mouse*

Table C-14. Final mouse PBPK parameters for dose-response modeling and rodent-to-human extrapolation

Parameter code variable	Parameter value	Notes
BW (g)	50	Body weight. The time-weighted average body weight of mice in the NTP 2008 bioassays. Additional study-specific values of rodent body weight were used when necessary.
VSLC ($L/kg^{0.75}$)	0.00696	Volume of the stomach lumen contents (scaled by $BW^{3/4}$). Based on Mcconnell et al. (2008) "comfortably full" volume (0.37 mL in 18–22g mice). For a 50 g mouse, this equates to a stomach volume of 0.736 mL.
PHS	4.5	Gastric pH. Value unchanged from Kirman et al. (2012) and Kirman et al. (2017) since reduction data in mice are available only for pH 4.5 (and thus, confidence is highest for the mouse reduction rate at that pH). This parameter can vary with both fed status and stomach region (forestomach vs. glandular stomach) (Beasley et al., 2015; Kohl et al., 2013; Mcconnell et al., 2008; Browning et al., 1983). The reduction model used in this assessment by Schlosser and Sasso (2014) performs well for the available data of Cr(VI) reduction in rodent gastric juices.
KLSD (h^{-1})	4.33	Gastric emptying rate (1st order). Value changed from default value of 9.4 h^{-1} by Kirman et al. (2012) Kirman et al. (2017). Based on the default fed-state GastroPlus stomach transit time of 19.2 min. This is consistent with the literature, which estimates a half-emptying time for liquids in mice of approximately 10 min (Roda et al., 2010; Miyasaka et al., 2004; Bennink et al., 2003; Symonds et al., 2002) (see Table C-27). This parameter can vary based on fed status and gastric and dietary contents.
RORAL (mL/h)	3.2 (calculated)	Sum of drinking water/food/saliva/GI fluid introduction into gastric compartment. This value is not set but calculated on the basis of steady-state volume of stomach contents and stomach emptying rate (see text). As a comparison, the value of RORAL by Kirman et al. (2017) for the NTP (2008) data ranges from 0.65 to 6.2 mL/h (varying with drinking rate). In Kirman et al. (2017), this parameter was the sum of multiple individually defined rates that had high uncertainty and variability. The value for the gastric fluid (acid) production component defined in the Kirman et al. (2017; 2012) models was a central estimate by Thompson et al. (2011a) based on (Tibbitts, 2003; Wang et al., 2000; Friis-Hansen et al., 1998; Ito and Schofield, 1974). Those data varied significantly with time, fed status, and other factors, and the exact source of the Thompson et al. (2011a) estimate could not be determined. The saliva secretion rate component defined in Kirman et al. (2017; 2012) was based on a model by Timchalk et al. (2001), although it was not a measured parameter (it was instead

Parameter code variable	Parameter value	Notes
		calibrated to lead pharmacokinetic data). Values defined in Kirman et al. (2017; 2012) for the food and water intake component of RORAL were study specific.
VSIC (fraction)	0.0393	Volume of small intestine (fraction of body weight). Used for pyloric flux estimates only. Value unchanged from Kirman et al. (2012), which is based on fractional tissue volumes of the duodenum, jejunum, and ileum measured in that study. Value is consistent with Brown et al. (1997) (which estimates it to be 2–4 % of body weight).

For additional kinetic parameters used in the model, see Schlosser and Sasso (2014).

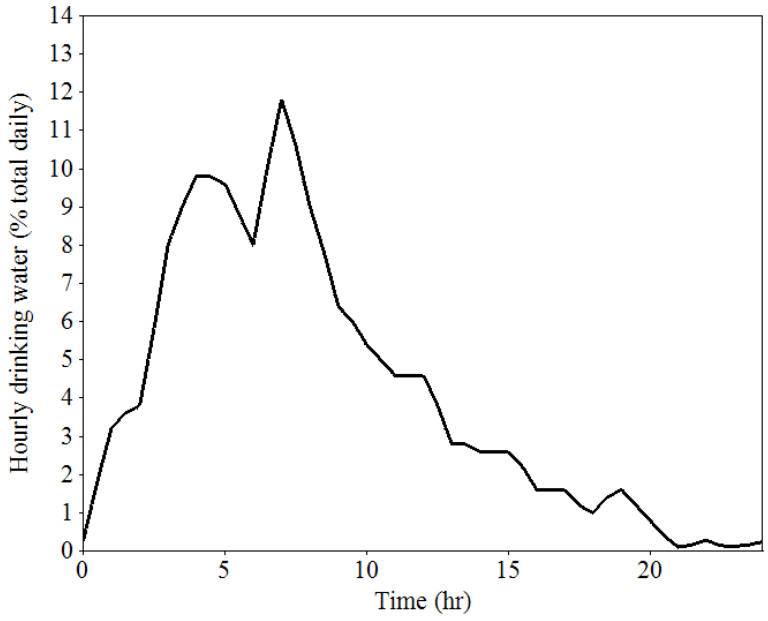

Figure C-11. Distribution of the average daily oral Cr(VI) dose in the mouse. Exposure to Cr(VI) was assumed to occur ad libitum in drinking water according to observed circadian drinking water data (**Yuan, 1993**).

PBPK simulations were run assuming standard adult rodent physiology (Table C-14), with circadian drinking water pattern (Figure C-11), until steady-state was achieved (7 weeks). This was done to prevent an underestimation of the internal dose, which could result from assuming continuous mg/kg-day exposure (less reducing agent depletion occurs if the dose is spread evenly over 24 hours).

Local sensitivity analyses were performed on selected model parameters at a lower dose level and an upper dose level using the finite difference method. For the rodent model, dose region had less effect on model sensitivity (Table C-15). However, the rodent model was very sensitive to changes in pH (Figure C-12), since the kinetic function of rate vs. pH by Schlosser and Sasso (2014) is steep in the region around pH 4.5. Ex vivo rodent kinetic data are available only at pH = 4.5

(mice) and pH = 4.38 (rats) Proctor et al. (2012). The kinetic model by Schlosser and Sasso (2014) adequately fits the rodent ex vivo data at these values of pH. Because the true value of the rodent whole stomach pH (glandular stomach + forestomach) during the NTP (2008) 2-year bioassay is uncertain, and because no ex vivo data are available for rodent kinetics at low pH, the model will be run only at pH = 4.5 (mice) and pH = 4.38 (rats) when used for the dose-response assessment. These values are fair approximations for the model since they fall within the range observed in rodents, but they are not without uncertainty (Beasley et al., 2015; Kohl et al., 2013; Mcconnell et al., 2008; Browning et al., 1983).

Table C-15. Normalized sensitivity coefficients of mouse gastric model parameters with respect to pyloric flux dose metric

Parameter	Sensitivity coefficient at 0.302 mg/kg-d	Sensitivity coefficient at 8.89 mg/kg-d
CRE01 (reducing capacity of fast binary reaction, mg/L)	−0.5083	−0.3009
CRE02 (reducing capacity of slow binary reaction, mg/L)	−0.3576	−0.6615
KLSD (gastric emptying rate, h^{-1})	0.8101	0.3231
VSLC (stomach lumen volume, fraction of BW)	−0.0301	−0.3243
K (rate constant for fast binary reaction, L/mg-h)	−0.5173	−0.1001
KS (rate constant for slow binary reaction, L/mg-h)	−0.3582	−0.5428
KVF (rate constant for slowest binary reaction, L/mg-h)	−0.0031	−0.0077
PHS (stomach pH)	7.8453	6.0116

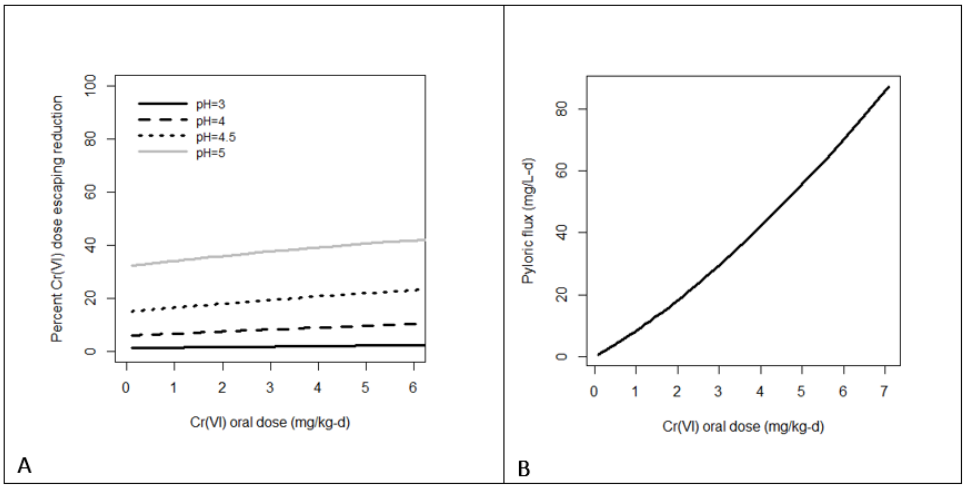

Figure C-12. (a) Percent Cr(VI) escaping stomach reduction (and being emptied to the small intestine) as a function of oral Cr(VI) dose for different

values of baseline stomach pH (mouse); (b) pyloric flux for the mouse using standard assumption at PHS = 4.5.

Because the internal dose is very close to linear (Figure C-12), benchmark dose modeling can be performed on the basis of the external oral dose, and PBPK model adjustments can be done in subsequent steps. Table C-16 below lists the predicted internal doses for the (NTP, 2008) 2-year drinking water bioassay. Table C-17 lists average daily internal doses for the female mouse (F0 dams) during the NTP (1997) bioassay.

Table C-16. Lifetime average daily internal doses for the mouse during the NTP (2008) 2-year bioassay of sodium dichromate dihydrate

Cr(VI) (mg/L)	TWA dose (mg/kg-d)	Dose escaping (mg/kg-d)	Pyloric flux (mg/L-d)
Females			
5	0.302	0.0463	1.18
20	1.18	0.197	5.00
60	3.24	0.636	16.2
180	8.89	2.31	58.7
Males			
5	0.450	0.0700	1.78
10	0.914	0.149	3.79
30	2.40	0.443	11.3
90	5.70	1.29	32.9

TWA dose: Time-weighted average daily dose.

Table C-17. Average daily internal doses for the female mouse (F0 dams) during the NTP (1997) bioassay

TWA dose (mg/kg-d)	Dose escaping (mg/kg-d)
11.6	3.09
24.4	8.61
50.6	24.8

BW = 24 g.

C.1.5.4. *PBPK model assumptions for the rat*

Table C-18 outlines the kinetic parameters used for a standard rat. For additional kinetic parameters used in the model, see Schlosser and Sasso (2014).

Table C-18. Final rat PBPK parameters for dose-response modeling and rodent-to-human extrapolation

Parameter code variable	Parameter value	Notes
BW (g)	450/395 (males) 260/215 (females)	Body weight (2-yr/12-mo). The time weighted average body weights of male and female rats in the NTP 2008 bioassays. Additional study-specific values of rodent body weight were used when necessary.
VSLC (L/kg$^{0.75}$)	0.0125	Volume of the stomach lumen contents (scaled by BW$^{3/4}$). Based on Mcconnell et al. (2008) "comfortably full" volume (3.38 mL for 160–190 g rats). For a 260-g rat, this yields a stomach volume of 4.55 mL. For a 450-g rat, it yields 6.87 mL.
PHS	4.38	Gastric pH. Value unchanged from Kirman et al. (2017), since reduction data in rats are available only for pH 4.38 (and thus, confidence is highest for the rat reduction rate at that pH). This parameter can vary with both fed status and stomach region (forestomach vs. glandular stomach) (Beasley et al., 2015; Kohl et al., 2013; Mcconnell et al., 2008; Browning et al., 1983). The reduction model used in this assessment by Schlosser and Sasso (2014) performs well for the available data of Cr(VI) reduction in rodent gastric juices.
KLSD (h^{-1})	2.77	Gastric emptying rate (1st order). Changed from default value of 2.4 h^{-1} defined by Kirman et al. (2012) and Kirman et al. (2017). Based on the default fed-state GastroPlus stomach transit time of 30 min. This is consistent with the literature, which estimates a half-emptying time for liquids in rats of approximately 15 min (Scarpignato et al., 1984; Purdon and Bass, 1973). This parameter can vary on the basis of fed status and gastric and dietary contents.
RORAL (mL/h)	12–19 (calculated)	Sum of drinking water/food/saliva/GI fluid introduction into gastric compartment. This value is not set but calculated on the basis of the steady-state volume of stomach contents and stomach emptying rate (see text). As a comparison, the default value calculated by Kirman et al. (2017) for the NTP (2008) study is 4–33 mL/h (varying with drinking rate). In Kirman et al. (2017), this parameter is the sum of multiple individually defined rates that had high uncertainty and variability. The value for the gastric fluid (acid) production component defined in the Kirman et al. (2017; 2012) models was a central estimate by Thompson et al. (2011a) based on (Runfola et al., 2003; Tibbitts, 2003; Kitamura et al., 1999; Takeuchi et al., 1998; Kuwahara et al., 1990; Wallmark et al., 1985). Those data varied significantly with time, fed status, and other factors, and the exact source of the Thompson et al. (2011a) could not be determined. The saliva secretion rate component defined in Kirman et al. (2017; 2012) was based on a model by Timchalk et al. (2001), although it was not a measured parameter (it was instead calibrated to lead pharmacokinetic data). Values defined in Kirman et al. (2017; 2012) for the food and water intake component of RORAL were study specific.

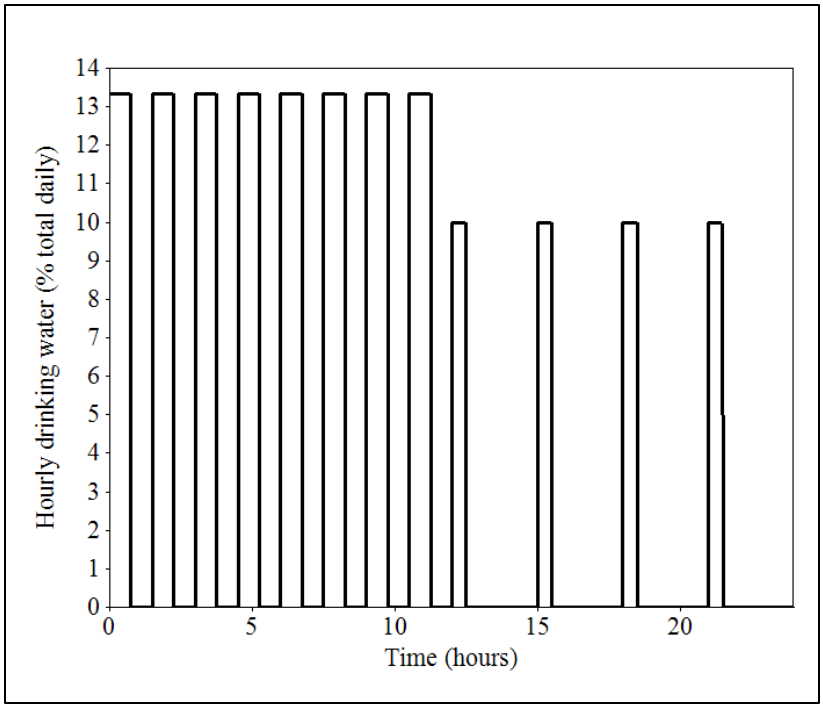

Figure C-13. *Ad libitum* drinking water assumptions applying data from the rat (Spiteri, 1982).

PBPK simulations were run assuming standard adult rodent physiology, with circadian drinking water pattern (see Figure C-13), until steady-state was achieved (7 weeks). This was done to prevent an underestimation of the internal dose, which could result from assuming continuous mg/kg-day exposure (less reducing agent depletion occurs if the dose is spread evenly over 24 hours).

Local sensitivity analyses were performed on selected model parameters at a lower dose level and an upper dose level using the finite difference method (see Table C-19).

Table C-19. Normalized sensitivity coefficients of rat gastric model parameters with respect to average daily dose escaping stomach reduction

Parameter	Sensitivity coefficient at 0.2 mg/kg-d	Sensitivity coefficient at 7.13 mg/kg-d
CRE01 (reducing capacity of fast binary reaction, mg/L)	−0.7410	−0.4692
CRE02 (reducing capacity of slow binary reaction, mg/L)	−0.2142	−0.6868
KLSD (gastric emptying rate, h^{-1})	0.8916	0.1877
VSLC (stomach lumen volume, fraction of BW)	−0.0410	−0.6081
K (rate constant for fast binary reaction, L/mg-h)	−0.7010	−0.0683
KS (rate constant for slow binary reaction, L/mg-h)	−0.2138	−0.4880

Parameter	Sensitivity coefficient at 0.2 mg/kg-d	Sensitivity coefficient at 7.13 mg/kg-d
KVF (rate constant for slowest binary reaction, L/mg-h)	−0.0046	−0.0206
PHS (stomach pH)	8.3698	5.2725

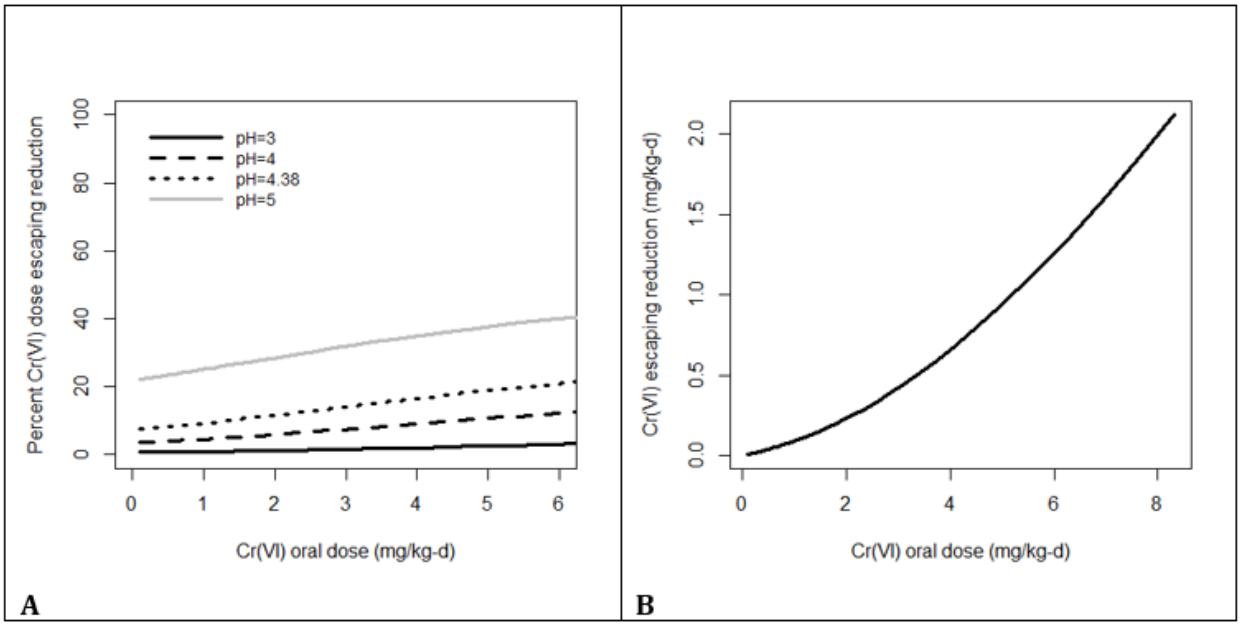

Figure C-14. (a) Percent Cr(VI) escaping stomach reduction (and being emptied to the small intestine) as a function of oral Cr(VI) dose for different values of baseline stomach pH (rat); (b) dose escaping stomach reduction for the rat using standard assumption at PHS = 4.38.

Because the internal dose is very close to linear (Figure C-14), benchmark dose modeling can be performed on the basis of the external oral dose, and PBPK model adjustments can be done in subsequent steps. Table C-20 lists the predicted internal doses for the (NTP, 2008) 2-year drinking water bioassay. This table includes values calculated at the 1-year timepoint for males. Additionally, BMD modeling was performed on the basis of internal dose to evaluate the difference between PODs derived from internal-dose and external-dose BMD modeling (difference was 1.2% for liver ALT).

Table C-20. Lifetime average daily internal doses for the rat during the NTP (2008) 2-year bioassay of sodium dichromate dihydrate (pH = 4.38)

Cr(VI) concentration	TWA dose (mg/kg-d) at 2 years	Cr(VI) dose escaping stomach reduction (mg/kg-d) at 2 years	TWA dose at 1 year (mg/kg-d)	Cr(VI) dose escaping stomach reduction at 1 year (mg/kg-d)	TWA dose at 90 days (mg/kg-d)	Cr(VI) dose escaping stomach reduction at 90 days (mg/kg-d)
Females						
5	0.248	0.0195	0.0294	N/A	N/A	N/A
20	0.961	0.0881	1.14	N/A	N/A	N/A
60	2.60	0.339	3.01	N/A	N/A	N/A
180	7.13	1.66	8.28	N/A	N/A	N/A
Males						
5	0.200	0.0156	0.237	0.0187	0.401	0.0325
20	0.796	0.0721	0.938	0.0875	1.58	0.165
60	2.10	0.264	2.49	0.336	4.16	0.699
180	6.07	1.40	7.19	1.79	11.7	3.66

TWA BW at 2 years: 450 g (males), 260 g (females). TWA BW at 1 year: 395 g (males), 215 g (females). TWA BW at 90 days: 246 g (males). No relevant dose-response 1-year data for female rats. Oral doses assumed the circadian rat drinking water profile (Spiteri, 1982).

Table C-21. Lifetime average daily internal doses for the rat during the NTP (2007f) 90-day bioassay of sodium dichromate dihydrate (pH = 4.38)

Cr(VI) concentration	TWA dose (mg/kg-d) at 90 days	Cr(VI) dose escaping stomach reduction (mg/kg-d) at 90 days
Females		
0	0	0
21.8	1.74	0.181
43.6	3.49	0.500
87.2	6.28	1.26
174.5	11.5	3.33
349	21.3	9.00
Males		
0	0	0
21.8	1.74	0.188

Cr(VI) concentration	TWA dose (mg/kg-d) at 90 days	Cr(VI) dose escaping stomach reduction (mg/kg-d) at 90 days
43.6	3.14	0.446
87.2	5.93	1.22
174.5	11.2	3.38
349	20.9	9.22

BW_A = 0.160 kg (females), 0.232 kg (males).

Table C-22. Comparison of internal-dose points of departure based on external-dose BMD modeling and internal-dose BMD modeling

Species/ Sex	Dataset	BMR	Internal[a] BMD mg/kg-d	Internal[a] BMDL mg/kg-d (linear model)[b]	Internal dose derived from external $BMDL_{1RD}$ (exponential 2 model)[b]	% diff.
Rat/M	Liver ALT (NTP, 2008)	1RD	0.214	0.166	0.168	1.2

[a]Dose escaping stomach reduction in rodent (mg/kg-d) estimated by pharmacokinetic modeling.
[b]Data were amenable to BMD modeling with the highest dose omitted. Note: the time weighted average daily doses used in this example were slightly (<5%) different than the final calculated values used elsewhere in this assessment. As a result, the value deviates slightly from the final internal dose POD presented elsewhere.

C.1.5.5. *General PBPK model considerations*

Model estimates are based on physiological parameters near the standard reference values in each species. Chromium ingestion can be associated with water intake (which increases volume of the stomach contents and potentially dilutes reducing agent) and food intake (which increases gastric juice production and volume and alters pH and gastric emptying).

Simulations in the human and the rodents assume RORAL (total gastric contents rate into stomach, L/h) is equal to KLSD (gastric emptying rate, h^{-1}) multiplied by VSL (gastric contents volume, L). The Kirman et al. (2017) model instead calculates gastric contents volume as a function of RORAL and KLSD. For rats and humans, the model produces reasonable values for stomach contents volume, but for mice, the stomach volume is outside the range measured by Mcconnell et al. (2008). Since the individual-level components of the RORAL parameter (gastric juice production, saliva production, and time-varying water and food ingestion) have higher uncertainty than stomach volume (which is a single, measurable parameter), this assessment defines a value for VSL rather than for RORAL.

Previously, in Kirman et al. (2012) and Sasso and Schlosser (2015), a mathematical discrepancy existed since the chromium concentration was determined by the volume of the stomach lumen, while the reducing agent concentration was determined by volume of stomach contents (which was a function of RORAL and gastric emptying). The volumetric basis for Cr(VI) and reducing agent concentrations should be the same because they coexist in the same reaction

volume. If RORAL, gastric contents volume, and gastric emptying are related by a mass balance equation, the volumetric basis for concentration calculation is the same for Cr(VI) and the reducing agent, and the discrepancy is resolved. Simulating gastric kinetics using physiology that is not harmonized (i.e., with the discrepancy between gastric lumen volume and steady-state gastric contents volume) leads to high internal doses in all species (i.e., >20–70% of the dose escaping reduction). This is because the mass balance of the gastric contents consistently produces a volume significantly lower than the stomach lumen volume. The rate of reduction is dependent on the chromium concentration, and the predicted chromium concentration may be overdiluted if chromium mass is divided by lumen volume instead of gastric contents volume.

If most of the Cr(VI) that escapes the stomach reduction is assumed to be absorbed into the system (which is reasonable given the high pH and surface area in the small intestine, and rapid uptake of Cr(VI)), the modeling results in this assessment agree with in vivo pharmacokinetic studies. Studies in rodents (Fébel et al., 2001; Thomann et al., 1994) have estimated that approximately 10% of an ingested Cr(VI) dose might ultimately be absorbed into the system as Cr(VI) when compared to Cr(III) (which is absorbed less readily). In humans, the Cr(VI) absorbed following oral ingestion has been estimated to be lower (Finley et al., 1997; Kerger et al., 1997; Kerger et al., 1996; Paustenbach et al., 1996). An in vitro Cr(VI) bioaccessibility study estimated a significant percentage of Cr(VI) may be bioaccessible in humans at pH>3, even at low doses, but bioaccessibility decreases sharply at lower values of pH (Wang et al., 2022).

C.1.6. Literature Overview of Studies Identified as ADME

Table C-23 presents a summary of studies that contain primary in vivo pharmacokinetic data in rats, mice, and humans following Cr(VI) exposure. These tables indicate whether studies contained concurrent data for Cr(III) exposure, as these data are informative in directly assessing differences between Cr(VI) and Cr(III) kinetics.

Table C-24 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. Tables C-23 and C-24 also indicate whether a study has been used quantitatively or qualitatively in the development of any previously published PBPK model.

Table C-25 presents a summary of studies related to the distribution and reduction of Cr(VI) in a variety of systems. These studies differ from those in Table C-24 in that the experiments primarily focused on mechanisms by modifying the enzymes or transport carriers in the systems tested. Tables C-23 to C-25 include only those studies pertaining primarily to Cr(VI) *pharmacokinetics* and do not include studies that primarily address Cr(VI) *toxicity*.

Table C-26 presents a summary of studies related to human biomonitoring of Cr(VI) in industrial or volunteer populations that focus primarily on data on biomarkers of exposure as opposed to human health effects. These differ from the human studies in Table C-23 in that the exposure profiles are not controlled or may be difficult to estimate.

All tables in this section are slightly modified from those released in September 2014 due to a rescreening of articles from the literature search, addition of new studies, and public comments.

Table C-23. In vivo Cr(VI) pharmacokinetic studies

Reference	Species	Tissue matrices and notes	Cr(III) control[a]
Intravenous (IV) injection			
Cavalleri et al. (1985)	Rat	Bile, whole blood, and plasma. 2-h time-course data.	N
Cikrt and Bencko (1979)	Rat	Total body burden, urine, feces, liver, kidneys, plasma, and GI tract wall. 24-h time-course data.	Y
Marouani et al. (2012)	Mouse	Fetus, placenta, liver, kidney, serum. Injection to pregnant mice at day 13 or 16 of gestation. Spot sample 1-h after injection.	Y
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-min time-course data.	N
Norseth et al. (1982)	Rat	Bile and liver. 2-h time-course data.	Y
Merritt et al. (1989)	Hamster	Urine, plasma, RBC, kidney, spleen, liver, and lung. Monthly or weekly injections. 5-wk postexposure time-course data.	N
Richelmi et al. (1984)	Rat	Blood. In vivo Cr VI measurement of reduction and capacity. Spot sample at 1-min postexposure.	N
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 h postexposure.	N
Balakin et al. (1981)	Rat	Liver, whole body (excluding liver), wall of cecum, chime of cecum, urine, and feces. Spot sample 30 min postexposure. This is a chelation study that included a Cr VI-only group.	Y
Bryson and Goodall (1983)	Mouse	Total body burden, urine, and feces. 21-d time-course data.	Y
Bulikowski et al. (1999)	Rat	Skin. Injections over 30 d. Micronutrient interaction study with Cr VI-only groups.	N
Devoy et al. (2019)	Rat	Plasma, RBC, and urine. Single IV injection. Multiple doses and time-course data (hourly, daily, to 90 d for some groups).	Y
Döker et al. (2010)	Mouse	Liver, kidney, brain, lung, heart, and testis. Effect on other essential metals analyzed. Spot sample at 12 h postexposure.	N
Manzo et al. (1983)	Rat	Bile, plasma, liver, urine, feces, stomach, small intestine, and large intestine. Detection in GI tissues postexposure. 2-h time-course data.	Y
Ogawa et al. (1976)	Mouse	Urine, feces, and whole body. Spot sample data at 48 h postexposure.	Y
Sankaramanivel et al. (2006)	Rat	Bone (vertebrae, femur, and calvaria). IP injections once per d for 5 d.	N
Suzuki (1988b)	Rat	Plasma, whole blood. 60-min time-course data.	N
Ueno et al. (1995)	Mouse	Liver. Total Cr and pentavalent (Cr V). 12-h time-course data.	N

Reference	Species	Tissue matrices and notes	Cr(III) control[a]
Minigaliyeva et al. (2014)	Rat	Liver, kidney, spleen, and brain. Injection 3 times per wk (less than 7 wk). Spot sample at end of study.	N
Yamamoto et al. (1981)	Mouse, rabbit	Urine, feces, blood, and liver. Single IP (50 or 200 µmol/kg), time-course data over undetermined length (at least 7 d).	N
Subcutaneous injection			
Mutti et al. (1979)	Rat	Urine, spleen, liver, renal cortex, renal medulla, lung, and bone. 48-h (single exposure) and 12-wk (repeated exposure) time-course data.	N
Pereira et al. (1999)	Mouse	Liver, kidney, and spleen. Multiple injections (once per wk for varying number of weeks). Spot sample at 1 wk after last exposure.	N
Yamaguchi et al. (1983)	Rat	Urine, feces, lung, liver, kidney, brain, heart, spleen, testis, muscle, hair, and blood. 30-d time-course data.	Y
Dermal			
Corbett et al. (1997)	Human	Urine, RBC, and plasma. 4-d time-course data.	
Oral			
Collins et al. (2010) (National Toxicology Program studies) NTP (2008) NTP (2007f)	Rat, mouse, Guinea pig	Urine, feces, erythrocytes, plasma, liver, kidney, glandular stomach, and forestomach (2-yr study). Multiple studies. Blood, kidney, and femur (21-d study in rats only). No mouse urinary data for chronic Cr III study. Chronic Cr III/Cr VI data at multiple sacrifice times (after 2-d washout period). Time-course (2-d) gavage data (urine/feces only) for Cr III only. Guinea pig data only at 21 d.	Y
Donaldson and Barreras (1966)	Human, rat	Urine, feces. Oral dose and perfusion to the small intestine (bypassing stomach reduction) to assess Cr VI reduction and absorption.	Y
Iranmanesh et al. (2013)	Rat	Liver, kidney, intestine, spleen, and testicle. Drinking water exposure for 60 d. Spot sample after 7-d washout period. This is a chelation study that included a Cr VI-only group.	N
Finley et al. (1997) Finley et al. (1996) Kerger et al. (1997) Kerger et al. (1996) Paustenbach et al. (1996)	Human	Human pharmacokinetic 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
Kirman et al. (2012)	Rat, mouse	Oral cavity, stomach, duodenum, jejunum, ileum, plasma, red blood cell, and liver. Spot sample at end of 90-d exposure period.	N
Saxena et al. (1990)	Rat, mouse	Oral (drinking water) study in pregnant rodents. Maternal blood, placenta, and fetus.	N

Reference	Species	Tissue matrices and notes	Cr(III) control[a]
Sutherland et al. (2000)	Rat	Bone, kidney, liver, and testes. Exposure for 44 wk, with spot samples 4–6 d postexposure (no time-course data).	N
Thomann et al. (1994)	Rat	Blood, liver, kidney, spleen, bone, and total carcass. 6-wk exposure followed by 140 d postexposure. Time-course data of pre- and postexposure periods.	N
Wang et al. (2015)	Rat	Heart, kidney, spleen, liver, lung, brain, stomach, testis, and duodenum. Spot sample at end of 4-wk exposure period (after overnight starvation).	N
Witmer et al. (1989)	Rat	Blood, kidney, spleen, liver, lung, brain, and testes. Spot sample at end of 7- and 14-d exposure periods (24 h after last treatment).	N
Yawets et al. (1984)	Rat	Liver. Single dose, spot sample.	N
Intratracheal			
Bragt and van Dura (1983)	Rat	Urine, feces, blood, heart, lungs, spleen, kidneys, liver, pancreas, testes, and bone marrow (femur). 50-d postexposure time-course data for whole-body retention and blood. 10-d time-course data for urine and feces. Spot sample data for other tissues at 50 d postexposure. 3 different Cr VI formulations.	N
Edel and Sabbioni (1985)	Rat	Lung, trachea, kidney, liver, spleen, pancreas, epididymis, 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 h postexposure. 7-d time-course data of excretion.	Y
Perrault et al. (1995)	Sheep	Bronchoalveolar lavages (BAL), lung. Exposure and analysis of particulate forms. 30-d time-course data for BAL; spot sample for lung at day 30.	Y
Gao et al. (1993)	Rat	Blood, plasma, urine, and lymphocytes. 72-h time-course data.	Y
Vanoirbeek et al. (2003)	Rat	Lung, liver, plasma, RBC, and urine. Spot tissue samples at 2 and 7 d postexposure. 7-d time-course data of urinary excretion.	Y
Wiegand et al. (1988) Wiegand et al. (1987) Wiegand et al. (1984a)	Rabbit	Blood, plasma, RBC, liver, kidneys, urine, lung, and trachea. 4-h postexposure time-course data.	Y
Song et al. (2014)	Rat	Blood, plasma, RBC, and lung. Once-per-wk exposure for 28 d. Spot sample after overnight fast.	
Inhalation			
Antonini et al. (2010)	Rat	Lung, heart, kidney, liver, spleen, and brain. Exposure to welding fume at 1, 4, 25, 105 d.	N
Cohen et al. (1997)	Rat	Lung (and lung fluids/subcompartments), liver, kidney, and spleen. Exposure for 5 h/d, 5 d/wk. Spot samples at 2 or 4 wk (24 h postexposure)	N

Reference	Species	Tissue matrices and notes	Cr(III) control[a]
Kalliomäki et al. (1983; 1982)	Rat	Blood, liver, kidneys, stomach, spleen, and lung. Welding arc fumes (with chromium concentration measurement). Exposures vary in h per d or number of days exposed. Spot samples at 24 h postexposure. 106-d time-course data for elimination study.	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 h. 7-d time-course data.	Y
Multiple routes			
Coogan et al. (1991b)	Rat	Red blood cells, and white blood cells. Oral and IV injection. Spot samples at 1 h, 24 h, and 7 d postexposure.	N
Fébel et al. (2001)	Rat	Oral and intrajejunal injection. Urine, feces, jejunum, liver, portae, hepatica, and cava caudalis. Spot sample data (at 60 min for intrajejunal injection, and 3 d for oral exposure).	Y
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 wk for chronic drinking water, 4 and 14 d for repeated IP injections. Spot 24/72 h data for single IP exposures.	N
MacKenzie et al. (1959)	Rat	Oral and injection into intestine. Stomach, intestine, blood, liver, kidney, spleen, urine, and feces. Spot samples 1, 7, and 14 d postexposure after single oral dose. Spot sample 4 h after intestinal injection and stomach tube experiments.	Y
Miyai (1980) Miyai et al. (1980)	Rat, mouse	Inhalation, intratracheal. Lung, plasma, RBC, spleen, kidney, duodenum, testes, urine, and feces. Long-term (30+ d) time-course data.	Y
O'Flaherty and Radike (1991)	Rat	Oral and inhalation. Lung, liver, intestine, kidney, muscle, blood, urine, and feces. Exposure for 40 d, with time-course data over 60 d.	Y
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-d time-course data of feces/urine and body retention. 5-d time-course data for tissues.	Y
Susa et al. (1988)	Mouse	Oral and IP injection. Liver, kidney, spleen, testes, urine and feces. Spot sample 24 h postexposure. 3-d time-course data for urine and feces. This is a chelation study that included Cr VI-only groups.	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 C-24. In vitro and ex vivo Cr(VI) studies primarily focused on pharmacokinetics in the GI tract and blood

Reference	Species	Test system	Notes
Gastric systems			
De Flora et al. (1987a)	Human	Gastric juice	Hourly gastric juice samples via nasogastric tube. Cr VI reduction capacity estimated for fed and fasted humans. Circadian effects also observed.
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).
De Flora et al. (2016)	Human	Gastric juice	Reduction and mutagenic activity of Cr VI analyzed at 60 min.
Donaldson and Barreras (1966)	Human, rat	Gastric juice; intestinal rings	Binding of Cr VI and Cr III by gastric juice (at low and high pH), and uptake by intestinal rings observed.
Gammelgaard et al. (1999)	Rat	Artificial gastric juice; small intestine	1st-order reduction rate half-life derived; permeability parameters through rat jejunum derived.
Kirman et al. (2013)	Human	Gastric juice (fasted)	2nd-order reduction kinetics for human gastric juice derived. pH-dependent model derived.
Kirman et al. (2016)	Human	Gastric juice (multiple types)	Revised 2nd-order reduction kinetics and pH model. Analysis of fed, fasted, and proton pump inhibitor (PPI) gastric samples.
Proctor et al. (2012)	Rat, mouse	Gastric juice and contents	2nd-order reduction kinetics derived. Reduction capacities estimated for both species.
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.
Skowronski et al. (2001)	N/A	Artificial gastric juice	Oral bioaccessibility study. Examined Cr VI reduction in a simulated soil matrix/gastric juice environment.
Wang et al. (2022)	Human	Artificial gastric juice and tissue	In vitro model of intestinal injury. Examined Cr VI reduction and injury as a function of dose and gastric pH.
Reduction or uptake in red blood cells			
Aaseth et al. (1982)	Human	RBC	Reduction rate of Cr VI in RBC, and trapping of reduced Cr III observed.
Afolaranmi et al. (2010)	Human	Plasma, RBC, whole blood	Distribution into different blood components (RBC and plasma) observed.
Alexander and Aaseth (1995)	Human, rat	Human RBC, rat liver cells	Cellular uptake and reduction analyzed. Effect of pH and anion carrier inhibitors observed.
Beyersmann et al. (1984)	Human	RBC	RBC permeability and reduction analyzed.
Branca et al. (1989)	Human	Human RBC	Reduction of Cr VI in RBC observed.

Reference	Species	Test system	Notes
Coogan et al. (1991b)	Human, rat	RBC, WBC, whole blood	Uptake kinetics, and distribution in cells examined.
Corbett et al. (1998)	Human	Plasma, blood	Reduction in plasma quantified in fed/fasted individuals.
Devoy et al. (2016)	Human	Plasma, RBC, whole blood	Uptake and retention by RBCs for different Cr VI and Cr III species.
Kortenkamp et al. (1987)	Human	RBC	Cellular uptake rates analyzed.
Richelmi et al. (1984)	Rat	RBC, plasma	Reduction of Cr VI in RBC and plasma observed.
Sakurai et al. (1999)	Rat	Blood	Reduction and fate in blood (focus on pentavalent, Cr V).
Wiegand et al. (1985)	Human, rat	RBC	Uptake into RBC analyzed.

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

Table C-25. In vitro studies primarily examining distribution and reduction mechanisms

	Human	Rat
Liver	Jannetto et al. (2001) Lewalter and Korallus (1989) Levina et al. (2007) Myers and Myers (1998) Pratt and Myers (1993)	Aiyar et al. (1992) Alexander et al. (1982) Alexander et al. (1986) Arillo et al. (1987) 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 (1991a) Ueno et al. (1990) Wiegand and Bolt (1985) Wiegand et al. (1986b)
Lung	Harris et al. (2005) Krawic et al. (2017) Luczak et al. (2016) Levina et al. (2007) Petrilli et al. (1986) Petruzzelli et al. (1989) Wong et al. (2012)	De Flora et al. (1985) Standeven and Wetterhahn (1992) Suzuki (1988a) Suzuki and Fukuda (1990)
RBC	Buttner and Beyersmann (1985) Buttner et al. (1988)	

	Human	Rat
	Ormos and Mányai (1974) Ormos and Mányai (1977) Ottenwälder et al. (1987) Ottenwaelder et al. (1988) Wiegand et al. (1984b) Wiegand and Ottenwaelder (1985) Wiegand et al. (1986a)	
Other		Arslan et al. (1987) (thymocytes) Berndt (1976) (kidney) Debetto et al. (1988) (thymocytes) Liu et al. (1997) (skin) Mertz et al. (1969) (embryo) Standeven and Wetterhahn (1991a) (kidney)
Miscellaneous systems		

Denniston and Uyeki (1987), Ortega et al. (2005), Sehlmeyer et al. (1990), Sognier et al. (1991): Chinese hamster ovary
Dillon et al. (2002): Chinese hamster lung
Kitagawa et al. (1982): Bovine RBCs.
Krepkiy et al. (2003): Rabbit liver metallothionein
Merritt et al. (1984): Rabbit blood
O'Brien et al. (1992): Glutathione and other thiols (not specific to a particular tissue or species).
Wei et al. (2016): HeLa cells and MCF-7 cells.
Wada et al. (1983): Dog liver.

Table C-26. Human biomonitoring and biomarker studies

Reference	Biomarker and industry/exposure notes
Bertram et al. (2014)	Urine/Welding (controlled experiment)
Black et al. (2015)	Urine/House dust (remediation study)
Caglieri et al. (2006) Goldoni et al. (2006) Goldoni et al. (2010)	Exhaled breath, plasma, RBCs, urine/Chrome plating
Cena et al. (2015)	Lung deposition (via deposition sampler)/Welding
Chang et al. (2006)	Whole blood/Residents living near electroplating factories
Coniglio et al. (1990)	Urine/Review
Gargas et al. (1994)	Urine/Human volunteer study of ingested chromite ore processing residue in soil
Goldoni et al. (2008)	Exhaled breath, pulmonary tissues/Lung cancer patients
Kalahasthi et al. (2006)	Plasma/Chrome plating (Cr(VI) and Cr(III) workers)
Lukanova et al. (1996)	Lymphocytes, RBCs, urine/Chrome plating
Mignini et al. (2009)	Urine blood/Leather working

Reference	Biomarker and industry/exposure notes
Mignini et al. (2004)	
Miksche and Lewalter (1995)	RBCs, plasma, urine, whole blood/Review of multiple studies and workshop proceedings containing some original data
Minoia and Cavalleri (1988)	Plasma, RBCs, urine/Dichromate-producing factory (multiple job categories)
Minoia et al. (1983)	Urine/Workers exposed to Cr(VI) and Cr(III)
Muttamara and Leong (2004)	Blood, urine/Chromium alloy factory
Nomiyama et al. (1980)	Urine/Population from geographic areas of known chromium pollution
Ohta and Inui (1992)	Lung tissue (autopsy)/Chromate factory
Pierre et al. (2008)	Urine/Chrome plating
Martin Remy et al. (2021)	Urine/Chrome plating
Santonen et al. (2022)	Urine, RBC, exhaled breath condensate, dermal samples/Multiple industries
Sjogren et al. (1983) Welinder et al. (1983)	Urine/Stainless steel welding
Verdonck et al. (2021) Viegas et al. (2022)	Urine, RBC, blood, exhaled breath condensate/Multiple industries
Verschoor et al. (1988)	Urine/Chrome plating
Zhao et al. (2020)	Urine/Residential exposure

Table C-27. Gastric emptying rates for rats, mice, and humans expressed as half-emptying time ($T_{1/2}$) and transit time (KLSD). Vehicle indicated in parentheses if known.

$T_{1/2}$ (minutes)	KLSD[a] (h^{-1})	Reference
Rat		
17	2.4	Kirman et al. (2012)
15 (fed)	2.77	GastroPlus defaults
7.5 (fasted)	5.55	
77 (liquid/semisolid)	0.54	Qualls-Creekmore et al. (2010)
118 (solids)	0.35	Enck and Wienbeck (1989)
1.1 fasted (liquid)	38	Takashima et al. (2013)
62 fed, 9 fasted[b] (liquid)	0.67, 4.6	Poulakos and Kent (1973)
119–138 (solid)	0.30–0.35	Schoonjans et al. (2002)
21–27 (semisolid)	1.5–2	Purdon and Bass (1973)
4.95 fasted (liquid)	8.4	Kataoka et al. (2012)
16.5 (liquid)	2.52	Scarpignato et al. (1984)
Mouse		
4.4	9.4	Kirman et al. (2012)
9.6 (fed)	4.33	GastroPlus defaults
2.4 (fasted)	17.3	
30.6	1.36	Inada et al. (2004)
16–17 fed (semisolid)	2.60	Roda et al. (2010)
2 fasted (semisolid)	20.8	
9–11 (liquids)	3.78–4.62	Symonds et al. (2002)
158 (solids)	0.26	
20 (nonnutrient liquid)	2.08	Symonds et al. (2008)
36 (nutrient liquid)	1.16	
91 (solids)	0.46	Choi et al. (2007)
30.6 (semisolid)	1.36	Osinski et al. (2002)
10 (nonnutrient liquid)	4.2	Miyasaka et al. (2004)
90 min (young mice); 58–67 min (old mice); pharmaceuticals	0.46 (young); 0.62–0.72 (old)	De Smet et al. (2006)
28 (solids, 19–38)	1.49 (1.09–2.19)	Bennink et al. (2003)
15 (liquids, 11–19)	2.77 (2.19–3.78)	
Human		
35	1.2	Kirman et al. (2013)
13 (liquid, fasted)	3.20	Mudie et al. (2014)
Fasted	2.63; 3.47; 0.55	

$T_{1/2}$ (minutes)	KLSD[a] (h^{-1})	Reference
15.8 (water); 12 (saline); 75 (glucose)		Mudie et al. (2010) (review article; see citation for further details of individual studies)
Fed 44 ± 15, 40 ± 13, 32 ± 7, 48 ± 9, 76 ± 6 (liquids); 105 ± 21 (solids)	0.55–1.30 (liquids); 0.40 (solids)	
30	1.39	ICRP (2006, 2002)
30 (fed)	1.39	GastroPlus defaults
7.5 (fasted)	5.55	

[a]KLSD = $\log_e(2)/T_{1/2} \times 60$.
[b]Poulakos and Kent (1973) values from gastric emptying equation (1-exp(-t/tau), tau = 13 minutes fasted, 89 minutes fed, derived assuming 90% emptying at 30 minutes for the fasted state, 74% emptying at 120 minutes for the fed state).

Time-weighted average daily doses differ from doses presented in the evidence tables of the April 2014 preliminary materials document (U.S. EPA, 2014b) because those values were based on the average of three lifestages (and not weekly/monthly time-course data). Round-off error occurred at the low doses due to lack of significant figures reported in NTP lifestage summary data. Time-weighted average daily doses for mice and rats are presented in Tables C-28 and C-29, respectively. Lifetime average daily internal doses for the rat during the NTP 2-year bioassay (at different data collection times) are presented in Table C-30.

Table C-28. Time-weighted average daily doses in mice for the NTP (2008) 2-year bioassay of sodium dichromate dihydrate. Doses in mg/kg-day Cr(VI).

Original average daily dose (mg/kg-d)	Time-weighted average daily dose (mg/kg-d)	Percent difference
Female mice		
0.38	0.302	20
1.4	1.18	15
3.1	3.24	4
8.7	8.89	2
Male mice		
0.38	0.450	18
0.91	0.914	0.4
2.4	2.40	<0.1
5.9	5.70	3

Table C-29. Time-weighted average daily doses in rats for the NTP (2008) 2-year bioassay of sodium dichromate dihydrate. Doses in mg/kg-day Cr(VI).

Original average daily dose (mg/kg-d)	Time-weighted average daily dose (mg/kg-d)	Percent difference
Female rats		
0.24	0.248	3
0.94	0.961	2
2.4	2.60	8
7	7.13	2
Male rats		
0.21	0.200	4
0.77	0.796	1
2.1	2.10	<0.1
5.9	6.07	3

Table C-30. Time-weighted average daily doses in rats for the NTP (2008) 2-year bioassay of sodium dichromate dihydrate at different time periods. Doses in mg/kg-day Cr(VI).

Cr(VI) concentration	TWA dose at 2 years (mg/kg-d)	TWA dose at 1 year (mg/kg-d)	TWA dose at 90 days (mg/kg-d)
Females			
5	0.248	0.0294	--
20	0.961	1.14	--
60	2.60	3.01	--
180	7.13	8.28	--
Males			
5	0.200	0.237	0.401
20	0.796	0.938	1.58
60	2.10	2.49	4.16
180	6.07	7.19	11.7

TWA BW at 2 years: 450 g (males) and 260 g (females). TWA BW at 1 year: 395 g (males) and 215 g (females). No dose-response data for female rats at 1 year for this assessment.

C.2. SUPPORTING EVIDENCE FOR SPECIFIC HEALTH EFFECTS

C.2.1. Respiratory Effects

C.2.1.1. *Mechanistic studies relevant to noncancer respiratory toxicity*

Mechanistic evidence investigating the biological pathways involved in respiratory toxicity following the inhalation of Cr(VI) is summarized in Table C-31. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "inhalation" if they were studies of humans or animals exposed via inhalation or intratracheal instillation and conducted in lung tissues or cells or in cells derived from lung tissues. Studies of systemic toxicity following inhalation exposures are summarized in Appendix C.3.2. A total of 255 potentially relevant respiratory mechanistic studies were identified. A prioritization strategy was used to identify the evidence most informative to chronic human exposures:

- Studies of respiratory organs and tissues from humans with quantified inhalation exposure to Cr(VI)
- Experimental animal (mammalian) studies of respiratory organs and tissues exposed to Cr(VI) via inhalation or intratracheal instillation
- In vitro studies in human primary or immortalized cells derived from respiratory tissues
- Any outcome measured in lung tissues except for those relevant to genotoxicity (see Appendix C.3.2.2)

Forty-one studies meeting these prioritization criteria were identified; these studies focused primarily on oxidative stress, apoptosis, and cellular toxicity of the lung. Mechanistic evidence relevant to Cr(VI)-induced genotoxicity is reviewed in Appendix C.3.2.2.

Table C-31. Mechanistic studies prioritized for informing potential Cr(VI)-induced respiratory toxicity

System	Exposure[a]	Results	Comments	Reference
Oxidative stress				
Exposed: lead chromate pigment factory workers (n = 22) *Referents:* office workers from chromate factory (n = 16)	Mean (SD) duration of work among chromate pigment workers = 9.7 (20.5)* yr. Chromium measured in urine, blood, and air; air sampling for 200 min at flow rate 2–3 L/min; urine and blood measured with flameless atomic absorption spectrophotometer. Chromium in air ranged from below LOD (0.0005 mg/m^3 among office workers to 0.5150 mg/m^3 in high-exposure area of factory (pulverizing process); mean (SD) chromium among exposed group in blood: 6.75 (3.30) µg/L; in urine: 12.97 (16.31) (µg/g creatinine).	In blood and sputum: No difference in 8-OHdG adducts (in respiratory epithelial and white blood cells) between exposed and control groups, or with duration of employment among exposed groups	Chromium levels in blood (which are a marker of recent exposure) were similar between exposed and control groups; this suggests that exposure misclassification might be contributing to the null effects reported in the study The authors also suggest urinary chromium reflects chromium in reduced form, which might not reflect genotoxicity in blood cells No adjustment for supplements/vitamins or diet *SD appears incorrect	Kim et al. (1999)
Rat, Sprague-Dawley	0.25 mg/kg $Na_2Cr_2O_7$ (0.09 mg Cr(VI)/kg) per day via intratracheal instillation, 3 d.	↑ 8-OHdG adducts ([32P] postlabeling) were detected in lung, but not liver ↑ DNA-protein crosslinks ↑ DNA fragmentation	No measure of cytotoxicity	Izzotti et al. (1998)
Rat, Sprague-Dawley, male	0.18 or 0.9 mg/m^3 Na_2CrO_4 solution mist inhalation, whole-body exposures in 1 m^3 volumetric inhalation chambers for 1, 2, or 3 wk	↑ 8-OHdG in lung only at 1 wk (only stat. sig. for 0.18 mg/m^3) ↓ 8-OHdG repair 1–3 wk	Cr levels confirmed in inhalation chambers with personal air samplers and measured in whole blood and urine Indicates Cr(VI) exposure both increases oxidative DNA damage and inhibits repair of these lesions	Maeng et al. (2003)

System	Exposure[a]	Results	Comments	Reference
	Cr levels in blood and urine increased with dose and duration.			
Rat, Sprague-Dawley, male	0.063 or 0.630 mg Cr/kg (as $K_2Cr_2O_7$) via intratracheal instillation, 1×/wk, 4 wk	↑ 8-OHdG ↑ NF-κB; ↓ CC16 in club cells	Weekly instillations allow recovery period, which could underestimate the responses, but significant effects were still reported. Also ↑ relative lung weight, ↑ albumin and total protein level in BALF	Zhao et al. (2014)
Apoptosis				
Exposed: Chromium workers diagnosed with lung cancer (n = 67 males) *Referent*: male controls with lung cancer but without known exposure to chromium (n = 104)	Mean exposure time 16.7 ± 10.0 (SD) yr (range 1–41 yr). Total and hexavalent Cr measured in soil and air samples taken "in the vicinity of the workplace" using atomic absorption spectrometry. Mean values of Cr(VI) in air of smelting plants was 0.019–0.03 mg/m^3. Soil chromium was 137 mg/kg.	In lung cancer tissues (preserved in paraffin blocks): ↓ survivin protein levels (anti-apoptotic) ↑ p53 protein levels (pro-apoptotic)	The information regarding potential exposure is sparse. Observed differences in the type of lung cancer between exposed and referent could impact results. No information on smoking, which may be important to consider given all participants had lung cancer.	Halasova et al. (2010)
Rat, Sprague-Dawley, male	0.25 mg/kg $Na_2Cr_2O_7$ per day via intratracheal instillation, 3 d.	↑ apoptosis in bronchial epithelium and lung parenchyma ↑ 13/18 apoptosis-related genes (cDNA array analysis) in lung	Exposures to Cr(VI) alone. TUNEL analysis, used to measure apoptosis, is a sensitive method of detection. State another lab saw no lung cancer after similar treatment for 30 mo, so predict apoptosis is protective post-genotoxicity	D'Agostini et al. (2002)
Lung cellular responses				
Exposed: Electroplaters (n = 42 females) *Referent:* Jail wardens, frequency matched on age, BMI, alcohol, and smoking (n = 43 females)	Cr(VI) in plasma measured using atomic absorption spectrophotometry. Total Cr was not different between exposed and referent	↑ cytotoxicity in exfoliated buccal and nasal mucosa	Workers performed bright plating that has lower potential for Cr(VI) exposure, and state that there was good compliance with PPE usage. This might account for the low plasma Cr(VI) levels and similarity between exposed and referent. Co-exposure to cobalt occurred, although levels	Wultsch et al. (2017)

System	Exposure[a]	Results	Comments	Reference
	(means of 0.44 and 0.41 µg/L, respectively).		were not different between exposed and referent. High prevalence of smoking (frequency matched between exposed and referent), which could affect results.	
Rat, F-344, male	360 µg/m^3 K_2CrO_4 via inhalation, 5 h/d, 5 d/wk, 2 or 4 wk.	↑ total recoverable cells, neutrophils (PMN), and monocytes at 2 and 4 wk in BALF; decline at 4 wk compared to 2 wk ↓ % PAM in BALF; no change in total PAM levels No changes in cell viability (80–90%) among exposure groups	Moderately informative: shorter exposure period but results generally support similar findings from chronic duration studies from same group. Ex vivo PAMs (exposed in vivo to K_2CrO_4): • Spontaneous: ↑ H_2O_2, no changes in superoxide anion • LPS-inducible: ↑ NO, ↓ IL-1 and TNFα, ↑ IL-6	Cohen et al. (1998)
Rat, Long-Evans hooded, male	2 µg $CaCrO_4$ (insoluble) or 2 µg CrO_3 (soluble) via intratracheal instillation, 9 h.	In vivo exposure: no effect on cell viability In vitro exposure: ↓ viability	Less informative: short exposure period; trypan blue dye exclusion is a less sensitive measure to determine cell viability	Galvin and Oberg (1984)
Rat, Sprague-Dawley, male and female	0.01, 0.05, 0.25 mg/kg $Na_2Cr_2O_7$-$2H_2O$, 5×/wk, or 0.05, 0.25, 1.25 mg/kg, 1×/wk via intratracheal instillation, 30 wk.	Tumors that appeared to arise from tissues with cellular inflammatory foci involving alveolar macrophages, proliferation of bronchiolar epithelium or alveolar type II cells, and chronic inflammatory thickening of alveolar septa. The other main type of nontumor lesion was severe damage to the bronchioloalveolar region with alveolar		Steinhoff et al. (1986)

System	Exposure[a]	Results	Comments	Reference
		atelectasis and subsequent confluent fibrosis.		
Rat, Sprague-Dawley, male	0, 0.063 and 0.630 mg Cr/kg (as $K_2Cr_2O_7$) via intratracheal instillation, 1×/, 4 wk	↑ relative lung weight ↑ albumin and total protein level in BALF ↑ NF-κB; ↓ CC16 in club cells	More informative: weekly instillations allow recovery period, which could underestimate the responses, but significant effects were still reported. Also ↑ 8-OHdG	Zhao et al. (2014)
In vitro studies of oxidative stress, cellular toxicity, and death in primary and immortalized human lung cells				
HLF fetal human lung fibroblasts L-41 human epithelial-like cells	1, 2, 5, 10, 15, 20, 25, and 30 µM $K_2Cr_2O_7$, 2, 24 or 48 h	↑ cytotoxicity (MTT assay), dose- and duration dependent (significant ≥20 µM); cytotoxicity recovered ≤5 µM after 24 h ↑ ROS (DCFH-DA) at 2 h ↑ antioxidant enzymes (glutathione peroxidase, glutathione reductase, catalase) 1–5 µM	Oxidative stress and antioxidant enzymes induced at mildly toxic µM concentrations	Asatiani et al. (2011; 2010)
H460 human lung epithelial cells	10–50 µM $Na_2Cr_2O_7$, 12 h	↑ ROS ↑ apoptosis; abrogated by antioxidants MnTBAP, catalase, DPI, or ROT, in cells transfected with antioxidant enzymes SOD or GPx, or by specific caspase inhibitors ↓ Bcl-2; abrogated by MnTBAP	Cr(VI) induces apoptosis by downregulating Bcl-2 via superoxide anion-mediated ubiquitin-proteasomal degradation and mitochondrial caspase-9 activation	Azad et al. (2008)
Human lung epithelial cells		↑ Src family kinases (SFK) → ↑ JNK	SFK activation was not completely reliant on ROS signaling	Barchowsky (2006)

System	Exposure[a]	Results	Comments	Reference
BEAS-2B human bronchial epithelial cells	0.3 (nontoxic) or 1.8 (toxic) µM Cr(VI), 48 h	Cytotoxic signaling pathways: glycolysis regulation (GSK3beta, p70S6K), oxidative stress and inflammation (JNK, MTF-1), and protein degradation (UBC)		Bruno et al. (2016)
A549 human lung adenocarcinoma cells BEAS-2B human bronchial epithelial cells	0.5, 1, and 2 µM Cr(VI) (compound not reported), 3, 8, or 24 h	In BEAS-2B: ↑ cytotoxicity (≥1 µM; MTT) ↓ glutathione (3 h only) ↑ lipid peroxidation (TBARS) ↑ heme oxygenase-1 (HO-1) A549: ↑ lipid peroxidation (TBARS)	BEAS-2B cell line more sensitive to Cr(VI) effects than A549 cell line; polymorphisms for GST genes might be responsible for differing cellular responses to Cr(VI)	Caglieri et al. (2008)
HLF human lung fibroblasts (LL-24 cell line)	3, 6, and 9 µM Na_2CrO_4, 24 h	↑ cytotoxicity, duration and dose dependent (stat. sig. ≥6 µM) ↑ apoptosis ↑ p53 (4–6 fold)	Pretreatment with 1 mM ascorbate or 20 µM tocopherol had no ameliorative effects Also ↑ Cr-DNA adducts	Carlisle et al. (2000a)
A549 (human lung adenocarcinoma) and BEAS2B human bronchial epithelial cells	0.1, 0.5, 1.0 and 10 µM Na_2CrO_4, 0.5, 1, and 4 h	↑ apoptosis at 10 µM (caspase-3 activity and morphology)	Oxidative role in DNA damage decreased with time at lower Cr(VI) concentrations and increased with time at higher concentrations A549 more sensitive than BEAS2B Also ↑ oxidative DNA damage (Fpg-modified comet assay)	Cavallo et al. (2010)
BEAS-2B human bronchial epithelial cells	1 µM Cr(VI), 48 h	↑ glycolysis ↓ respiration	Cr(VI) caused shift to fermentative metabolism	Cerveira et al. (2014)

System	Exposure[a]	Results	Comments	Reference
		↓ protein levels of β-F1-ATPase ↑ GAPDH		
Human non-small cell lung carcinoma CL3 cells	10–80 µM $K_2Cr_2O_7$, 1–12 h	↑ JNK ↑ MAPK11-14 (P38) ↑ MAPK3, MAPK1 (ERK1/2)	Activation increased with dose and duration Use of multiple oxidants and antioxidants shows activation of these redox-initiated pathways do not clearly correlate with Cr(VI)-induced cytotoxicity	Chuang et al. (2000)
BEAS-2B human bronchial epithelial cells transformed by chronic Cr(VI) exposure	$Na_2Cr_2O_7$	In Cr(VI)-transformed cells: ↑ metabolic adaptation and antioxidant defense, ATP production and mitochondrial proton leak via SIRT3 ↑ mitophagy proteins Pink1 and PRKN (Parkin), though mitophagy was suppressed	SIRT3 upregulation by Cr(VI) suppresses mitophagy; knockdown of SIRT3 suppressed cell proliferation NRF2 constitutively activated in Cr(VI)-transformed cells	Clementino et al. (2019)
BEAS-2B human bronchial epithelial cells	5–20 µM $Na_2Cr_2O_7$	↑ NOTCH1 (Notch1) ↑ CDKN1A (P21) ↓ FBP1	FBP1, involved in gluconeogenesis, is lost in Cr(VI)-transformed cells Reintroduction of FBP1 caused ↑ROS and ↑apoptosis	Dai et al. (2017a)
LL 24 human lung cells and A549 human lung adenocarcinoma cells	5−200 µM Cr(VI)	↑ heme oxygenase gene (only in LL 24 cells) No effect on catalase, GST, glutathione reductase, Cu/Zn- and Mn-SODs, GPx, NAD(P)H:quinone oxidoreductase, or IL-8 gene expression	RT-PCR and northern blot gene (RNA) expression analyses Authors conclude heme oxygenase is responsible for Cr(VI)-induced stress responses and not intracellular increases in glutathione and ROS	Dubrovskaya and Wetterhahn (1998)

System	Exposure[a]	Results	Comments	Reference
BEAS-2B human bronchial epithelial cells MOLT-4 lymphoblastic leukemia cell line	0.5, 3, 6, 9, and 200 µM $K_2Cr_2O_7$, 4, 12, or 24 h	↑ apoptosis (PI; TUNEL flow), dose and time dependent ↑ p53 at 0.5 µM (12 h) and 3 µM (4 h) in MOLT-4 but not BEAS-2B cells Inhibition of caspase-3, -8 and -9 did not reduce apoptosis	Cr(VI) induces apoptosis that could involve p53 in MOLT-4 cells but not in BEAS-2B; apoptosis did not involve caspases 3, 8, or 9 in these cells	Gambelunghe et al. (2006)
A549 human lung adenocarcinoma cells	0.2 µM $K_2Cr_2O_7$, 6, 12, or 24 h	↑ endoplasmic reticulum (ER) stress via ↑ GRP78 and p-PERK is associated with ↑ apoptosis and autophagy ↓ mitochondrial membrane potential (MMP) at 6−12 h but not 24 h	Inhibiting ER stress (4PBA) reduced apoptosis and autophagy Suppressing apoptosis (Z-VAD-FMK) also suppressed autophagy Inhibiting autophagy (3-MA) increased apoptosis Authors surmise Cr(VI)-induced autophagy rescues ↓ MMP at 24 h via phagocytosing damaged mitochondria and then inhibiting apoptosis	Ge et al. (2019)
A549 human lung adenocarcinoma cells	10−500 µM $Na_2Cr_2O_7$, 1 or 16 h	↑ 8-OHdG ↓ OGG1 mRNA, dose dependent (RT-PCR and RNase protection assay); not affected by adding H_2O_2 No effect on hAPE or GAPDH	Authors conclude Cr(VI)-induced oxidative DNA damage could be due partly to a reduced capacity to repair endogenous and Cr(VI)-induced 8-OHdG lesions Also ↑ DNA strand breaks, dose dependent (comet assay) that were 10× higher with FAPY	Hodges et al. (2002; 2001)
A549 human lung adenocarcinoma cells	12.5−800 µM Cr(VI)	↑ ROS and NF-κB, dose dependent Effects abrogated by catalase, SOD, or D-mannitol No change in 8-OHdG levels or hogg1 expression	Possible that ≤800 µM doses of Cr(VI) are sufficient to induce ROS and NF-κB but too low to induce oxidative DNA lesions	Kim et al. (2003)

System	Exposure[a]	Results	Comments	Reference
A549 human lung adenocarcinoma cells	5–80 µM $Na_2Cr_2O_7$, 2 h	↑ cytotoxicity >5 µM, dose dependent Cr(VI) + 1 mM ascorbate ↑ ROS Cr(VI) + glutathione ↓ ROS	Ascorbate (max intracellular 80 µM) might promote Cr(VI)-induced oxidative stress by reducing intracellular Cr(VI) and stabilizing Cr(VI) and Cr(IV)	Martin et al. (2006)
Primary human bronchial epithelial cells BEAS-2B human bronchial epithelial cells	25 and 50 µM Na_2CrO_4, 3 or 6 h	Irreversible inhibition of thioredoxin reductase (TrxR) Oxidation of protein thiols thioredoxins (Trx) and peroxiredoxins (Prx); scavenging peroxynitrite (MnTBAP) or adding ascorbate did not abrogate these effects Inhibition of aconitase, electron transport complexes I and II	Cr(VI) oxidizes and inhibits mitochondrial and cellular thioredoxins and peroxiredoxins involved in cell survival and redox signaling, leading to increased sensitivity to ROS damage and decreased survival	Myers et al. (2011; 2010; 2009; 2008)
A549 human lung adenocarcinoma cells	10 µM Cr(VI)	↑ ROS and JNK activation at subcytotoxic levels ↑ Src family kinases (Fyn, Lck) at levels that did not induce ROS		O'Hara et al. (2003)
BEAS-2B human bronchial epithelial cells SAECs (human small airway epithelial cells)	0.2, 2.0, 20, and 200 µM $K_2Cr_2O_7$, 1, 2, 6, or 48 h	↑ cytotoxicity (MTT assay) at 0.2 µM (20%) in BEAS-2B, 20 µM in SAEC, dose dependent In SAECs: ↑ cellular phosphoprotein ↑ IL-6, IL-8 (precytotoxic, at 0.2 and 2.0 µM, respectively)	Cytotoxicity associated with inflammation and immune response via protein phosphorylation and cytokine signaling	Pascal and Tessier (2004)

System	Exposure[a]	Results	Comments	Reference
		Null for TNF-α		
A549 human lung adenocarcinoma cells	0.13, 0.67, 3.38, 16.9, and 84.57 μM CrO_3 or $K_2Cr_2O_7$	↑ cytotoxicity ≥3.38 μM (colony formation assay), dose dependent	Cytotoxicity induced at μM concentrations	Popper et al. (1993)
Primary human lung IMR90 fibroblasts H460 human lung epithelial cells	0.2–8 μM K_2CrO_4, 3 h	↑ DNA DSB with ascorbate caused by aberrant mismatch repair ↑ cytotoxicity and apoptosis with ascorbate; effects reversed by suppressing DNA mismatch repair but p53 status had no effect ↑↑ cytotoxicity and cell cycle delay in cells deficient in oxidative DNA damage repair (XRCC1 knockdown); effects reversed by ascorbate	By restoring intracellular ascorbate to physiological levels via DHA (max intracellular 0.9 mM), it was shown ascorbate can suppress Cr(VI)-induced oxidative damage but promotes Cr-DNA lesions that are either repaired by mismatch repair, independently of p53, or lead to cytotoxicity and apoptosis Chromosomal aberrations not affected by XRCC1 status	Reynolds et al. (2012; 2007; 2007)
A549 human lung adenocarcinoma cells	1–20 μM $Na_2Cr_2O_7$, 4 or 12 h	↑ cytotoxicity with dose (stat. sig. at 20 μM) at 4 h ↓ specific activity and level of urokinase-type plasminogen activator (uPA) activity ↑ uPA receptor protein	Cr(VI) inhalation leads to a net loss of urokinase-type plasminogen activator activity that has been shown to promote pulmonary fibrosis	Shumilla and Barchowsky (1999)
A549 human lung adenocarcinoma cells	0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 μM $K_2Cr_2O_7$, 24 h	↑ cell proliferation ≤0.2 μM (A549 cells) ↑ cytotoxicity ≥3.2 μM	Cr(VI)-induced autophagy is correlated with transcription factor HMGA2 expressed in lung cancer patients	Yang et al. (2017)

System	Exposure[a]	Results	Comments	Reference
		↑ autophagosomes; this effect was blocked by silencing HMGA2 ↑ expression of LC3II, Atg12-Atg5, Atg4, Atg10, HMGA1 and HMGA2 proteins ↓ expression of p62		

BALF: bronchoalveolar lavage fluid.

ICP-AES: inductively coupled argon plasma atomic emission spectroscopy.

MMA-SS: manual metal arc-stainless steel.

PAM: pulmonary alveolar macrophages.

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.2. Gastrointestinal Effects

C.2.2.1. *Apical outcomes relevant to toxicity of the gastrointestinal tract*

The results relevant to GI tract toxicity from the four *high* confidence animal studies synthesized in Section 3.2.2.2 of the toxicological review (Thompson et al., 2012c; Thompson et al., 2011b; NTP, 2008, 2007f) are summarized in Table C-32. In addition to these four studies are other reports that continued to evaluate the same tissues from these studies, and a fifth study (Thompson et al., 2015b) that was evaluated only for genotoxicity endpoints but also reported evidence of hyperplasia and Cr accumulation in GI tissues following drinking water exposures.

Table C-32. Experimental animal studies providing apical evidence of toxic effects of ingested Cr(VI) in the GI tract

System	Exposure[a]	Results	Reference
Mouse (B6C3F1), male and female	0, 22, 44, 87, 174, 349 mg/L Cr(VI) 0, 3.1, 5.3, 9.1, 15.7, 27.9 mg/kg-d Cr(VI) 90 d	Diffuse epithelial hyperplasia of the duodenum (≥3.1 mg Cr(VI)/kg-d) Duodenal villi short, thick, and blunted, with cytoplasmic vacuolization in the epithelial cells lining the villi tips (all doses, not quantitatively measured)	NTP (2007f)
Mouse, BALB/c, C57BL/6, and B6C3F1, male (strain comparison study)	0, 22, 44, 87 mg/L Cr(VI) 0, 2.8, 5.2, 8.7 mg/kg-d Cr(VI) 90 d	Diffuse epithelial hyperplasia of the duodenum (≥2.8 mg Cr(VI)/kg-d)	
Rat, F344/N, male and female	0, 22, 44, 87, 174, 349 mg/L Cr(VI) 0, 1.7, 3.5, 5.9, 11.2, 20.9 mg/kg-d Cr(VI) 90 d	Epithelial hyperplasia, squamous metaplasia, and ulcers in the glandular stomach (20.9 mg/kg-d)	
Rat (F344/N), male	0, 5, 20, 60, or 180 mg/L Cr(VI) 0.200, 0.760, 2.10, 6.07 mg/kg-d Cr(VI) 2 yr	No observed GI hyperplasia/metaplasia or stomach ulcers No salivary gland atrophy	NTP (2008)
Rat (F344/N), female	0, 5, 20, 60, or 180 mg/L Cr(VI) 0.248, 0.961, 2.60, 7.13 mg/kg-d Cr(VI) 2 yr	No observed GI hyperplasia/metaplasia or stomach ulcers Mild salivary gland atrophy at highest dose (≥7.13 mg Cr(VI)/kg-d)	

System	Exposure[a]	Results	Reference
Mouse (B6C3F1), male	0, 5, 10, 30, or 90 mg/L Cr(VI) 0.450, 0.914, 2.40, or 5.70 mg/kg-d Cr(VI) 2 yr	Diffuse epithelial hyperplasia of the duodenum (≥0.45 mg Cr(VI)/kg-d) Focal epithelial hyperplasia ≥2.40 mg/kg-d, not statistically significant Short, broad, and blunt duodenal villi (no overt damage, necrosis, or degeneration indicative of atrophy)	
Mouse, (B6C3F1), female	0, 5, 20, 60, or 180 mg/L Cr(VI) 0.302, 1.18, 3.24, or 8.89 mg/kg-d Cr(VI) 2 yr	Diffuse epithelial hyperplasia of the duodenum (≥0.3 mg Cr(VI)/kg-d) and jejunum (8.89 mg/kg-d) Focal epithelial hyperplasia ≥3.24 mg/kg-d, not statistically significant Short, broad, and blunt duodenal villi (no overt damage, necrosis, or degeneration indicative of atrophy)	
Mouse, B6C3F1 female Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) 7 d (n = 5) or 90 d (n = 10)	7-d: Duodenal hyperplasia (no statistically significant change), villous atrophy (no statistically significant change), and cytoplasmic vacuolization (statistically significant at 31.1 mg/kg), with no change in crypt apoptosis indices, mitotic activity, or increases in karyorrhectic nuclei in crypts 90-d: Diffuse epithelial hyperplasia of the small intestine (≥11.6 mg Cr(VI)/kg-d) Villous atrophy in duodenum and jejunum (31.1 mg/kg-d) Apoptosis in duodenal villi (31.1 mg/kg-d) Cytoplasmic vacuolization in duodenum and jejunum (≥4.6 mg Cr(VI)/kg-d	Thompson et al. (2011b)
Rat, Fischer 344/N female Oral, drinking water	0, 0.1, 1.4, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.015, 0.21, 2.9, 7.2, 20.5 mg/kg-d Cr(VI) 7 d (n = 5) or 90 d (n = 10)	Diffuse epithelial hyperplasia of the small intestine (≥7.2 mg Cr(VI)/kg-d), villous cytotoxicity (≥7.2 mg Cr(VI)/kg-d) Apoptosis in duodenal villi (≥7.2 mg Cr(VI)/kg-d) (no atrophy or vacuolization) 7 d: No statistically significant changes in GSH/GSSG in oral mucosa or small intestine except in jejunum at 20.5 mg/kg-d and at 0.015 mg/kg-d in the oral mucosa. Note: sample size is 5 for 7-d data. 90 d: ↓ GSH/GSSG in oral mucosa and jejunum (≥2.9 mg/kg-d) and in plasma (≥7.2 mg/kg-d), dose-dependent, statistically significant. No changes in duodenum, or signs of lipid peroxidation (8-isoprostane) in any tissues.	Thompson et al. (2012c)

System	Exposure[a]	Results	Reference
Mouse, B6C3F1 Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) 7 and 90 d	In scraped duodenal epithelium: ↑ crypt enterocyte proliferation, dose dependent ↑ villus cytotoxicity (disruption of cellular arrangement, desquamation, nuclear atypia, blunting) ↑ crypt enterocyte proliferation, dose dependent No effect on mitotic/apoptotic indices in crypt compartment 7 d: ↑ aberrant nuclei at villi tips but not in crypts (≥11.6 mg/kg-d) 90 d: ↑ aberrant nuclei at villi tips but not in crypts (≥4.6 mg/kg-d)	O'Brien et al. (2013) Continued analysis of tissues from Thompson et al. (2011b)
Mouse (B6C3F1) and rat (F344), female Oral, drinking water	0 and 180 mg/L Cr(VI) 0 and 31.1 mg/kg-d Cr(VI) 90 d	In duodenal villi and crypts: X-ray fluorescence (spectro)microscopy (μ-XRF) was used to image the Cr content in the villus and crypt regions of duodena. Cr(VI) was detected in crypts, slightly above detection limits, and was >30× higher in villi. Villous blunting and crypt hyperplasia in the duodenum (lengthening of the crypt compartment by ~2-fold) 1.5-fold increase in the number of crypt enterocytes No aberrant foci indicative of transformation	Thompson et al. (2015a) Continued analysis of tissues from Thompson et al. (2011b)
Mouse, B6C3F1 Oral, drinking water	0, 1.4, 21, and 180 mg/L Cr(VI) 0, 0.32, 4.6, and 31.1 mg/kg-d Cr(VI) 7 d	21 and 180 mg/L Cr(VI) significantly increased the number of crypt enterocytes Synchrotron-based X-ray fluorescence (XRF) microscopy revealed the presence of strong Cr fluorescence in duodenal villi, but negligible Cr fluorescence in the crypt compartment No effect on aberrant villous foci, and X-ray fluorescence detection of Cr(VI)	Thompson et al. (2015b)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.2.2. *Mechanistic endpoints relevant to toxicity of the gastrointestinal tract*

Studies examining mechanistic endpoints relevant to interpretations of toxic effects in the GI tract are summarized in Table C-33. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "GI" if conducted in GI tissues or cells. Only studies conducted in vivo in animals or in vitro in human cells from the GI tract are prioritized for consideration here:

- Studies of gastrointestinal organs and tissues from humans with quantified exposure to Cr(VI)

- Experimental animal studies of gastrointestinal tissues (except liver; these studies are summarized in Appendix C.2.3) using quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation exposures

- In vitro studies in human primary or immortalized cells derived from gastrointestinal tissues

- Mechanistic endpoints relevant to interpretations of gastrointestinal toxicity in humans except for genotoxicity studies (see Appendix C.3.2.2) (apical outcomes synthesized for noncancer hazard identification have been summarized above in Appendix C.2.2.1)

Ten studies in experimental animals and four studies in GI-derived cells in vitro were identified. No human exposure studies of toxicity of the GI tract were identified (studies in exposed workers reporting genotoxic endpoints in buccal cells are summarized in Appendix C.3.2.2).

Table C-33. Supporting mechanistic studies prioritized for informing Cr(VI)-induced GI tract toxicity

System	Exposure[a]	Results	Reference
Mouse, B6C3F1 female Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) 7 d (n = 5) or 90 d (n = 10)	7 d: No change in crypt apoptosis indices, mitotic activity, or increases in karyorrhectic nuclei in crypts ↓ GSH/GSSG in oral (≥11.6 mg/kg-d) and duodenal (≥4.6 mg/kg-d) epithelium; no change in plasma. Note: sample size is only 5 for the 7-d group, and some observed changes occurred at slightly lower doses but were not statistically significant. 90-d: ↓ GSH/GSSG in duodenum and jejunum (≥1.1 mg/kg-d) and in plasma (≥11.6 mg/kg-d) No statistically significant increases in protein carbonyls or 8-OHdG levels in any tissues Some altered cytokines and chemokines	Thompson et al. (2011b)
Rat, Fischer 344/N female Oral, drinking water	0, 0.1, 1.4, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.015, 0.21, 2.9, 7.2, 20.5 mg/kg-d Cr(VI) 7 d (n = 5) or 90 d (n = 10)	7 d: No statistically significant changes in GSH/GSSG in oral mucosa or small intestine except in jejunum at 20.5 mg/kg-d and at 0.015 mg/kg-d in the oral mucosa. Note: sample size is 5 for 7-d data. 90 d: ↓ GSH/GSSG in oral mucosa and jejunum (≥2.9 mg/kg-d) and in plasma (≥7.2 mg/kg-d), dose dependent, statistically significant. No changes in duodenum, or signs of lipid peroxidation (8-isoprostane) in any tissues.	Thompson et al. (2012c)
Mouse, B6C3F1 Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) 7 and 90 d	In scraped duodenal epithelium: No effect on mitotic/apoptotic indices in crypt compartment 7 d: ↑ aberrant nuclei at villi tips but not in crypts (≥11.6 mg/kg-d) 90 d: ↑ aberrant nuclei at villi tips but not in crypts (≥4.6 mg/kg-d)	O'Brien et al. (2013) Continued analysis of tissues from Thompson et al. (2011b)

System	Exposure[a]	Results	Reference
F344 rats and B6C3F1 mice Oral, drinking water	0, 0.1, 1.4, 4.9 (mice only), 20.9, 59.3, and 181 mg/L Cr(VI), 90 0, 0.015, 0.21, 2.9, 7.2, 20.5 mg/kg-d Cr(VI) (rats) 0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) (mice)	Dose-dependent decreases in Fe levels in the duodenum, liver, serum, and bone marrow Considered in hematological effects; not in GI effects synthesis. This assessment determined that evidence indicates Cr(VI) is likely to cause hematological effects based on iron-deficient anemia-like observations in rodents (see Section 3.2.5 of the toxicological review). Such observations were made in some of the studies cited in this table (including NTP (2008, 2007f)). This table does not list the observed hematological effects or effects related to iron homeostasis. See Section 3.2.5 of the toxicological review for a synthesis of hematological effects, or click the HAWC link for a summary of selected datasets.	Suh et al. (2014) Continued analysis of tissues from Thompson et al. (2011b) and Thompson et al. (2012c)
Mouse, SKH-1 hairless, female Oral, drinking water	0, 5, and 20 mg/L Cr(VI) 1.20 and 4.82 mg Cr(VI)/kg-d 9 mo	No effect on oxidative 8-OHdG adducts in forestomach, glandular stomach, duodenal cells, lung or skin No measure of cytotoxicity No changes in body weight	De Flora et al. (2008)
Mouse, C57BL/6J Oral, drinking water	0, 0.019, 0.19, 1.9 mg/L Cr(VI) 150 d 2 animals per dose group	In proximal and distal sections of GI tract: Histopathology: no effects on villous atrophy/blunting or inflammation; slight enterocyte hypertrophy and crypt hyperplasia Immunohistochemistry: no effect on Ki67	Sánchez-Martín et al. (2015)
Rat, Wistar Oral, drinking water	0, 87, 174, 262, 349, 436 mg/L Cr(VI) 0, 1.7, 3.5, 5.2, 7.0, 8.7 mg/kg-d 60 d	Stomach: ↓ p53 protein (≥87 mg/L) and mRNA (≥174 mg/L) ↑ c-Myc protein and mRNA (≥174 mg/L) ↑ galectin-1 protein (≥174 mg/L) and mRNA (≥87 mg/L) ↓ RKIP protein and mRNA (≥262 mg/L) ↓ Rho-GDIα protein and mRNA (≥262 mg/L) Colon: ↓ p53 protein and mRNA (≥262 mg/L) ↑ c-Myc protein (≥262 mg/L) and mRNA (≥87 mg/L) ↑ galectin-1 protein (≥349 mg/L) and mRNA (≥174 mg/L) ↓ RKIP protein (≥436 mg/L) and mRNA (≥349 mg/L) ↓ Rho-GDIα protein (≥262 mg/L) and mRNA (≥349 mg/L)	Tsao et al. (2011)
Rat, Sprague-Dawley male Intragastric injection	1.77 mmol/kg Cr(VI); bile sampling every 40 min	Alpha-(4-pyridyl 1-oxide)-N-tert-butylnitrone (POBN) carbon-centered radical adduct in bile of rats exposed to Cr(VI)	Kadiiska et al. (1998)

System	Exposure[a]	Results	Reference
Rat Oral gavage	530 mg/kg-d Cr(VI), 3 d 106 mg/kg-d Cr(VI), 30 d Note: The administered gavage potassium dichromate doses (1,500 mg/kg and 300 mg/kg) are higher than the LD_{50} for rats listed in MSDS (130 mg/kg)	Intestinal epithelial cells, 3-d exposure: ↓ glucose-6-phosphate dehydrogenase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase and catalase ↓ glutathione and total thiols ↑ lipid peroxidation Intestinal epithelial cells, 30-d exposure: ↑ superoxide dismutase, glutathione peroxidase Null glucose-6-phosphate dehydrogenase, glutathione reductase and catalase ↓ glutathione-S-transferase	Sengupta et al. (1990)
Rat, Wistar, female i.p. injection	8.8 mg/kg Cr(VI) Single dose, 48 h	Type 2 cystatins were induced in kidneys and submandibular acini salivary glands. Not detected in parotid or sublingual glands, or in trachea, lung, stomach, small intestine, large intestine, spleen, liver, or pancreas.	Cohen et al. (1993)
In vitro human primary and immortalized GI cells or gastric fluid			
Caco-2 human colorectal adenocarcin-oma cells	0.1, 0.3, 1, 3, 10, 30, 100 µM Cr(VI)	Increase in 8-OHdG at nontoxic and cytotoxic concentrations No change in p53, annexin-V (apoptosis markers), LC3B (autophagy marker) Translocation of ATF6 to nucleus (ER stress response marker)	Thompson et al. (2012a)
Human wild-type HCT116 colon cancer cells	30 µM Cr(VI) (formulation and compound uncertain)	Upregulated p53, p21CIP1/WAF1, ATM, DNA-PK, ATR, AKT and p38 (upstream p53 kinases) ↑ apoptosis involves DNA-PK-mediated p53 activation and increased PUMA concurrent with loss of p21 Note: chemical formulation preparation information not provided. The only information given is the chemical was 30 µM Cr(VI) and it was "a gift from Professor Naresh Dalal, Department of Chemistry, Florida State University." The true dose is therefore unclear (it is possible it is 1/3 this value if the concentration is in units of the parent chromate compound)	Hill et al. (2008b; 2008a)
Human gastric cancer SGC-7901 cells	3.53 µM Cr(VI)	Oxidative stress, apoptosis and necrosis all increased when the Unconventional prefoldin RPB5 Interacting protein (URI) is knocked down	Luo et al. (2016)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.3. Hepatic Effects

C.2.3.1. *Mechanistic studies relevant to hepatic toxicity*

A large body of mechanistic information exists (125 studies) to inform the potential hepatotoxicity of Cr(VI). Therefore, studies more informative for chronic human exposure were prioritized:

- Studies of the liver or liver enzymes from humans with quantified exposure to Cr(VI)
- Experimental animal studies of the liver or liver enzymes using quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation exposure to Cr(VI)
- In vitro studies in human primary or immortalized cells derived from liver
- Mechanistic endpoints relevant to interpretations of hepatic health effects in humans, including genotoxicity tests in liver tissues

This prioritization strategy identified 49 relevant studies. These include mammalian studies of the liver or liver enzymes that focused on exposure routes more relevant to humans (oral drinking water, gavage, and diet; inhalation) and repeat dose studies of longer duration (≥28 days). Shorter duration studies, however, also provided some supporting information, and in vitro studies in human liver primary cells or cell lines provided insight into biological plausibility and human relevance of the observed mechanisms. These studies, summarized in Table C-34, primarily reported evidence of Cr(VI)-induced oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, inflammation, apoptosis, DNA damage, and cell proliferation.

Table C-34. Mechanistic studies prioritized for informing potential Cr(VI)-induced hepatic toxicity

System	Route	Exposure[a]	Results	Comments	Reference
Oxidative and endoplasmic reticulum stress					
Mouse, ICR male	Oral feed	1 and 4 mg/kg/ $K_2Cr_2O_7$-d, 36-d repeat dose Confirmation by detection of ↑ Cr content in liver	↑ hepatic lipid peroxidation and MDA ↑ GSH levels ↑ CAT and GPx activity and mRNA ↑ Ho-1, Atf6, CHOP gene expression		Jin et al. (2014)
Rat, Wistar male	Oral gavage	30 mg/kg/ $K_2Cr_2O_7$-d, 28-d repeat dose	↑ hepatic lipid peroxidation ↓ SOD, CAT, and GST activity ↑ Atf1 (MAPK stress response pathway)		Navya et al. (2017)

System	Route	Exposure[a]	Results	Comments	Reference
Mouse, C57BL/J5, male and female	Oral drinking water	55–5500 µg/L $Na_2Cr_2O_7$, 5 mo, repeat dose 2 animals per dose group	↑ GCLC (glutamyl-cysteine ligase catalytic subunit) Null NRF2 (NF-E2-related factor 2)	↑ GCLC but the mRNA expression was down For this study, n = 2 males and 2 females	Sánchez-Martín et al. (2015)
Rat, Sprague-Dawley, female	Oral gavage	2.5 and 10 mg/kg-d $Na_2Cr_2O_7$; 30, 60, 90, and 120 d	↑ hepatic mitochondrial and microsome peroxidation with concurrent excretion of lipid metabolites MDA, FA, ACT, and ACON	(n) not given, concerns with results interpretation 2002: 4 animals/group	Bagchi et al. (2002b; 1997b; 1995a), Stohs et al. (2001)
Rat, Sprague-Dawley, female	Oral gavage	25 mg/kg $Na_2Cr_2O_7$ (reported as 0.5 LD_{50}), 48 h	↑ hepatic mitochondrial and microsome peroxidation with concurrent excretion of lipid metabolites	1995b n = 4–6 animals per group	Bagchi et al. (1995b)
Mouse, C57BL/6NTac and N12 p53-deficient C57BL/6TSG-p53, female	Oral gavage	2000&2002: 0.50 LD_{50}, 0.10 LD_{50}, 0.01 LD_{50}. 2001: 0.50 LD_{50} reported as 95 mg/kg $Na_2Cr_2O_7$ after 24 h; 24 h, 48 h, and time course up to 96 h, respectively	↑ hepatic cytochrome C (reported as SOA production) ↑ hepatic lipid peroxidation	Dosing and (n) not given (2000&2002)	Bagchi et al. (2002a; 2001; 2000a)
Rat, albino	Oral gavage	50 mg/kg-d $K_2Cr_2O_7$, 20 d repeat dose	↑ liver triglycerides and phospholipids	Uninformative factors expected to decrease confidence in mechanistic reporting	Kumar and Rana (1982)
Rat, Sprague-Dawley (SD), male and female	Oral gavage	9 mg/kg and 17.5 mg/kg $K_2Cr_2O_7$, 7 d	↓ free radical scavenging capacity (benzoic acid hydroxylation method) ↓ GSH	Dose-dependent decreases	Zhong et al. (2017c)
Rat, Wistar, female	Oral drinking water	5 and 20 mg/L $K_2Cr_2O_7$, 15 d	Null results CYP2E1 activity ↓ GSH (at both doses)		Ma et al. (2015)
Rat, Sprague-Dawley, male	i.p.	2.5, 5.0, 7.5, and 10 mg/kg-d $K_2Cr_2O_7$, 5 d	↑ ROS, MDA ↑ SOD, CAT activity	Results dose dependent	Patlolla et al. (2009b)
Mouse, ddY, male	i.p.	20 mg/kg $K_2Cr_2O_7$, single dose,	↑ lipid peroxidation (TBARS)		Susa et al. (1989)

System	Route	Exposure[a]	Results	Comments	Reference
		reports at 24 and 48 h			
Rat, Sprague-Dawley, male	i.p.	10–40 mg/kg $Na_2Cr_2O_7$, single dose	↑ GSH 20 mg/kg		Standeven and Wetterhahn (1991b)
Mouse, Swiss albino, male	i.p.	1 mg/kg CrO_3, single dose, reports at 5–8 wk	↑ SOD, peroxidase, CAT, lipid peroxidation, ascorbic acid content in liver tissue	Mice from live animal supply farm, "around" 48 mice range from 15 to 25 g body weight. Increases were not time dependent	Acharya et al. (2004a)
Rat, Wistar, male	i.p.	20 mg/kg body weight of $K_2Cr_2O_7$, single dose; 3-min, 3-h, 24-h time course	↑ SOD at 24 h Null for changes in CAT, lipid peroxidation (TBARS), CYP450		Tagliari et al. (2004)
Rat, Wistar, male	i.p.	20 mg/kg $K_2Cr_2O_7$, single IP dose, 24 h	↑ lipid peroxidation, GSH level and GPx-1 activity; no change in GR activity ↓ TrxR-1 activity		Kotyzova et al. (2015)
Mouse, BALB/c	i.p.	0 or 400 µmol $K_2Cr_2O_7$ (20.8 mg Cr(VI)/kg), single dose	In liver: ↑ lipid peroxidation ($p < 0.05$) ↑ heme oxygenase ($p < 0.001$) ↓ GSH-peroxidase activity ($p < 0.1$); slight but nonsignificant reduction in GSH levels	Significantly decreased %PCEs (PCE/NCE ratio = 0.64 ± 0.14) ($p < 0.01$) Also ↑ micronucleus frequency in bone marrow cells ($p < 0.001$)	Wroñska-Nofer et al. (1999)
HepG2 cells (human hepatocytes)	In vitro	5, 10, 20, 40 µM $K_2Cr_2O_7$	↑ SOD, Nrf2, Keap1 mRNA at 10 µM ↓ SOD, Nrf2, Keap1 mRNA over 10 µM	In a separate study X. Zhong shows SOD activity decrease starting at 1 µM but in L-02 (human fetal) cells	Zhong et al. (2017a)
HepG2 cells (human hepatocytes)	In vitro	3–25 µM $K_2Cr_2O_7$	↑ ROS production and MDA ≥ 12.5 µM		Patlolla et al. (2009a)
Hep3B cells (human hepatocytes)	In vitro	20 µM $K_2Cr_2O_7$	↑ levels of SOD, GR, NO, CAT, MDA		Zeng et al. (2013)
-02, human etal epatocytes	n vitro		↑ Endoplasmic reticulum stress and mitochondrial damage, and apoptosis; effects reversed by		Liang et al. (2019)

System	Route	Exposure[a]	Results	Comments	Reference
			antioxidant treatment		
L-02 cells (human fetal liver)	In vitro	Various (Yuan 1–32 µM; Xiao 2012 4–32 µM Xei 4 µM for caspase 3/beclin, Ca+2 and ROS; Xiao 2014 25 µM typically used for experiments (65–75% survival rate); Zhang 2016 10 nM for ROS, MRCC, p53); all units in Cr(VI) (parent compound was $K_2Cr_2O_7$)	↑ ROS production (Zhang 2016; Yuan 2012; Xiao 2012) ↑ CHOP, PERK, IRE1 mRNA and protein (ER stress 6–10 µM, Zhang 2017) ↓ SOD, TRx, and GHS (Zhong 2017a, 8 and 16 µM dose dependent)	Doses not overtly cytotoxic, could be some decline in viability. Zhang 2016, Xiao 2012, Yi 2016, Zhong 2017a and Yuan 2015 measured ROS with DCF	Zhang et al. (2017); Zhong et al. (2017c); Yi et al. (2016); Zhang et al. (2016); Xiao et al. (2012a); Xiao et al. (2012b); Yuan et al. (2012)
Mitochondrial dysfunction					
Rat, Sprague-Dawley, female	Drinking water	10 mg/kg-d and 2.5 mg/kg-d $Na_2Cr_2O_7$, respectively; 90 d and 120 d	↑ hepatic mitochondrial and microsome peroxidation with concurrent excretion of lipid metabolites	This is the same study/effect listed above under oxidative stress	Bagchi et al. (1997b; 1995a)
Mouse, female C57BL/6NTac N12 p53-deficient C57BL/6TSG-p53	Assume by gavage	2000&2002: 0.50 LD_{50}, 0.10 LD_{50}, 0.01 LD_{50}. 2001: 0.50 LD_{50} reported as 95 mg/kg $Na_2Cr_2O_7$ after 24 h. 24 h, 24 h, and time course up to 96 h respectively	↑ hepatic cytochrome C (reported as SOA production) ↑ hepatic lipid peroxidation	Dosing and (n) not given (2000&2002). LD_{50} (2001) not consistent with LD_{50} reported in 1995b.	Bagchi et al. (2002a; 2001; 2000a)
Mouse, ICR, male	Feed	1 and 4 mg/kg/ $K_2Cr_2O_7$-d, 36 d repeat dose	↑ cytochrome C		Jin et al. (2014)
Mouse, Swiss albino, male	Gavage	0, 25, 50, and 100 mg/kg $K_2Cr_2O_7$ single dose, 24 h	↑ cytochrome C (50&100 mg/kg)		Wang et al. (2010b)
L-02 human fetal hepatocytes	In vitro	Various (Yuan 1–32 µM; Xiao 2012 4–32 µM Cr(VI); Xei 4 µM for caspase 3/beclin, Ca+2 and ROS; Xiao 2014 25 µM typically used for experiments (65–75% survival rate); Yi 2015 2–	↓ ATP production (Yuan 2012, Xie 2014; Xiao 2014); ↓ mitochondrial respiratory chain complex (MRCC) I and II activity (25 µM Xiao 2014/ Zhang 2015, Zhong 2017a)	Xiao 2014 strong CC between mito ETC dysfunction and apoptosis	Yi et al. (2017); Zhong et al. (2017c); Zhang et al. (2016); Xiao et al. (2014); Xie et al. (2014); Xiao et al. (2012a); Xiao et al. (2012b); Yuan et al. (2012)

System	Route	Exposure[a]	Results	Comments	Reference
		16 µM Cr(VI) for mitochondrial effects; Zhang 2016 10 nM 24 h 2× for 4 wk - ROS, MRCC, p53), Zhong 2017a 8&16 µM; all units in Cr(VI) (parent compound was $K_2Cr_2O_7$)	↓ MMP, ATP dose dependent (1–4 µM, Xie 2014) ↑ VDAC expression (protein&mRNA, accelerates movement of Ca^{2+} from ER to IMM; Yuan 2012, Yi 2017), Ca2+ effects		
HepG2 human hepatocytes	In vitro	5, 10, 20, 40 µM $K_2Cr_2O_7$	↑ mtDNA copy number, mt mass, NDUFA1, Foxo1, Sirt1, Akt1, Creb1, ATP50 and ATP3J gene expression at 10 µM ↓ mtDNA copy number, mt mass, NDUFA1, Foxo1, AKT1, Creb1, MAPK2, Pten, ATP50 and ATP3J gene expression over 10 µM		Zhong et al. (2017a)
L-02 human fetal hepatocytes	In vitro	1–4 µM $K_2Cr_2O_7$, 24 h	↓ ETFDH, CoQ10, ATP production, SOD, Bcl-2 ↑ ROS, caspase-3, caspase-9, MDA (lipid peroxidation), mitochondrial membrane depolarization and permeability transition pore (MPTP) opening, Ca2+, Cyt c release, Bax	Cr(VI) induces CoQ10 deficiency (essential for cellular respiration and metabolism); effects reversed by pretreatment with CoQ10	Zhong et al. (2017b)
Inflammation					
Mouse, ICR, male	Feed	1 and 4 mg/kg/$K_2Cr_2O_7$-d, 36 d repeat dose	↑ Ho-1		Jin et al. (2014)
Rat, Wistar, male	Gavage	30mg/kg/$K_2Cr_2O_7$-d, 28 d repeat dose	↑ serum levels of ALT, AST, and ALP ↑ TNFα, MAPK gene expression		Navya et al. (2017)
Rat, Sprague-Dawley (SD), male and female	Gavage	9mg/kg and 17.5mg/kg $K_2Cr_2O_7$, 7 d	↑ serum levels of ALT, AST (17.5 mg/kg)		Zhong et al. (2017c)

System	Route	Exposure[a]	Results	Comments	Reference
L-02, human fetal hepatocytes	In vitro	4 and 8uM $K_2Cr_2O_7$ (85–80% viability Yi 2017); 2–32uM Yi 2016; Zhong 2017a 8–15 µM	↑ ALT, AST leakage ↑ TNFα, IL-1β, LBT4 ↑ Nf-kB p65 (Yi 2016, 16 µM)	All dose dependent	Yi et al. (2017); Zhong et al. (2017c); Yi et al. (2016)
Apoptosis					
Mouse, ICR, male	Feed	1 and 4 mg/kg/$K_2Cr_2O_7$-d, 36 d repeat dose	↑ Caspase 3, 7, 9 ↑ cytochrome C	ER stress response	Jin et al. (2014)
Rat, Wistar, male	Gavage	30mg/kg/$K_2Cr_2O_7$-d, 28-d repeat dose	↓ Bcl-2		Navya et al. (2017)
Mouse, Swiss albino, male	Gavage	0, 25, 50, and 100 mg/kg $K_2Cr_2O_7$ single dose, 24 h	↑ cytochrome C, p53, Casp 3 ↓ Bcl-2 (100 mg/kg)		Wang et al. (2010b)
HepG2 cells (human hepatocytes)	In vitro	5, 10, 20, 40 µM $K_2Cr_2O_7$	No significant change in cell viability at 10 µM ↓ Significant (20%) decline in cell viability at 40 µM		Zhong et al. (2017a)
HepG2 cells (human hepatocytes)	In vitro	3–25 µM $K_2Cr_2O_7$	↓ Significant (20%) decline in cell viability at 25 µM		Patlolla et al. (2009a)
Hep3B cells (human hepatocytes)	In vitro	2.5–100 µM $K_2Cr_2O_7$	↓ cell viability at 10 µm (10%), 20 µM (20%) ↑ caspase activity 20 µM		Zeng et al. (2013)
L-02 human fetal hepatocytes	In vitro		↑ autophagosomes, LC3-II, and protein degradation; ↓ p62/SQSTM1	Autophagy associated with ROS-AKT-mTOR pathway Autophagy blocked by antioxidants Inhibition of autophagy induced apoptosis	Liang et al. (2018)
L-02 human fetal hepatocytes	In vitro	Various (Yuan 1–32 µM; Xiao 2012 4–32 µM; Xei 4 µM for caspase 3/beclin, Ca+2 and ROS; Xiao 2014 25 µM typically used for experiments (65–75% survival rate 12h); Yi 2015 2–16 µM for	↑ p53 (Zhang 2016) ↑ Caspase 3 (25 µM Xiao 2014, Xie 2014 activity 1–4 µM 24 h; Xiao 2012 dose dependent) ↑ apoptosis (25 µM, Xiao 2014; sig at 8 µM in Yuan 2012) ↑ Beclin-1 mRNA (1–4 µM, Xie 2014)		Yuan et al. (2012); Xiao et al. (2012a); Xiao et al. (2012b); Xie et al. (2014); Xiao et al. (2014); Zhang et al. (2016); Zhong et al. (2017c), Zhang et al. (2017)

System	Route	Exposure[a]	Results	Comments	Reference
		mitochondrial effects; Zhang 2016 10 nM 24 h 2× wk for 4 wk); all units in Cr(VI) (parent compound was $K_2Cr_2O_7$)	↓ Bcl-2, ↑ Bax&cyto C (Zhang 2017 dose dependent 6–10 µM)		
L-02 human fetal hepatocytes	In vitro	0, 5, 10, 15 µM Cr(VI)	↑ Clusterin (CLU), dose dependent	Overexpression of CLU can counteract Cr(VI)-induced MRCC l inhibition, preventing apoptosis	Xiao et al. (2019)
DNA damage					
Rat, Wistar, male	Gavage	30 mg/kg/ $K_2Cr_2O_7$-d, 28-d repeat dose	↓ OGG-1 ↑ GADD45		Navya et al. (2017)
Mouse, C57BL/J5	Drinking water	$Na_2Cr_2O_7$; dose range 55–5500 µg/L, 5 mo, repeat dose 2 animals per dose group	↑ p73 ↑ P-γH2AX positive (no dose dependence)	For this study n = 2 males and 2 females	Sánchez-Martín et al. (2015)
Rat, Sprague-Dawley, female	Gavage	25mg/kg $Na_2Cr_2O_7$ (reported as 0.5 LD_{50}), single dose	↑ DNA SSBs in hepatic tissue	(n) not given	Bagchi et al. (1995b), Stohs et al. (2001)
Mouse, female C57BL/6NTac N12 p53-deficient C57BL/6TSG-p53	Assume by gavage	2000&2002: 0.50 LD_{50}, 0.10 LD_{50}, 0.01 LD_{50}. 2001: 0.50 LD_{50} = 95 mg/kg $Na_2Cr_2O_7$, single dose (?), 48 h, 24 h, up to 96 h time course, respectively	↑ DNA fragmentation in hepatic tissue	Dosing and (n) not given (2000&2002), DNA fragmentation measured by % 600-nm absorbance in supernatant (2000). DNA fragmentation by electrophoresis (2001)	Bagchi et al. (2002a; 2001; 2000a)
Rat, Fischer 344, male	Drinking water	100 and 200 mg/L $K_2Cr_2O_7$, 3 wk	↑ hepatic DPCs	Quantitative analysis performed but not presented, results not visually convincing	Coogan et al. (1991a)
Rat, Wistar, female	Drinking water	5 and 20 mg/L $K_2Cr_2O_7$, 15 d	Null results for O6-MeG adducts		Ma et al. (2015)
Mouse, Swiss albino, female	Drinking water	5 and 10 mg/L $Na_2Cr_2O_7$ and 10 mg/L $K_2Cr_2O_7$, 18 d (duration of pregnancy)	Null results for hepatic MN in fetuses		De Flora et al. (2006)

System	Route	Exposure[a]	Results	Comments	Reference
Mouse, C56BL/6 Big Blue, female	Intra-tracheal instilla-tion	6.75 mg/kg $K_2Cr_2O_7$, 28 d, single dose	↑ mutation frequency in liver, but only compared to pooled controls (p = 0.043; not statistically significant compared to concurrent liver controls (p = 0.085)	MF higher in lung than in liver or kidney	Cheng et al. (2000)
Rat, Sprague-Dawley, male	Intra-tracheal instilla-tion	0.25 mg/kg $Na_2Cr_2O_7$, 3 d	No effect on DNA-protein crosslinks, DNA fragmentation, 8-OHdG levels, or gene expression, including those associated with apoptosis, or various forms of DNA alterations in liver tissue		D'Agostini et al. (2002); Izzotti et al. (2002; 1998)
Mouse, BDF1, female	i.p.	25 mg/kg $Na_2Cr_2O_7$ – acute; 12.5 mg/kg – subchronic, single injection for acute (1–14 d) or every 4 wk for 128 d	↑ changes in ploidy in acute group	N ranged from 3 to 5 per group. All regions of liver	Garrison et al. (1990)
Rat, Sprague-Dawley, male	i.p.	20 or 50 mg/kg-d $Na_2Cr_2O_7$	1 h: DNA-DNA and DNA-protein crosslinks in liver, lung and kidney ↑ DNA strand breaks in liver 36–40 h: DNA-protein crosslinks in lung and kidney		Tsapakos et al. (1981), Tsapakos et al. (1983)
Mouse, albino male	i.p.	0 or 20 mg Cr(VI)/kg, single dose	DNA damage (comet assay), 15 min postinjection (all back to control levels at 3 h): ↑ liver, kidney No increases in spleen, lung, brain	Same pattern as Cr(V) complexes Cytotoxicity not reported DNA damage reduced with deferoxamine	Ueno et al. (2001)
Mouse	i.p.	80 mg/kg K_2CrO_4	DNA damage (comet assay) in liver, lung, kidney, spleen, and bone marrow		Sasaki et al. (1997)
Hep3B cells (human hepatocytes)	In vitro	20 µM $K_2Cr_2O_7$	↑ DNA damage (30% comet cells) in p53-deficient Hep3B cells		Zeng et al. (2013)

System	Route	Exposure[a]	Results	Comments	Reference
			when caspase-3 was blocked		
HepG2 cells (human hepatocytes)	In vitro	3–25 µM $K_2Cr_2O_7$	↑ DNA damage (comet assay), dose-dependent		Patlolla et al. (2009a)
Cell proliferation					
Mouse, C57BL/J5	Drinking water	$Na_2Cr_2O_7$; dose range 55–5,500 µg/L, 5 mo, repeat dose 2 animals per dose group	↓ p16 and p19	For this study n = 2 males and 2 females	Sánchez-Martín et al. (2015)
Mouse, C57BL/J5	Drinking water (in vitro study)	10 nM $K_2Cr_2O_7$ for 24 h 2× wk for 4 wk, 5 mo, repeat dose	↑ senescence	Cr(VI) concentration was chosen according to the Cr(VI) values recorded in the blood circulation of exposed workers	Zhang et al. (2016)

i.p. = intraperitoneal injection.

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.4. Hematological Effects

C.2.4.1. *Mechanistic studies relevant to hematological effects*

Mechanistic evidence indicating the biological pathways involved in hematological toxicity following Cr(VI) exposure is summarized in Table C-35. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "hematology" if involving red blood cells (erythrocytes) or reporting other endpoints relevant to hematological toxicity (e.g., measures of hemoglobin levels). Studies were prioritized for consideration in the synthesis of mechanistic evidence for hematological effects if they were conducted in mammalian species:

- Studies in humans with quantified oral or inhalation exposure to Cr(VI)
- Studies in experimental animals with quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation exposure to Cr(VI)
- In vitro studies in human primary erythrocytes
- Mechanistic endpoints relevant to interpretations of hematological effects in humans

Twelve hematological studies were identified to include in the mechanistic syntheses, including four drinking water exposure studies in rats and mice, one i.p. injection study in mice, and seven investigations using human primary erythrocytes.

Table C-35. Mechanistic studies prioritized for informing potential Cr(VI)-induced hematological effects

System/Route	Exposure[a]	Results/Comments	Reference
Rat, Wistar, male	700 mg/L $K_2Cr_2O_7$ (67 mg/kg) in drinking water, 14 d	In plasma: ↑ IL-1β, TNF-α, 8-iso-PGF(2a), and creatinine In plasma and urine: ↑ 11-dehydro-TXB2 Markers indicating arachidonic acid peroxidation	Mitrov et al. (2014)
Rat, Wistar females, GD 9–21 Oral, drinking water	0, 50, 100, 200, and 400 mg/L $K_2Cr_2O_7$	In pregnant rats: ↓ RBC counts, hemoglobin, hematocrit, and MCV levels at 200 and 400 mg/L	Samuel et al. (2012)
F344 rats and B6C3F1 mice Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI), 90 d 0, 0.015, 0.21, 2.9, 7.2, 20.5 mg/kg-d Cr(VI) (rats) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) (mice)	Dose-dependent decreases in Fe levels in the duodenum, liver, serum, and bone marrow Induction of divalent metal transporter 1 and transferrin receptor 1 in duodenum ↑ Cr RBC:plasma ratios in rats ≥20.9 mg/L	Suh et al. (2014)
Rat, Sprague-Dawley Oral, drinking water	0, 30, 100, and 300 mg/L $K_2Cr_2O_7$ (0, 10.6, 35.4, and 106.1 mg/L Cr(VI)) 0, 2.49, 7.57, 21.41 mg/kg-d Cr(VI) 4 wk	Mean body weight gain, mean water consumption, clinical chemistry determinations, and oxidative stress levels in plasma Mild anemic effects and ↑ plasma malondialdehyde (MDA) levels correlated with ↓ global DNA methylation at 35.4 and 106.1 mg/L ↓ plasma glutathione peroxidase (GSH-Px) activity (all exposed groups) No effect on p16 methylation or plasma 8-OHdG levels	Wang et al. (2015)
Mouse, Swiss Intraperitoneal injection	4 mg/kg-d $K_2Cr_2O_7$, 5 d/wk, 2 wk	↓ Hemoglobin, hematocrit, and RBC counts Echinocytic transformation Leucopenia after 2 wk	Ray and Sarkar (2012)
Human, primary erythrocytes	0, 0.1, 0.5, 1.0, 2.5, and 5 mM $K_2Cr_2O_7$, 1 h	↑ erythrocyte hemolysis and protein carbonyl content, dose-dependent ↑ lipid peroxidation (MDA levels) ↓ total SH content, NO levels ↑ SOD and glutathione S-transferase ↓ catalase, G6PD, glutathione peroxidase, glutathione reductase, and thioredoxin reductase	Ahmad et al. (2011)

System/Route	Exposure[a]	Results/Comments	Reference
Human, primary erythrocytes	0 or 8 mM $Na_2Cr_2O_7$, 0, 2, and 4 h	↑ lipid peroxidation (TBARS) ≥2 h No hemolysis, but observed echinocytic transformation of RBCs ↓ GSH levels and GSSG-R activity No effect on catalase, GSH-Px, or SOD activities ↑ methemoglobin (hemoglobin oxidation) and ↓ NADH-methemoglobin reductase activity in RBCs	Fernandes et al. (1999)
Human, primary erythrocytes	5–25 µg Cr(VI)/L blood	↓ glutathione reductase No effect on other erythrocyte enzymes	Koutras et al. (1964)
Human, primary erythrocytes	0, 1, 10, or 20 µM Cr(VI), 48 h	Evidence of eryptosis (apoptotic-like death of erythrocytes): ↑ intracellular Ca^{2+}, ↓ ATP, ↓ cell volume, ↑ annexin-V (phosphatidylserine) binding ↑ hemolysis No effect on ceramide formation (inconsistent with eryptosis)	Lupescu et al. (2012)
Human, primary erythrocytes and mitochondria from placenta tissue	0.05, 0.5, 1, 5 µg/mL $K_2Cr_2O_7$	↑ lipid peroxidation level (TBARS) (decreased with coadministration of estrogen metabolite 4-OHE2) ↓ SOD and GST activity ↓ nitric oxide levels in blood	Sawicka et al. (2017; 2017)
Human, primary erythrocytes	0, 1.25, 2.5, 5, 10, 20, 40, 80, and 160 µM Cr(VI), 48 h	↑ hemolysis, dose dependent Evidence of eryptosis: ↑ intracellular Ca^{2+}, ↓ ATP, ↓ cell volume, ↑ annexin-V (phosphatidylserine) binding Blocking Ca influx lessened cell volume reduction ↑ ROS; incubation with NAC did lower ROS levels but did not affect annexin-V binding	Zhang et al. (2014)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; Sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.5. Immune Effects

C.2.5.1. *Immune toxicity evidence tables*

The immune evidence from experimental animals synthesized in Section 3.2.6 of the toxicological review is summarized in Table C-36. These studies were identified using the main PECO criteria in Appendix A and screened for outcomes that inform Cr(VI)-induced immune toxicity. The evidence is organized by the immune toxicity endpoints identified in the World Health Organization's *Guidance for Immunotoxicity Risk Assessment for Chemicals* (IPCS, 2012).

Table C-36. Data summary tables for immunological outcomes included in the immune effects animal evidence synthesis

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Host resistance						
Cohen et al. (2006)	Rats (male, F344)	Short-term (5 d)	118.57 µg/m^3 for 5 h/d for 5 consecutive d	Inhalation	Pathogen clearance	Decreased 72 h postinfection, but not 24 or 48 h postinfection and only in the high-dose group. Effect observed in both soluble and insoluble forms of Cr(VI), but the effect was not correlated with chromium lung burden.
Cohen et al. (2010)	Rats (male, F344)	Short-term (5 d)	118.57 µg/m^3 for 5 h/d for 5 consecutive d	Inhalation	Pathogen clearance	Decreased 72 h postinfection, but not 24 or 48 h postinfection and only in the high-dose group. Effect observed in both soluble and insoluble forms of Cr(VI), but the effect was not correlated with chromium lung burden.
Antibody responses						
NTP (2005)	Mice (female, B6C3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	IgM AFC/10^6 cells	Increased ~30% for 31.3 and 62.5 mg/L Not reproducible in second assay.
					IgM AFC/spleen	34% incr. for 62.5 mg/L dose only. Not reproducible in second assay.
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	IgM AFC/10^6 cells	No effect.
					IgM AFC/spleen	No effect.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	IgM AFC/10^6 cells	66% incr. at 57.3 mg/L dose only.
					IgM AFC/spleen	62% incr. at 57.3 mg/L dose only.
Glaser et al. (1985)	Rats (male, Wistar TNO-W 74)	Short-term (28 d)	0.025, 0.050, 0.10 mg/m^3	Inhalation	# spleen cells necessary for lysis of 50% hemolysis SRBCs	No effect.
		Subchronic (90 d)	0.025, 0.050, 0.10, 0.20 mg/m^3		# spleen cells necessary for lysis of 50% hemolysis SRBCs	Increased response for 0.050 mg/m^3, 0.050 mg/m^3 + 2-mo recovery and 0.20 mg/m^3 groups.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
***Ex vivo* WBC function**						
NTP (2005)	Mice (female, BC3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	MLR	No effect.
					NK cell activity	No effect.
					Spleen cell proliferation	No effect on anti-CD3 spleen cell proliferation.
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	NK cell activity	No effect.
					Spleen cell proliferation	No effect on anti-CD3 spleen cell proliferation.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	NK cell activity	No effect.
					Spleen cell proliferation	No effect on anti-CD3 spleen cell proliferation.
Glaser et al. (1985)	Rats (male, Wistar TNO-W 74)	Short-term (28 d) & subchronic (90 d)	Short-term (0.050 mg/m^3), subchronic (0.025, 0.050, 0.20 mg/m^3)	Inhalation	Phagocytosis	For both exposure regimens, phagocytosis significantly increased at lower Cr(VI) levels (up to 0.050 mg/m^3). Following subchronic exposure to 0.20 mg/m^3, phagocytosis decreased significantly. In both instances, the investigators verified cellular viability prior to initiating the assay.
		Subchronic (90 d)	0.20 mg/m^3		Spleen cell proliferation	Compared to control, ConA stimulated T cell proliferative response (30 µg/mL, not 15 µg/mL ConA) was elevated in rats exposed to Cr(VI).
Shrivastava et al. (2005b)	Mice (Swiss)	Short-term & subchronic (3, 6, 9 wk)	14.8 mg/kg	Drinking water	Phagocytosis	Compared to week 0, phagocytosis of spleen macrophages was significantly reduced to 36 ± 7% at the 9-wk timepoint.
					Spleen cell proliferation	Compared to week 0, ConA stimulated T cell proliferative response was increased two-fold in mice exposed to Cr(VI), but the investigators did not analyze the findings statistically.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Snyder and Valle (1991)	Rat (F344)	Short-term (3 or 10 wk)	100, 200 m/L	Drinking water	Spleen cell proliferation	Compared to control, proliferative response to ConA was elevated at 100 mg/L and decreased at 200 mg/L in splenocytes isolated from rats exposed to chromium in drinking water. Response to LPS was increased at 100 mg/L and similar to control at 200 mg/L (3-wk exposure) in splenocytes isolated from rats exposed to chromium in drinking water. No dose-related pattern apparent.
					MLR	Chromium (100 mg/L) had no effect on thymidine uptake from rats exposed for 10 wk unless splenocytes were cultured in the presence of 0.1 mg/L chromate; investigators did not analyze findings statistically.
Cohen et al. (1998)	Rat (F344)	Short-term (28 d)	360 µg/m^3	Inhalation	Reactive oxygen species Nitric oxide	Potassium chromate had no effect on O_2– or H_2O_2 production in the presence or absence of IFN-γ at 4 wk, but increased opsonized zymosan-stimulated O_2– and decreased H_2O_2 production in the presence IFN-γ. Chromium had no effect on LPS-stimulated nitric oxide production at 4 wk, but reduced IFN-g-stimulated production at 4 wk.
					Mitogen-stimulated cytokine production (LPS) by pulmonary alveolar macrophages exposed in vivo for 4 wk	Decreased IL-1, TNFα Nonstatistically significant increase in IL-6.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Johansson et al. (1986)	Rabbit (strain not specified)	Chronic	0.9 ± 0.4 mg/m^3	Inhalation	Phagocytosis	No effect. Note: Study outcome could have been affected by the 3-d gap between exposure to chromium and evaluation of effects on phagocytosis.
Karaulov et al. (2019)	Rat (Wistar)	Chronic	20 mg/kg-d	Drinking water	Mitogen-stimulated cytokine production (ConA) by splenocytes exposed in vivo for 45, 90, or 135 d	Increased IL-4 (days 45, 90, and 135) and decreased IL-6 (day 135). No effect on IL-10 and IFNγ.
Immune organ pathology						
NTP (2005)	Mice (female, B6C3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	Gross spleen and thymus lesions	No effect.
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Gross spleen and thymus lesions	No effect.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Gross spleen and thymus lesions	No effect.
NTP (2007f)	Rats (male and female, F344)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD	Drinking water	Gross spleen and thymus lesions Histopathology on spleen, thymus, lymph nodes (mandibular, mesenteric and pancreatic)	No effect. Note: Although the effect is unlikely to be due to immunotoxicity, histiocytic cellular infiltration of pancreatic lymph nodes was reported in male (≥125 mg/L) and female (1,000 mg/L) rats.
	Mice (male and female, B6C3F1)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD			No effect. Note: Although the effect is unlikely to be due to immunotoxicity, histiocytic cellular infiltration of mesenteric lymph nodes was reported in male and female mice exposed to 125 mg/L or more.
	Mice (male, BALB/c)	Subchronic (3 mo)	62.5, 125 and 250 mg/L SDD			No effect.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
	Mice (male, am3-C57BL/6)	Subchronic (3 mo)	62.5, 125 and 250 mg/L SDD			No effect. Note: Although the effect is unlikely to be due to immunotoxicity, histiocytic cellular infiltration of mesenteric lymph nodes was reported in male mice exposed to 250 mg/L.
NTP (2008)	Rat (male and female, F344/N)	2-yr (day 22, 6 and 12 mo)	14.3, 57.3, 172, or 516 mg/L SDD	Drinking water	Gross spleen and thymus lesions Histopathology on spleen, thymus, lymph nodes (mandibular and mesenteric)	No effect. Note: Although the effect is unlikely to be due to immunotoxicity, histiocytic cellular infiltration of mesenteric and pancreatic lymph nodes was reported in male and female rats exposed to 57.3 mg/L or greater.
	Mice (male and female, B6C3F1)	2-yr (day 22, 6 and 12 mo)	Male and female rats – 14.3, 57.3, 172, 516; Male mice – 14.3, 28.6, 85.7, or 257.4 mg/L SDD; Female mice – 14.3, 57.3, 172, or 516 mg/L SDD			No effect. Note: Although the effect is unlikely to be due to immunotoxicity, histiocytic cellular infiltration of the mesenteric lymph nodes of all exposed groups of males and females and of the pancreatic lymph nodes of 85.7 and 257.4 mg/L males and 172 and 516 mg/L females.
Karaulov et al. (2019)	Rats (male, Wistar)	Chronic (135 d)	20/mg/kg-d	Drinking water	Histopathology of spleen, thymus, lymph nodes	Compared to control, structural changes including decreased reticular epitheliocytes and associations with T cells that could lead to functional impairment of the central immune system, data not reported for other timepoints.
						Compared to control, structural changes structural effects including increased B-zone and a decrease in the T-zone were observed in spleens across all timepoints.
						Lymph node size was increased and was attributed to changes in cellular elements.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
NTP (1996)	Mice (female, BALBC)	Subchronic (90 d)	15, 50, 100, 400 mg/L PDC	Oral diet	Gross spleen and thymus lesions	No effect.
Glaser et al. (1986)	Rats (male, Wistar TNO-W 74)	Chronic (18 mo exposure + 12 mo recovery)	0.025, 0.050, 0.010 mg/m^3 Cr(VI)	Inhalation	Histopathology of spleen	No effect. Note: Animals were evaluated only after the full 30-mo study duration (i.e., including the 12-mo recovery period).
Immunoglobulin levels						
NTP (2005)	Mice (female, B6C3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	Antigen-specific IgM	No effect on serum titers of antigen-specific IgM (SRBC).
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Antigen-specific IgM	No effect on serum titers of antigen-specific IgM (KLH).
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Antigen-specific IgM	No effect on serum titers of antigen-specific IgM (SRBC).
Glaser et al. (1985)	Rats (male, Wistar TNO-W 74)	Short-term (28 d)	0.025, 0.050, 0.10 mg/m^3	Inhalation	Total serum Ig	Total serum Ig data not shown or mentioned in the results.
		Subchronic (90 d)	0.025, 0.050, 0.10, 0.20 mg/m^3			Dose-responsive increase in total serum Ig, significant at concentrations ≥0.025 mg/m^3, peaked at 0.10 mg/m^3, and declined to control levels at 0.20 mg/m^3.
Glaser et al. (1986)	Rats (male, Wistar TNO-W 74)	Chronic (18 mo exposure + 12 mo recovery)	Sodium dichromate – 0.025, 0.050, 0.10 mg/m^3	Inhalation	Total serum Ig	According to the investigators, total serum Ig levels decreased in all sodium dichromate exposure groups and for all timepoints (monthly for first 6 mo, every 3 mo thereafter), but observed effects were not significant; data not shown.
Glaser et al. (1990)	Rats (male, albino Wistar)	Short-term (30 d)	0.050, 0.10, 0.20, 0.40 mg/m^3	Inhalation	Total serum Ig	No effect on total serum Ig levels; data not shown.
		Subchronic (90 d)				No effect on total serum Ig levels; data not shown.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
		Subchronic + recovery (90 d + 30-d recovery)				No effect on total serum Ig levels; data not shown.
Immune organ weight						
NTP (2005)	Mice (female, B6C3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	Absolute and relative spleen and thymus weight	Nonreplicated decrease in relative spleen weight (31.3 mg/L). No effect on relative thymus weight. Note: Since significant changes in body weight were reported, absolute weights are not reliable.
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Absolute spleen, thymus, and lymph node weight	No effect (spleen, thymus). Protocol indicates lymph node weight was collected, but data were not reported.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Absolute spleen, thymus, and lymph node weight	No effect (spleen, thymus). Protocol indicates lymph node weight was collected, but data were not reported.
NTP (2007f)	Rats (male and female, F344/N)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD	Drinking water	Absolute and relative spleen and thymus weight	Males – Relative spleen weights of 250 and 500 mg/L significantly less than control. Thymus weight unaffected. Females – Relative spleen weights of 500 and 1,000 mg/L significantly less than control. Thymus weight unaffected.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
	Mice (male and female, B6C3F1)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD			Males – No effect on absolute spleen or thymus weight. Increased relative spleen and thymus weight (500 mg/L and 1,000 mg/L). Females – No effect on spleen weight. Absolute thymus weight increased for single dose group. Relative thymus weight increased for 125, 250, 500, and 1,000 mg/L dose groups. NOTE: Effects on organ weight were attributed to reduced body weights of the mice.
	Mice (male, B6C3F1)	Subchronic (3 mo)	62.5, 125, and 250 mg/L SDD			Absolute thymus weight decreased (250 mg/L), considered treatment related. Spleen weight unaffected.
	Mice (male, BALB/c)	Subchronic (3 mo)	62.5, 125, and 250 mg/L SDD			No effect on spleen or thymus weight.
	Mice (male, am3-C57BL/6)	Subchronic (3 mo)	62.5, 125, and 250 mg/L SDD			Significant decrease in absolute thymus weight and relative spleen weights (250 mg/L) NOTE: Effects on organ weight were attributed to reduced body weights of the mice.
Karaulov et al. (2019)	Rats (male, Wistar)	Chronic (135 d)	20/mg/kg-d	Drinking water	Absolute spleen and thymus weight	Absolute spleen and thymus weight decreased in rats exposed to chromium in drinking water for up to 135 d.
Shrivastava et al. (2005b)	Mice (male, Swiss)	Short-term & subchronic (3, 6, 9 wk)	14.8 mg/kg	Drinking water	Relative spleen weight	Compared to week 0, relative spleen weight decreased gradually and achieved statistical significance at the 9-wk timepoint.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Jin et al. (2016)	Mouse (male, ICR)	Short-term	50 mg/L for 7 d or 200 mg/L for 21 d	Drinking water	Relative spleen weight	Compared to control, relative spleen weight was significantly increased following exposure to 50 mg/L potassium dichromate on day 7. Compared to control, relative spleen weight was increased following exposure to 50 mg/L potassium dichromate for 21 d, but the effect was not significant.
Glaser et al. (1985)	Rats (male, Wistar TNO-W 74)	Short-term (28 d)	0.025, 0.050, 0.10 mg/m^3	Inhalation	Relative spleen weight	Compared to control, relative spleen weight increased for concentrations (≥0.050 mg/m^3).
		Subchronic (90 d)	0.025, 0.050, 0.10, 0.20 mg/m^3		Relative spleen weight	Compared to control, relative spleen weight increased for concentrations (≥0.050 mg/m^3).
Glaser et al. (1986)	Rats (male, Wistar TNO-W 74)	Chronic (18 mo exposure + 12 mo recovery)	Sodium dichromate – 0.025, 0.050, 0.10 mg/m^3	Inhalation	Spleen weight	No effect on spleen weight (relative or absolute not specified). Note: animals were evaluated only after the full 30-mo study duration (i.e., including the 12-mo recovery period).
Kim et al. (2004)	Rats (male, Sprague-Dawley)	Subchronic (13 wk)	0.2, 0.5, 1.25 mg/m^3	Inhalation	Relative spleen weight	No effect on relative spleen weight.
WBC counts (spleen cells)						
NTP (2005)	Mice (female, BC3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	Total WBCs Absolute and relative splenic phenotypic analysis	No effect on total WBC counts. No effect on splenic absolute or relative levels B cells (ig+), T cells (CD3+), T helper cells (CD4+/CD8), T cytotoxic cells (CD4−/CD8+), immature T cells (CD4+/CD8+), and monocytes (Mac-3+ cells).

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Total WBCs Absolute and relative splenic phenotypic analysis	No effect on total WBC counts. No effect on splenic absolute number of B cells (CD45+), T cells (CD5+), T helper cells (CD4+/CD5+), T cytotoxic cells (CD8+/CD5+), and NK cells (CD8+). Percent macrophages increased in low and high dose Cr(VI) groups, no other subpopulations affected.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Total WBCs Absolute and relative splenic phenotypic analysis	No effect on total WBC counts. No effect on splenic absolute and relative numbers of B cells (CD45+), T cells (CD4+/CD5+), T helper cells (CD4+), and T cytotoxic cells (CD8+/CD5+). Absolute number of macrophages (HIS36+) increased at low dose. Increased NK cells (~40% change, single dose level 172 mg/L) and macrophages (~35% change, single dose level 14.3 mg/L).

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Karaulov et al. (2019)	Rats (male, Wistar)	Chronic (135 d)	20/mg/kg-d	Drinking water	Total WBCs Absolute and relative splenic phenotypic analysis	No effect on WBC counts after 90 d exposure. Decreased absolute number splenic karyocytes and myeloid cells. Timepoint-specific effects on absolute number splenic plasma cells. Absolute number of CD3+ cells decreased on days 90 and 135. Relative number of CD3+ cells unaffected. Absolute number of CD4+ cells decreased on days 90 and 135. Relative number of CD4+ cells decreased on day 45. Absolute and relative number of CD8+ cells decreased on day 90. Absolute number of thymocytes decreased, but a dose-response was not evident. Increased absolute number bone marrow myeloid cells, lymphocytes, neutrophils, and karyocytes at the 135-d timepoint.
WBC (hematology)						
NTP (2005)	Mice (female, B6C3F1)	Short-term (28 d)	15.6, 31.3, 62.5, 125, 250 mg/L SDD	Drinking water	Hematology	No effect.
NTP (2006b)	Rats (female, Sprague-Dawley)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Hematology	No effect.
NTP (2006a)	Rats (female, F344)	Short-term (28 d)	14.3, 57.3, 172, 516 mg/L SDD	Drinking water	Hematology	No effect.
NTP (2007f)	Mice (male and female, B6C3F1)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD	Drinking water	Hematology	No effect, either sex.
	Mice (male, BALB/c)	Subchronic (3 mo)	62.5, 125 and 250 mg/L SDD			No effect.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
	Mice (male, am3-C57BL/6)	Subchronic (3 mo)	62.5, 125 and 250 mg/L SDD			No effect.
NTP (2007f)	Rats (male and female, F344/N)	Subchronic (3 mo)	62.5, 125, 250, 500, and 1,000 mg/L SDD	Drinking water	Hematology	Elevated WBC and lymphocytes in males and females, primarily in high dose groups (500 and 1,000 mg/L). Increased neutrophil and monocyte counts (at higher exposures in males and females) were reported to be an inflammatory response associated with lesions observed histopathologically (e.g., gastric lesions) and not believed to fully account for increased leukocyte numbers.
NTP (2008)	Rat (male and female F344/N)	2-yr (day 22, 6 and 12 mo)	14.3, 57.3, 172, or 516 mg/L SDD	Drinking water	Hematology	Increased WBC, neutrophils and eosinophils, sporadically with time and generally in higher dose groups.
	Mice (male and female, B6C3F1)	2-yr (day 22, 6 and 12 mo)	Male and female mice – 14.3, 57.3, 172, 516; Male mice – 14.3, 28.6, 85.7, or 257.4 mg/L SDD; Female mice – 14.3, 57.3, 172, or 516 mg/L SDD			Increased WBC, monocytes and basophils, but only on day 22 in the higher dose groups. Neutrophils increased on day 22 in top two dose groups and at 12 mo for top dose group. Lymphocytes increased for day 22 (14.3 mg/L–516 mg/L).
Shrivastava et al. (2005a)	Mice (Swiss)	Short-term & subchronic (3, 6, 9 wk)	14.8 mg/kg	Drinking water	Hematology	WBC decreased significantly at the 3-wk timepoint. Compared to week 0, the relative number of lymphocytes, granulocytes, and monocytes decreased significantly at all timepoints.
NTP (1996)	Mice (female, BALBC)	Subchronic (90 d)	15, 50, 100, 400 mg/L PDC	Oral diet	Hematology	No effect.

Reference	Species (strain)	Exposure design	Dose[a]	Exposure route	Endpoint	Results
Krim et al. (2013)	Rat (male, albino Wistar)	Short-term (30 d)	15 mg/kg PDC	Oral gavage	Hematology	No effect.
Glaser et al. (1986)	Rats (male, Wistar TNO-W 74)	Chronic (18 mo exposure + 12 mo recovery)	Sodium dichromate – 0.025, 0.050, 0.10 mg/m^3	Inhalation	Hematology	No effect on total WBC counts observed in all sodium dichromate exposure groups and for all timepoints (monthly for first 6 mo, every 3 mo thereafter).
Glaser et al. (1985)	Rats (male, Wistar TNO-W 74)	Short-term (28 d) & subchronic (90 d)	Short-term (0.025, 0.050, 0.10 mg/m^3) & Subchronic (0.025, 0.050, 0.10, 0.20 mg/m^3 CrO_3)	Inhalation	Hematology	No effect.
Glaser et al. (1990)	Rats (male, Wistar BOR:WISW)	Short-term (30 d) & subchronic (90 d)	0.050, 0.10, 0.20, 0.40 mg/m^3 CrO_3	Inhalation	Hematology	Elevated blood WBCs (0.050–0.40 mg/m^3) at 30 d and 90 d, effect lost after 30–d recovery period (following 90 d of exposure).
Kim et al. (2004)	Rats (male, Sprague-Dawley)	Subchronic (13 wk)	0.2, 0.5, 1.25 mg/m^3	Inhalation	Hematology	No effect on total WBC counts.

SRBC = sheep red blood cell; KLH = keyhole limpet hemocyanin; MLR = mixed lymphocyte reaction; NK = natural killer; ConA = concanavalin A; LPS = liposaccharide.

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.5.2. *Mechanistic studies relevant to immunotoxicity*

Studies initially tagged as "mechanistic" in the preliminary title and abstract screening were further screened and tagged "immune" if they reported any immunotoxicological outcome. A large body of mechanistic information (329 studies) exists to inform the potential immunotoxicity of Cr(VI). Within this evidence base, studies were tagged with immune-related categories if they reported relevant outcomes: "chronic inflammation" (39 studies) or "immune suppression" (34 studies) if relevant to cancer (reviewed in Section 3.2.3 of the toxicological review) and "cytokines" if a study reported cytokine measures (28 studies). In addition, studies tagged as "dermal" in "potentially relevant supplemental material" were rescreened to identify allergic sensitization (68 studies) or immune stimulation (61 studies) outcomes that also appeared to involve nondermal exposures to Cr(VI).

Subsequent prioritization of the immune-relevant studies that are more informative for chronic human exposure was conducted to identify mammalian studies of the immune system that focused on exposure routes more relevant to humans (oral drinking water and inhalation) for durations ranging from short-term to chronic. In addition, supporting information in vitro studies in human and animal primary lymphocytes and cell lines provided insight into biological plausibility and human relevance of the observed mechanisms. These prioritization criteria are as follows:

- Studies in humans with quantified oral or inhalation exposure to Cr(VI)
- Studies in experimental animals with quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation exposure to Cr(VI)
- Ex vivo assays performed on immune-relevant cells exposed in vivo
- In vitro studies in primary or immortalized mammalian cells derived from immune organ or tissues
- Mechanistic endpoints relevant to interpretations of immune health effects in humans and animals

Fourteen studies were identified that primarily reported evidence of Cr(VI)-induced alterations in cell differentiation or activation, effector cell function, cell proliferation, and cell-cell communication; these studies are summarized in Table C-37. In addition, 21 studies reporting cytokine measures were prioritized; these studies are summarized in Table C-38.

Table C-37. Mechanistic studies prioritized for informing potential Cr(VI)-induced immune toxicity

System	Route	Exposure[a]	Results	Comments	Reference
Effects on immune cell differentiation or activation					
Human monocyte derived dendritic cells (MoDC)	Human monocyte derived dendritic cells (MoDC)	25, 50, 75, 100 nM $K_2Cr_2O_7$, 48 h	↑ CD86 (dose dependence with significance at 100 nM); no change in CD83	100 nM $K_2Cr_2O_7$ considered nontoxic dose when cells were 75% viable	Toebak et al. (2006)
Mouse splenocytes from male and female C57BL/6	In vitro	0, 2, 5 µM $K_2Cr_2O_7$, 24 h	↓ activation of T cells stimulated with anti-CD3 and anti-CD28 (↓ CD69 at both doses and ↓ CD25 at 5 µM)	Significant ↓ CD4+ T cell viability at 5 µM, but not 2 µM	Dai et al. (2017b)
Effects on immune effector function of specific cell types					
Mouse RAW264.7 macrophages	In vitro	50 µg/mL welding fumes (250 µg/mL), 3 or 6 h	↓ phagocytosis following exposure to Ni WF (50 µg/mL) at 3 and 6 h timepoints, but not by other welding fumes	↓ number live cells and percentage viable cells for all welding fumes (250 µg/mL) at 24 h, but only Ni-Cu WF caused a reduction in live cells at 50 µg/mL; GMA-MS = Cr(VI) not detected; GMA-SS = 2,600 ± 120 µg/g Cr(VI); Ni-Cu WF = 422 ± 35 µg/g Cr(VI)	Badding et al. (2014)
Human primary lymphocytes	In vitro	$K_2Cr_2O_7$, 7 d	↓ IgG production at 0.1–10 µM w/80% reduction at 2 µm by lymphocytes stimulated with PWM	Effects correlated with Cr content in cells	Borella and Bargellini (1993)
Mouse (BALB/cABOM) primary peritoneal macrophages	In vitro	0.313–40 µM, 18 h (random migration) or 2.5 µM and 10 µM, 24h (phagocytosis) Na_2CrO_4	No changes in random migration (chemokinesis) up to 2.5 µM, but ↓ random migration in concentrations at ≥5 µM for 18 h in "stimulated" macrophages ↓ phagocytosis in resting macrophages at ≥2.5 µM, but not at lower concentrations	Viability not affected by 2.5 and 1.25 µM Cr(VI) during 28 d of exposure. 5 µM showed decreased viability after 48h. Chemokinesis studies carried out using stimulated macs, but stimuli not specified.	Christensen et al. (1992)

System	Route	Exposure[a]	Results	Comments	Reference
Mouse splenocytes from male and female C57BL/6	In vitro	0, 2, 5 µM $K_2Cr_2O_7$, 24 h	↓ production cell surface expression of CD107a (indicates degranulation by CD8+ T cells)	Significant ↓ CD8+ T cell viability at 5 µM and 2 µM	Dai et al. (2017b)
Bovine alveolar macrophages	In vitro	10–1000 µg/mL MMA-SS, MIG-SS, MMA-MS, MMA-CI, MIG-MS welding fumes, or K_2CrO_4, 18 h	↓ phagocytosis by 50% at 0.018 µg/mL K_2CrO_4 Welding fumes with higher Cr(VI) content decreased phagocytosis more potently than fumes containing less Cr(VI)	Inhibited phagocytosis at concentration ~10× less than the LC_{50} (i.e., 1.59 µg/mL)	Hooftman et al. (1988)
Human PMBCs from shoe, leather, and hide industry workers	Ex vivo/In vitro	PBMCs collected from exposed humans exposed Cr(VI) in vitro to 10^{-5} mg/L, 1 h	↓ percent phagocytosis, phagocytosis index and percent killing by PMNs collected from exposed workers and treated with Cr(VI) ex vivo		Mignini et al. (2009)
Effects on immune cell proliferation					
Human primary lymphocytes	In vitro	0.1, 1, 10, 100 µM Cr(VI), 48 h	↓ anti-CD3 proliferation at all concentrations ↓ anti-CD3/anti-CD28 proliferation at 10 and 100 µM	Cr(VI) test substance reported as CrO_3 as source, given as ion concentration. Resting and CD3 activated lymphocytes showed decreased viability (to ~80%) at 1 µM, with drop after 10 µM.	Akbar et al. (2011)
Human primary lymphocytes	In vitro	$K_2Cr_2O_7$, 4 d	↑ proliferation by PHA-stimulated cells at 10^{-8}–10^{-6} mol/L (4 d) ↓ proliferation by PHA-stimulated cells at 10^{-6}–2.5×10^{-6} mol/L (4 d)	Biphasic pattern; effects correlated with Cr content in cells	Borella and Bargellini (1993)
Mouse splenocytes from male and female C57BL/6	In vitro	0, 2, 5 µM $K_2Cr_2O_7$, 96 h	↓ proliferation by anti-CD3/anti-CD28 stimulated CD4+ T cells at 2 and 5 µM and CD8+ cells at 5 µM	Significant ↓ CD4+ T cell viability at 5 µM, but not 2 µM.	Dai et al. (2017b)

System	Route	Exposure[a]	Results	Comments	Reference
Rat splenocytes, Fischer 344 (splenocytes from Sprague-Dawley rats served as stimulator cells in the mixed lymphocyte cultures)	In vitro	LPS/ConA assay: 0.01–100 mg/mL K_2CrO_4, cells cultured "up to" 72 h Mixed lymphocyte response (MLR): In vivo/ex vivo – 100 mg/L for 10 wk followed by 0.1 mg/L for 5 d of culture In vitro – 0.1 mg/L K_2CrO_4, 5 d	↓ mitogen stimulated proliferation by T lymphocyte (ConA) and B lymphocytes (LPS) cultures 0.1 mg/L and lower, no effect at higher doses ↑ MLR in cells exposed in vivo and in vitro (no statistics) ↑ or no effect on MLR at 0.1 mg/L in vitro (statistics provided for only one of two experiments)		Snyder and Valle (1991)
Cross-sectional study in Italy of 20 exposed and 24 unexposed workers	Ex vivo/In vitro	PBMCs collected from exposed workers treated with additional Cr(VI) ex vivo	No effect on ConA-stimulated proliferation in PBMCs collected from unexposed workers in the presence of Cr(VI) administered ex vivo No effect on ConA-stimulated proliferation in PBMCs isolated from exposed workers and treated with Cr(VI) ex vivo Nonsignificant biphasic response in Con-A stimulated proliferation in PBMCs collected from unexposed HLA-B8-DR3-negative subjects treated Cr(VI) ex vivo No effect on Con-A stimulated proliferation in PBMCs collected from exposed HLA-B8-DR3-positive subjects treated Cr(VI) ex vivo The effect of Cr(VI) exposure ex vivo on proliferation of lymphocytes collected from HLA-B8-DR3-negative and -positive subjects stimulated by ConA was investigated, but comparisons between exposed and unexposed subjects in the presence and absence of Cr(VI) were not reported. ↓ ConA-stimulated proliferation in PBMCs collected from exposed HLA-B8-DR3-negative group treated with Cr(VI) in vitro in the absence of the monocytic/macrophage component.		Mignini et al. (2004)

System	Route	Exposure[a]	Results	Comments	Reference
			The effect of Cr(VI) exposure ex vivo on proliferation of lymphocytes collected from HLA-B8-DR3-negative subjects stimulated by ConA in the absence of the monocytic/macrophagic component was investigated, but comparisons between exposed and unexposed subjects in the presence and absence of Cr(VI) were not reported.		
Cross-sectional study in Italy of 40 exposed tannery workers and 44 controls	Ex vivo/In vitro	Lymphocytes collected from exposed workers treated with additional Cr(VI) ex vivo	↑ ConA- and PHA-stimulated proliferation in PBMCs collected from workers exposed to high concentration of Cr(VI) (Group B) ex vivo No effect on LPS-stimulated proliferation in PBMCs collected from unexposed workers treated with low concentration of Cr(VI) ex vivo ↑ ConA- and PHA-stimulated proliferation in PBMCs collected from unexposed workers treated with 10^{-5} mg/mL Cr(VI) in vitro ↓ ConA- and PHA-stimulated proliferation in PBMCs collected from unexposed workers treated with 10^{-2} mg/mL Cr(VI) in vitro ↓ LPS-stimulated proliferation in PBMCs collected from unexposed workers treated with 10^{-2} mg/mL or 10^{-5} mg/mL Cr(VI) in vitro The effect of Cr(VI) exposure in vitro on proliferation of lymphocytes collected from exposed workers stimulated by ConA, PHA, and LPS was investigated, but comparisons between exposed and unexposed workers in the presence and absence of Cr(VI) were not reported.		Mignini et al. (2009)
Effects on communication between immune cells					
Human peripheral blood mononuclear	Ex vivo/In vitro	PBMCs collected from exposed humans exposed to Cr(VI) in vitro to 10^{-5} mg/L, 1 h	No change in ICAM-1, VCAM, and ELAM-1E-selectin levels		Mignini et al. (2009)

System	Route	Exposure[a]	Results	Comments	Reference
cells from shoe, leather, and hide industry workers					
Human peripheral blood lymphocytes	In vitro	588 µg/mL, 0.5 h	No effect on E-rosetting	Data not shown	Bravo et al. (1990)
Cross-sectional study in China of 56 workers exposed to potassium dichromate and 50 unexposed individuals living 20 km from factory	In vivo	14.4 ± 18.1 µg/m^3	C3 (g/L) – Exposed: 1.20 ± 0.24; Unexposed: 0.91 ± 0.13 C4 (g/L) – Exposed: 0.32 ± 0.07; Unexposed: 0.23 ± 0.05		Qian et al. (2013), low
Mouse splenic T cells	In vitro	2 or 5 µM, 24 h	Decreased anti-CD3/CD28-induced secretion of IL-2, IL-4, and IL-10 in splenocytes treated with 2 or 5 µM Cr(VI)		Dai et al. (2017b)

See Table C-38 for effects on cytokine levels following Cr(VI) exposure.

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Table C-38. Summary of cytokine levels measured following Cr(VI) exposure

Reference	Study design	Cytokines
Cytokines measured in blood, serum, and plasma		
Kuo and Wu (2002)	Blood collected from Cr(VI)-exposed workers	↑ IL-6 and IL-8 ↓ TNF-α (NS) No effect on IL-2, IL-4, IL-10, or IFN-γ
Sazakli et al. (2014)	Blood collected from people exposed to Cr(VI) in drinking water	↑ IL-12, dose dependent No effect on IL-6, IL-8, or IL-10
Snyder et al. (1996)	Blood collected from people exposed to Cr(VI) environmentally in Hudson County, New Jersey	↓ IL-6
Qian et al. (2013)	Serum collected from Cr(VI)-exposed workers	↓ IL-6, IL-10, IL-17A, IFN-γ, and IFN-γ/IL-4 No effect on IL-2 or TNF-α
Mignini et al. (2009)	Plasma collected from Cr(VI)-exposed workers	↑ IL-2 and IL-6 ↓ IL-12 No change in IL-1β, IL-4, TNF-α, or IFN-γ
Mitrov et al. (2014)	Plasma collected from rats exposed to Cr(VI)	↑ IL-1β and TNF-α
Jin et al. (2016)	Serum from LPS-stimulated mice exposed to Cr(VI)	↑ IL-6 and TNF-α
Thompson et al. (2012c)	Plasma from Cr(VI)-exposed rats	↓ IL-12 and CXCL10 (IP-10) No effect on IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-17, IL-18, TNF-α, IFN-γ, CCL5, CXCL1, Eotaxin, G-CSF, GM-CSF, MCP-1, or MIP-1α
Thompson et al. (2011b)	Plasma from Cr(VI)-exposed mice	"Few cytokines exhibited significant changes" but no specific data; tested IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-α, IFN-γ, CXCL1, CCL5, CXCL10, G-CSF, GM-CSF, MCP-1, and MIP-1α
Cytokines measured in BALF		
Cohen et al. (2010)	BALF from Cr(VI)-exposed rats	No effect on TNF-α, MIP-2, MCP-1, IL-6, IL-10, or IL-12
Cytokines secreted by MoDC		
Reutter et al. (1997)	Human MoDC exposed to Cr(VI) in vitro	↑ IL-1β
Toebak et al. (2006)	Human MoDC exposed to Cr(VI) in vitro	No effect on IL-8, CCL5, CCL17, CCL18, CCL20, and CCL22
Cytokines secretion by stimulated PBMCs, lymphocytes, splenocytes, and macrophages		
Akbar et al. (2011)	Stimulated (anti-CD3 or anti-CD3/anti-CD28) primary human lymphocytes	↓ IL-2 and IFN-γ
Ban et al. (2010)	ConA-stimulated lymph nodes collected from mice	↓ IL-4 (NS), IL-5 (NS), and IL-13 (NS) ↑ IFN-γ (NS)

Reference	Study design	Cytokines
Cohen et al. (1998)	Pulmonary macrophages collected from Cr(VI) exposed rats, stimulated with LPS ex vivo	↓ IL-1, TNF-α, and IL-6 (NS)
Dai et al. (2017b)	Stimulated (anti-CD3/anti-CD28) splenic lymphocytes collected from Cr(VI)-exposed mice	↓ IL-2, IL-4, and IL-10
Katiyar et al. (2008)	PHA and LPS-stimulated PBMCs collected from exposed workers	↑ PHA-stimulated IL-2 (NS) production ↑ PHA-stimulated IL-6 production No effect on LPS-stimulated TNF-α production
Karaulov et al. (2019)	Mitogen-stimulated (ConA) splenocytes collected from rats	↑ IL-4 and IL-10 (NS) ↓ IL-6 No effect on INF-γ
Cytokines secretion by unstimulated PBMCs		
Lindemann et al. (2008)	PBMCs collected from chromium sensitized workers and exposed to Cr(VI) in vitro	↑ IL-4, IL-10, and IFN-γ No effect on IL-2 or IL-12
Cytokines secretion by peritoneal macrophages		
Christensen et al. (1992)	Newcastle disease virus infected mouse peritoneal macrophages exposed to Cr(VI) in vitro	↓ IFN-α/β
Jin et al. (2016)	Mouse peritoneal macrophages	↑ IL-1α, IL-1β, IL-6, and TNF-α
Cytokines secretion by cell cultures		
Adam et al. (2017)	TPA stimulated THP-1 cells	↑ IL-1β
Badding et al. (2014)	RAW264.7 cells exposed to Cr(VI)	↑ TNF-α (NS) No effect on IL-6 or IL-1β
Ban et al. (2010)	Spleens collected from mice	↓ IL-4, IL-5, IL-13, and IFN-γ
Jin et al. (2016)	Serum from LPS-stimulated RAW264.7 cells exposed to Cr(VI)	↑ IL-6 and TNF-α
Cytokines secreted by HaCaT cultures		
Wang et al. (2010a)	Human HaCaT cells treated with Cr(VI)	↑ IL-1α and TNF-α
Lee et al. (2014)	Human HaCaT cells treated with Cr(VI)	↑ IL-1α and TNF-α
Cytokines secreted by duodenum		
Thompson et al. (2012c)	Duodenum from Cr(VI)-exposed rats	↑ IL-1α ↓ IL-4 ↑ IL-6 (60 mg/L SDD) No effect on IL-1β, IL-2, IL-5, IL-10, IL-12, IL-13, IL-17, IL-18, TNF-α, IFN-γ, CCL5, CXCL1, CXCL10, Eotaxin, G-CSF, GM-CSF, MCP-1, or MIP-1α

Reference	Study design	Cytokines
Thompson et al. (2011b)	Duodenum from Cr(VI)-exposed mice	↓ IL-1β and TNF-α, dose-dependent trends For all other cytokines, no specific data were reported, other than "Several cytokines were significantly altered—generally beginning at 60 mg/L SDD"; tested IL-1α, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, IFN-γ, CXCL1, CCL5, CXCL10, G-CSF, GM-CSF, MCP-1, and MIP-1α
Cytokines secreted by oral mucosa		
Thompson et al. (2012c)	Oral mucosa from Cr(VI)-exposed rats	No effect on IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-17, IL-18, TNF-α, IFN-γ, CCL5, CXCL1, CXCL10, Eotaxin, G-CSF, GM-CSF, MCP-1, or MIP-1α
Thompson et al. (2011b)	Oral mucosa from Cr(VI)-exposed mice	"Significant differences from control animals were generally limited to the highest treatment dose," but no specific data; tested IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-α, IFN-γ, CXCL1, CCL5, CXCL10, G-CSF, GM-CSF, MCP-1, and MIP-1α

NS = not statistically significant, BALF = bronchoalveolar lavage fluid, ConA = concanavalin A; HaCaT cells = immortalized human keratinocytes; LPS = lipopolysaccharide; MoDC = monocyte-derived dendritic cell; PBMC = peripheral blood mononuclear cell; TPA = 12-O-tetradecanoylphorbol-13-acetate.

C.2.6. Male Reproductive Effects

C.2.6.1. *Mechanistic studies relevant to male reproductive toxicity*

Mechanistic evidence indicating the biological pathways involved in male reproductive toxicity following Cr(VI) exposure is summarized in Table C-39. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "reproductive" if they involved reproductive tissues or cells; 49 studies were identified. Studies were prioritized for consideration in the synthesis of mechanistic evidence for male reproductive effects if they were conducted in mammalian species:

- Studies in humans with quantified oral or inhalation exposure to Cr(VI)
- Studies in experimental animals with quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation, or injection exposure to Cr(VI)
- In vitro studies in primary or immortalized mammalian cells derived from male reproductive tissues (i.e., Leydig, Sertoli, male germ cells)
- Mechanistic endpoints relevant to interpretations of male reproductive health effects in humans

A total of 25 reproductive studies were identified to include in the male reproductive mechanistic synthesis. Several of the included oral exposure animal toxicological studies in that section were identified as also reporting mechanistically relevant data, as well as i.p. injection studies that did not meet PECO criteria but were reviewed as being potentially relevant for

mechanistic analysis. In vitro studies that evaluated Leydig, Sertoli, or male germ cells were also considered for mechanistic evidence.

Table C-39. Mechanistic studies prioritized for informing potential Cr(VI)-induced male reproductive toxicity

System	Route	Exposure[a]	Results	Reference
Oxidative stress				
Mouse, male (strain not reported)	Oral (not specified)	5 mg/kg-d $K_2Cr_2O_7$, 30- or 60-d	↓ serum antioxidant enzymes (CAT, SOD, GPx) ↑ serum MDA	Rasool et al. (2014)
Rat, Sprague-Dawley, male	Oral (inferred to be gavage)	10 mg/kg-d [form of Cr(VI) not reported], 13-d	↓ testicular and epididymal CAT, SOD, GST, glutathione ↑ testicular and epididymal MDA	Kim et al. (2012)
Monkey, bonnet, male	Oral (drinking water)	100, 200, 400 mg/L $K_2Cr_2O_7$, 180-d	↓ testicular SOD, CAT, GPx, GR, G-6-PDH, γ-GT, and vitamins A, C, E ↑ testicular GST and reduced glutathione ↑ testicular H_2O_2 and OH–	Aruldhas et al. (2005)
Monkey, bonnet, male	Oral (drinking water)	50, 100, 200, 400 mg/L $K_2Cr_2O_7$, 6-mo	↓ SOD, and GDH in seminal plasma and sperm ↑ H_2O_2 in seminal plasma and sperm	Subramanian et al. (2006)
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14 or GD 15-21; F1 animals evaluated on PND 30	↑ lipid peroxidation, H_2O_2, OH– in Sertoli cells ↓ SOD, CAT, GPx, GSR, GST, and GSH in Sertoli cells	Shobana et al. (2020)
Rat, Wistar, male	Oral (gavage)	3.5 mg/kg-d Cr(VI), 8-wk	↑ testicular MDA, GSSG, NO ↓ testicular GSH, SOD, CAT, carnitine Mitigated by cotreatment with antioxidant	Bashandy et al. (2021)
Mouse, Swiss albino, male	i.p. injection	1 mg/kg CrO_3, single injection	↓ testicular SOD, CAT, peroxidase ↑ testicular lipid peroxidation potential	Acharya et al. (2006)
Rat, Wistar, male	i.p. injection	1–2 mg/kg-d $K_2Cr_2O_7$, 15-d	↓ testicular CAT ↑ testicular metallothionein ↑ testicular MDA, O_2–	Marouani et al. (2015a)
Rat, Wistar, male	i.p. injection	10 mg/kg-d $Na_2Cr_2O_7$, 10-d	↓ testicular SOD, CAT, GPx ↑ testicular MDA Mitigated by cotreatment with antioxidant	Hfaiedh et al. (2014)
Rat, Wistar, male	i.p. injection	2mg/kg-d, $K_2Cr_2O_7$, 21-d	↑ testicular indicators of lipid peroxidation (TBARS and H_2O_2) with significant effect decrease with antioxidant pretreatment ↓ testicular GSH and activity antioxidant, phosphatase, and aminotransferase mitigated by antioxidant pretreatment	El-Demerdash et al. (2019)

System	Route	Exposure[a]	Results	Reference
Mouse, Swiss albino, male	i.p. injection	10 mg/kg CrO_3, single dose with evaluation 5,6,7, and 8 wk after treatment (control 5 wk only)	↑ testicular indicators of lipid peroxidation (TBARS)	Acharya et al. (2004b)
Cultured mouse Leydig cells (TM3), Sertoli cells (TM4), and spermatogonial stem cells	In vitro	3.125–50 µM Cr(VI)	↑ ROS after 4 h ↓ mRNA expression of antioxidant enzymes (Sod, Cat, Gpx1, Gsta4) after 24 h ↑ mRNA expression of Gsta1 at all doses in somatic cells and low doses in germ cells after 24 h	Das et al. (2015)
Cultured mouse spermatogonial stem cells (C18-4)	In vitro	5–75 µM Cr(VI)	↑ ROS after 24 h	Lv et al. (2018)
Cell cycle regulation and apoptosis in somatic and germ cells				
Rat, Wistar, male	Oral (gavage)	3.5 mg/kg-d Cr(VI), 8-wk	↑ p53 expression in spermatogenic cells ↓ DNA content of spermatogenic cells Mitigated by cotreatment with antioxidant (melatonin)	Bashandy et al. (2021)
Rat, Wistar, male	i.p. injection	1–2 mg/kg-d $K_2Cr_2O_7$, 15-d	↑ BAX and DNA fragments in testis	Marouani et al. (2015a)
Mouse, ICR, male	i.p. injection	16.2 mg/kg-d Cr(VI) , 1-wk	↑ BAX and DNA fragments (γ-H2AX) in testis Qualitative histopathology showing degenerative changes in seminiferous tubules and germ cells; Cr(VI) treated males also had decreased litter sizes Mitigated by cotreatment with antioxidant (melatonin)	Lv et al. (2018)
Rat, Wistar, male	i.p. injection	2mg/kg-d, $K_2Cr_2O_7$, 21-d	Qualitative histopathology showed degeneration of spermatogenic cells in testes and moderate atrophy	El-Demerdash et al. (2019)
Mouse, Swiss albino, male	i.p. injection	10 mg/kg CrO_3, single dose with evaluation 5,6,7, and 8 wk after treatment (control 5 wk only)	↓ sperm count at all timepoints ↑ sperm abnormalities at all timepoints	Acharya et al. (2004b)
Rabbit, ITRC colony, male	i.p. injection	2mg/kg-d, $K_2Cr_2O_7$, evaluation at 3 and 6 wk 72 h after last injection	Qualitative histological analysis, progressive testicular interstitial edema, no spermatocytes in seminiferous tubules	Behari et al. (1978)

System	Route	Exposure[a]	Results	Reference
Cultured mouse Leydig cells (TM3), Sertoli cells (TM4), and spermatogonial stem cells	In vitro	3.125–50 µM Cr(VI)	↑ TUNEL-positive cells ↓ mitochondrial membrane potential ↑ biomarkers of intrinsic apoptosis (e.g., cleavage of caspases 3 and 9, ↓ BCL2/BAX ratio) ↓ biomarkers of extrinsic apoptosis (Fas, caspase 8) in somatic cells Mitigated by cotreatment with antioxidant (N-acetyl-L-cysteine)	Das et al. (2015)
Cultured mouse spermatogonial stem cells (C18-4)	In vitro	5–75 µM Cr(VI)	↑ TUNEL-positive cells ↑ DNA fragments (γ-H2AX) ↑ chromatin condensation ↑ biomarkers of intrinsic apoptosis (e.g., cleavage of caspases 3 and 9, ↑ BAX, ↓ BCL-2) Mitigated by cotreatment with antioxidant (melatonin) No effect on biomarkers of extrinsic apoptosis (caspase 8) (after 24 h)	Lv et al. (2018)
Primary coculture of rat (Wistar) Sertoli cells and germ cells	In vitro	0.5, 1, 10, 100 µg/L Cr(VI)	↓ late spermatocytes and round spermatids ↑ cells with alterations in meiotic prophase ↑ asynapsis and fragmented synaptonemal complexes	Geoffroy-Siraudin et al. (2010)
Altered steroidogenesis and effects on the hypothalamic-pituitary-gonadal axis				
Rat, Sprague-Dawley F1, male	Oral (gavage)	3–12 mg/kg-d Cr(VI), GD 12–21; F1 animals evaluated on PND 21	Biphasic effect on testosterone (↑ at low dose, ↓ at high dose) Biphasic mRNA and protein expression of LHR (↑ at low dose, ↓ at high dose) ↑ low dose expression of FSHR (mRNA only), SCARB1, LIF, PDGFA (no change at high dose) ↓ high dose expression of IGF1, CYP17A1 (protein only), HSD17B3 (mRNA only), StAR (protein only, not significant) No change in mRNA or protein expression of CYP11A1, insulin-like-3 hormone, NR5A1, SOX9, AMH, DHH	Zheng et al. (2018)
Rat, Wistar, male	Oral (gavage)	3.5 mg/kg-d Cr(VI)	↓ plasma testosterone, LH ↑ FSH Mitigated by cotreatment with antioxidant	Bashandy et al. (2021)
Rabbit, New Zealand white, male	Oral (gavage)	3.6 mg-kg/d Cr(VI), 10-wk	↓ plasma testosterone	Yousef et al. (2006)

System	Route	Exposure[a]	Results	Reference
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14, F1 animals evaluated on PND 60	↓ serum testosterone, prolactin ↑ serum estrogen, LH, FSH ↓ protein expression of AR, LHR, PRLR, and ERα in Leydig cells ↑ protein expression of ERβ in Leydig cells ↓ protein expression of StAR, CYP11A1, 3βHSD, CYP17A1, 17βHSD, 5α reductase, aromatase in Leydig cells ↓ specific activities of 3βHSD and 17βHSD in Leydig cells ↓ protein expression of AR, FSHR, ERα, ERβ, and 5α reductase in Sertoli cells	Navin et al. (2021)
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14 or GD 15–21, F1 animals evaluated on PND 30	↓ serum testosterone, prolactin ↑ serum estrogen, LH, FSH ↓ mRNA and protein expression of AR and FSHR in Sertoli cells ↓ protein expression of transcriptional regulators of Fshr (USF-1, USF-2, GATA-1, c-jun, c-fos) and Ar (Sp-1, ARA54, CBP, SRC-1) in Sertoli cells ↑ protein expression of cyclin D1 and p53 (inhibitors of Ar expression) ↓ mRNA expression of Ar and Fshr in Sertoli cells	Shobana et al. (2020)
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14; F1 animals evaluated on PND 120	↓ testosterone in serum and testicular interstitial fluid ↓ serum FSH and LH ↓ gene and protein expression of AR and FSHR in Sertoli cells	Kumar et al. (2017)
Rat, Wistar, male	Oral (drinking water)	$K_2Cr_2O_7$, 500 mg/L in drinking water [estimated to be 73.05 mg/kg-d Cr(VI)], 30-d	↓ serum prolactin (60% of control) No change in serum LH accumulation of Cr in target tissues (pituitary, hypothalamus, liver). 30% reduction in water intake and 11.6% reduction in BW. Study also includes in vitro study in primary anterior pituitary cells (see later in table).	Quinteros et al. (2007)

System	Route	Exposure[a]	Results	Reference
Rat, Wistar, male	Oral (drinking water)	$K_2Cr_2O_7$, 200 mg/L in drinking water [estimated to be 11.6 mg/kg-d Cr(VI)], 30-d	↑ Lipid peroxidation in pituitary and hypothalamus; no change in liver. ↑ SOD activity in pituitary only ↑ CAT activity in liver only ↑ glutathione reductase activity in hypothalamus only No changes in GPx activity ↑ in HO-1 mRNA expression in hypothalamus and pituitary only ↑ MT-3 in hypothalamus and MT-1 in anterior pituitary Accumulation of Cr in target tissues (pituitary, hypothalamus, liver). No significant change in water consumption or BW. Did not measure if oxidative effects impacted downstream hormones.	Nudler et al. (2009)
Rat, Wistar, male	i.p. injection	2mg/kg-d, $K_2Cr_2O_7$, 21-d	↓ serum testosterone ↑ serum FSH Mitigated by cotreatment with antioxidant	El-Demerdash et al. (2019)
Rat, Wistar, male	i.p. injection	1–2 mg/kg-d $K_2Cr_2O_7$, 15-d	↓ serum testosterone and LH ↑ serum FSH	Marouani et al. (2012)
Rat, Wistar, male	i.p. injection	10 mg/kg-d $Na_2Cr_2O_7$, 10-d	↓ serum testosterone Mitigated by cotreatment with antioxidant	Hfaiedh et al. (2014)
Cultured mouse Leydig cells (TM3) and Sertoli cells (TM4)	In vitro	6.25–25 µM Cr(VI)	↓ testosterone secretion by TM3 cells ↓ mRNA expression of steroidogenic enzymes (Cyp11a1, Hsd3b1, Cyp17a1, Cyp19a1) in TM3 cells ↓ mRNA expression of Fshr, Ar in TM4 cells ↑ mRNA expression of Star in TM3 cells	Das et al. (2015)
Primary anterior pituitary cells from male Wistar rat	In vitro	$K_2Cr_2O_7$, 0.1–10 µM up to 72 h	↓ prolactin at 0.1 µM at 72 h, 1 and 10 µM at 48 h and72 h No change in LH ↑ Caspase 3 and 10 µM [cytotoxic, prevented pretreatment with an antioxidant (NAC)] Same study that showed decreased prolactin and no change in LH in vivo (see earlier in table). Cell viability significantly reduced after 24 h at 10 µM (~65%); 1 µM after 72 h.	Quinteros et al. (2007)
Primary anterior pituitary cells from male Wistar rat	In vitro	$K_2Cr_2O_7$, 10 µM for 72 h	Mechanisms involved in apoptosis include decreased CAT, GPx, increased p53 and Bax Data not fully reviewed because cytotoxic concentration was used, as demonstrated in Quinteros et al. (2007)	Quinteros et al. (2008)
Effects on Sertoli cells and the blood-testis barrier				
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14 or GD 15–21, F1 animals	↓ secretory products of Sertoli cells (inhibin, androgen binding protein, transferrin, lactate, pyruvate, retinoic acid)	Shobana et al. (2020)

System	Route	Exposure[a]	Results	Reference
		evaluated on PND 30	↓ mRNA and protein expression of tight junction proteins (claudin-11 and occludin) in Sertoli cells	
Rat, Wistar F1, male	Oral (drinking water)	50–200 mg/L $K_2Cr_2O_7$, GD 9–14, F1 animals evaluated on PND 120	↓ mRNA and protein expression of tight junction proteins (claudin-11 and occludin) in Sertoli cells	Kumar et al. (2017)
Rat, Druckrey, male	i.p. injection	2 mg/kg-d $K_2Cr_2O_7$, 15-d	Leakage of Sertoli cell tight junctions and adverse effects on late-stage spermatids	Murthy et al. (1991)[b]
Mouse Sertoli cells (TM3)	In vitro	6.25–25 µM Cr(VI)	↓ mRNA expression of tight junction signaling molecules (tight junction protein 1, vimentin, occludin)	Das et al. (2015)
Primary coculture of rat (Sprague-Dawley) Sertoli cells and germ cells	In vitro	10 µg/L Cr(VI)	↓ gap junction signaling and delocalization of connexin 43 from the membrane to the cytoplasm after 8 d; no effects on adherin or tight junction proteins (claudin-11 and N-cadherin) ↑ transepithelial resistance	Carette et al. (2013)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.
[b]Note: Scientific integrity is a concern due to evidence of self-plagiarism within this research group.

C.2.7. Female Reproductive Effects

C.2.7.1. *Mechanistic studies relevant to female reproductive toxicity*

Mechanistic evidence indicating the biological pathways involved in female reproductive toxicity following Cr(VI) exposure is summarized in Table C-40. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "reproductive" if they involved reproductive tissues or cells. Studies were prioritized for consideration in the synthesis of mechanistic evidence for female reproductive effects if they were conducted in mammalian species:

- Studies in humans with quantified oral or inhalation exposure to Cr(VI)
- Studies in experimental animals with quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation, or injection exposure to Cr(VI)
- In vitro studies in primary or immortalized mammalian cells derived from female reproductive tissues (e.g., thecal and granulosa cells)
- Mechanistic endpoints relevant to interpretations of female reproductive health effects in humans

A total of 12 reproductive studies were identified to include in the female reproductive mechanistic synthesis. Several of the included oral exposure animal toxicological studies in that section were identified as also reporting mechanistically relevant data, as well as i.p. injection studies that did not meet PECO criteria but were reviewed as being potentially relevant for mechanistic analysis. In vitro studies conducted in relevant cell types, such as thecal and granulosa cells, were also considered for mechanistic evidence.

Table C-40. Mechanistic studies prioritized for informing potential Cr(VI)-induced female reproductive toxicity

System	Route	Exposure[a]	Results	Reference
Altered steroidogenesis				
Rat, lactating Sprague-Dawley	Oral (drinking water)	50, 100, 200 mg/L $K_2Cr_2O_7$, PNDs 1–21; F1 animals evaluated on PNDs 25, 45, 65	For F1: ↓ FSH receptor gene expression in ovary ↓ E2, T, P4 (dose dependent, in hormone section of animal tox) ↑ FSH (not dose dependent) Mitigated by cotreatment with vitamin C	Stanley et al. (2013)
Rat, lactating Sprague-Dawley	Oral (drinking water)	5, 10, 25, 50, 100, and 200 mg/L $K_2Cr_2O_7$, PNDs 1–21; F1 animals evaluated on PNDs 25, 45, 65	For F1: ↓ E2, T, P4 (50 mg/L, PND 25) ↑ time to puberty (50 mg/L) Cotreatment with estradiol restored the ovarian protein expression of several antioxidant enzymes (Gpx1, catalase, Prdx3, and Txn2)	Stanley et al. (2014)
Rat, lactating Sprague-Dawley	Oral (drinking water)	50 mg/L $K_2Cr_2O_7$, PNDs 1–21; F1 animals evaluated on PND 25	For F1: ↓ ovarian expression of steroidogenic acute regulator protein (StAR), 3β-hydroxysteroid dehydrogenase, and aromatase ↑ genes involved in the metabolic clearance of estradiol (Cyp1a1, Cyp1b1, UDP-glucuronosyltransferases, Sult1a1, NAD(P)H quinone oxidoreductase 1) Mitigated by cotreatment with resveratrol	Banu et al. (2016)
Rat, Wistar, female, GDs 9–21; female pups PND 65	Oral (drinking water)	Group 1: 50, 100, 200, and 400 mg/L $K_2Cr_2O_7$, GDs 9–21; F1 animals evaluated on PND 0 Group 2: 200 mg/L $K_2Cr_2O_7$, GDs 9–PND 65; F1 animals evaluated on PNDs 0, 3, 7, 18, 45, 65	For F1: ↓ serum progesterone, estradiol, testosterone, prolactin, growth hormone ↑ serum LH and FSH	Samuel et al. (2012)
Primary rat granulosa cells	In vitro	10 µM $K_2Cr_2O_7$, 12 or 24 h	↓ FSH receptor protein expression Pretreatment with vitamin C mitigated	Stanley et al. (2013)

System	Route	Exposure[a]	Results	Reference
Primary Sprague-Dawley rat granulosa cells (immature rats, 23–25 d old); immortalized rat granulosa cells	In vitro	10 µM $K_2Cr_2O_7$, 12 or 24 h	↓ Erβ and FSH receptor gene expression Pretreatment with vitamin C mitigated	Stanley et al. (2011)
Immortalized rat granulosa cells	In vitro	12.5 µM $K_2Cr_2O_7$, 12 and 24 h	↓ gene expression of FSH receptor, LH receptor, Erα, Erβ, StAR, SF-1 (24 h only), and 17β-hydroxysteroid dehydrogenases ↓ cell proliferation 50%	Banu et al. (2008)
Oxidative stress				
Rat, lactating Sprague-Dawley	Oral (drinking water)	50, 100, 200 mg/L $K_2Cr_2O_7$ (2013) 5, 10, 25, 50, 100, and 200 mg/L $K_2Cr_2O_7$ (2014) PND 1–21; F1 animals evaluated on PND 25 (2014) or PNDs 25, 45, 65 (2013)	For F1: ↓ ovarian SOD, catalase, glutathione peroxidase, and glutathione reductase activity (100 mg/L 2013; 50 mg/L, 2014) ↓ ovarian protein expression of GPx1, Txn2, Prdx3, CAT expression (2014) ↑ ovarian protein expression of glutathione-S-transferase (2013) ↑ ovarian LPO, H_2O_2 (dose dependent 2013; 50 mg/L, 2014) Mitigated by cotreatment with VitC (2013) or EDA (2014)	Stanley et al. (2014; 2013)
Rat, strain not reported (assume Sprague-Dawley)	Oral (drinking water)	25 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5; F1 animals evaluated on PND 1	For F1: ↑ p53/SOD2 protein colocalization in the ovary; p53 has been demonstrated to reduce SOD2 antioxidant activity	Sivakumar et al. (2014)
Rat, lactating Sprague-Dawley	Oral (drinking water)	50 mg/L $K_2Cr_2O_7$, PND 1–21; F1 animals evaluated on PND 25	For F1: ↓ ovarian protein expression of catalase, glutathione peroxidase (GPx1), peroxiredoxin (PRDX) 3, and thioredoxin (TXN). ↑ ovarian protein expression of SOD1 and SOD2 ↑ oxidative damage in ovary (LPO, H_2O_2) Oxidative damage mitigated by cotreatment with resveratrol	Banu et al. (2016)
Mouse, Swiss albino, female	Oral (gavage)	5 and 10 mg $K_2Cr_2O_7$/kg, 30-d	↑ Lipid peroxidation in ovary (MDA) ↓ ovarian SOD and CAT activity, and ↓ levels of vitamin C and glutathione (dose-dependent) Mitigated by cotreatment with vitamin E	Rao et al. (2009)

System	Route	Exposure[a]	Results	Reference
Rat, Wistar, female, GD 9–21; female pups PND 65	Oral (drinking water)	Group 1: 50, 100, 200, and 400 mg/L $K_2Cr_2O_7$, GDs 9–21; F1 animals evaluated on PND 0 Group 2: 200 mg/L $K_2Cr_2O_7$, GD 9–PND 65; F1 animals evaluated on PNDs 0, 3, 7, 18, 45, 65	For F1: ↓ ovarian SOD, CAT, GPx activity ↓ ovarian ascorbic acid ↑ ovarian LPO and H_2O_2 at all ages	Samuel et al. (2012)
Rat, Wistar, female	i.p. injection	1 and 2 mg $K_2Cr_2O_7$/kg, 15-d	↑ Superoxide anion in uterus (as measured by cytochrome C and iodonitrotetrazolium reduction) ↓ CAT activity in uterus ↑ lipid peroxidation in uterus ↓ metallothionine All dose dependent	Marouani et al. (2015b)
Primary rat granulosa and theca cells; immortalized rat granulosa cells	In vitro	10 µM $K_2Cr_2O_7$, 12 h and 24 h	↓ intracellular vitamin C levels ↓ SOD1, SOD2, CAT, GLRX1, GSTM1, GSTM2, GSTA, GR, TXN1, TXN2, TXNRD2, and PRDX3 gene expression (time dependent) ↓ GR, GST, GPx, SOD, CAT activity ↑ H_2O_2, LPO Immortalized GCs showed similar effect. Cell viability not reported. Vitamin C failed to mitigate CrVI effects on GSTM1, GSTM2, TXN1, and TXN2 in TCs	Stanley et al. (2013)
Apoptosis				
Rat, lactating Sprague-Dawley	Oral (drinking water)	50 mg/L $K_2Cr_2O_7$, PNDs 1–21; F1 animals evaluated on PND 25	For F1: ↑ follicular cell apoptosis (TUNEL) ↑ ovarian protein expression of cytochrome C, caspase-3 ↓ ovarian protein expression of Bcl-2, Bcl-XL, HIF-1α Mitigated by cotreatment with resveratrol	Banu et al. (2016)
Rat, pregnant Sprague-Dawley	Oral (drinking water)	25 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5; F1 animals evaluated on GDs 15.5 and 17.5, PNDs 1, 4, 25	For F1: ↑ germ cell apoptosis (TUNEL)	Banu et al. (2015)

System	Route	Exposure[a]	Results	Reference
Rat, lactating Sprague-Dawley	Oral (drinking water)	5, 10, 25, 50, 100, and 200 mg/L $K_2Cr_2O_7$ (2014) 50, 100, 200 mg/L $K_2Cr_2O_7$ (2013) PNDs 1–21; F1 animals evaluated on PND 25 (2014) or PNDs 25, 45, 65 (2013)	For F1: ↑ dose-dependent follicular (granulosa) cell apoptosis (TUNEL) and atretic % ↑ ovarian protein expression of caspase-3 (50 mg/L, 2014) ↓ ovarian protein expression of Bcl-2, Bcl2l1 (50 mg/L, 2014) granulosa and theca cells with 50 mg/L were 50% positive PND 25 (2013). 5 mg/L were 30% positive PDN 25 (2014)	Stanley et al. (2014; 2013)
Rat, pregnant Sprague-Dawley	Oral (drinking water)	10 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5; F1 animals evaluated on PND 1	For F1: ↑ germ cell apoptosis (TUNEL) ↑ ovarian protein expression of acetyl-p53, cleaved caspase-3, BAX, PUMA ↓ ovarian protein expression of Bcl-2, Bcl-XL, p-AKT Effects other than p-AKT were exacerbated by SIRT1 inhibitor	Sivakumar et al. (2022)
Rat, strain not reported (assume Sprague-Dawley)	Oral (drinking water)	25 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5; F1 animals evaluated on PND 1	For F1: ↑ germ cell apoptosis (TUNEL) ↑ ovarian protein expression of BAX, caspase 3, p53, p27 ↓ ovarian protein expression of p-AKT, p-ERK, and XIAP	Sivakumar et al. (2014)
Rat, Wistar, female	i.p. injection	1 and 2 mg $K_2Cr_2O_7$/kg, 15-d	↓ relative ovary/uterine weight (with decreased bw; 40% and 137% of controls, dose dependent) ↑ apoptotic cells and protein expression of Bax in uterus Uterine Bcl-2 was not detected in control or Cr(VI) treatment groups Apoptosis was characterized by chromatin condensation, detected by borated toluidine blue staining; Bax/Bcl-2 by immunostaining	Marouani et al. (2015b)

System	Route	Exposure[a]	Results	Reference
Primary Sprague-Dawley rat granulosa cells (immature rats, 22–25 d old)	In vitro	10 µM $K_2Cr_2O_7$, 12 or 24 h	↑ apoptosis ↑ translocation of cytochrome C from mitochondria to cytosol, ↑ cleaved caspase-3 and PARP (important terminal events in apoptosis) ↑ Bax, t-Bad ↓ Bcl-2, Bcl-XL, pBad-112/136, Hsp-70, Hsp-90 ↑ p-ERK, p-JNK; ↓ p-AKT; no change in p-p38 (indicates suppression of AKT pathway but activation of ERK1/2 pathway) ↑ p53 (total and phosphorylated at specific serine sites); higher in mitochondria compared to cytosol, suggesting translocation to the mitochondria ↓ apoptosis after cotreatment with ERK1/2 and JNK inhibitor ↓ p53 activity after cotreatment with ERK1/2 inhibitor; no effect of JNK inhibitor ↑ p-ERK in mitochondria and nucleus Mitigated by pretreatment with vitamin C	Banu et al. (2011)
Primary Sprague-Dawley rat granulosa cells (immature rats, 23–25 d old); immortalized rat granulosa cells	In vitro	10 µM $K_2Cr_2O_7$, 12 or 24 h	Cell cycle arrest at G1 phase (decreased cell population at S and G2-M phases) ↓ protein expression of cyclin-dependent kinases 1, 2, 4, 6 in both cell types; cyclins D2&3, E2, B1; PCNA ↑ protein expression of p15, p16, p27 Results time dependent Mitigated by pretreatment with vitamin C	Stanley et al. (2011)
Ovarian extracellular matrix				
Rat, pregnant Sprague-Dawley	Oral (drinking water)	25 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5; F1 animals evaluated on GDs 15.5 and 17.5, PNDs 1, 4, 25	For F1: ↑ ovarian protein expression of Xpnpep2 and ↓ collagen (Col1, Col3, Col4) in fetuses ↓ ovarian protein expression of Xpnpep2 and ↑ collagen (Col1, Col3, Col4) in pups at PNDs 1, 4, and 25 Protein expression of Xpnpep2 and collagens measured using immunohistochemistry	Banu et al. (2015)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.2.8. Developmental Effects

C.2.8.1. *Mechanistic studies relevant to developmental toxicity*

Mechanistic evidence indicating the biological pathways involved in developmental toxicity following Cr(VI) exposure is summarized in Table C-41. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "developmental" if they involved embryonic development or survival. The following studies were prioritized:

- Studies in humans with quantified oral or inhalation exposure to Cr(VI)
- Studies in experimental animals with quantified oral (drinking water, gavage, diet), inhalation, or intratracheal instillation, or injection exposure to Cr(VI)
- In vitro studies in primary or immortalized mammalian cells derived from tissues relevant to mammalian development, including embryonic and placental tissues and cells and cells involved in organ development (e.g., osteoblasts)
- Mechanistic endpoints relevant to interpretations of effects on human development, including genotoxicity tests relevant to fetal development (e.g., rodent dominant lethal test)

A total of 14 developmental studies were identified to include in the developmental toxicity mechanistic synthesis. Studies were prioritized for consideration in the synthesis of mechanistic evidence for developmental effects if they were conducted in mammalian species. Several of the included oral exposure animal toxicological studies in that section were identified as also reporting mechanistically relevant data, as well as i.p. injection studies that did not meet PECO criteria but were reviewed as being potentially relevant for mechanistic analysis. In vitro studies conducted in relevant cell types derived from tissues relevant to mammalian development were also considered for mechanistic evidence. In vitro studies in human trophoblasts or mitochondria isolated from human placentas were considered as potentially relevant to effects in the placenta, and studies in osteoblasts were also considered as potentially relevant for the evaluation of skeletal effects. Effects are also expected to be more likely in in vitro embryonic studies compared to in vivo studies, as the in vitro studies incubated sperm or blastocytes directly with potassium dichromate.

Table C-41. Mechanistic studies prioritized for informing potential Cr(VI)-induced developmental toxicity

System	Route	Exposure[a]	Results	Reference
Fetal genotoxicity				

System	Route	Exposure[a]	Results	Reference
Mouse, pregnant Swiss albino	Oral (drinking water) or i.p. injection	Drinking water study: 5 and 10 mg/L $K_2Cr_2O_7$, duration of pregnancy i.p. study: 50 mg/kg $Na_2Cr_2O_7$ or $K_2Cr_2O_7$, single dose on GD 17 Euthanasia on GD 18	↑ significant increase in micronucleated polychromatic erythrocytes in maternal bone marrow, fetal liver, and fetal peripheral blood after i.p. injection. No effects after oral dosing.	De Flora et al. (2006)
In vitro evaluations of embryo development				
Dub:(ICR) mouse blastocysts from day 4 of gestation with 6 d of exposure or embryos from day 8 for 24 h	In vitro	0.25–2 µM $K_2Cr_2O_7$	↑ blastocyst (1 and 2 µM) and embryo (all concentrations) SCEs No effects on embryo hatching, attachment of trophoblast outgrowth ↓ blastocyst inner cell masses ↓ embryo development including crown-rump length	Iijima et al. (1983)
Sperm and untreated oocytes from BDF1 mice	In vitro	3.125, 6.25, 12.5, 25, or 50 µM $K_2Cr_2O_7$	↓ acrosome reaction (12.5 µM+) ↑ time to expanded and hatching blastocyst stage ↓ blastocyst ICM and TE cell proliferation ↓ ICM-TE expression sox2, pou5f1, klf4 all conc; cdx2 at 12.5 µM; eomes and krt8 at 25 µM (all pluripotent marker genes) Sperm viability was significantly decreased at 6.25 µM	Yoisungnern et al. (2015)
Balb/c mouse embryos at 2-cell stage	In vitro	$K_2Cr_2O_7$ and $CaCrO_4$ at 0.02–2.0 µg/L (20, 2 and 0.2 µM and 40, 4, and 0.4 µM, respectively)	↓ blastocyst maturation after 3 d of culture with both salts; $K_2Cr_2O_7$ arresting all at 4-cell stage at high dose ↓ hatching, both salts ↓ implantation $CaCrO_4$	Jacquet and Draye (1982)
Mechanisms affecting bone development				
Rat, Sprague-Dawley, male	i.p. injection	60 µg/kg $K_2Cr_2O_7$, single dose 48 h	↑ TSH, effects on follicle morphology including atrophy ↓ free T4, T3, follicle size Pretreatment (i.p.) with ascorbic acid inhibits effects on hormones, treatment with mixture produces nonstatistically significant effects on hormones and morphology	Qureshi and Mahmood (2010)
Immortalized rat osteoblasts (FFC cells)	In vitro	0.1–100 µM Cr(VI) oxide	↓ cell viability (measured as ALP activity as a marker of cytotoxicity) Mitigated by vitamin C; not by vitamins B2 and E	Ning and Grant (1999)

System	Route	Exposure[a]	Results	Reference
Immortalized rat osteoblasts (FFC cells)	In vitro	0.1, 0.5, 1.0 µM Cr(VI) oxide	↓ protein synthesis at 0.1 µM, ↓ DNA, RNA synthesis at all doses No change in collagen synthesis ↓ production of collagen fibers, mitigated by ascorbic acid Lower doses suppressed collagenase activity (measured by L-leucine release) more than high doses (up to 100 µM)	Ning et al. (2002)
Immortalized rat osteoblasts (FFC cells)	In vitro	0.1–100 µM Cr(VI) oxide	↓ cell viability (measured as ALP activity as a marker of cytotoxicity), partially mitigated by pretreatment to deplete GSH. No change in GSH content ↓ glutathione reductase activity after 48 h at 0.1–1 µM Cr(VI)	Ning and Grant (2000)
Mechanisms affecting insulin regulation				
Wistar rats, exposed via drinking water from GDs 9–14; F1 males evaluated on PND 59	Oral (drinking water)	50, 100, or 200 mg/L $K_2Cr_2O_7$, GDs 9–14. Euthanasia on PND 60	↓ insulin receptor protein, IRS-1, and p-IRS-1^{tyr632} in liver and gastrocnemius muscle ↑ Akt^{Ser473} and no change in AKT in liver ↓ Akt and nonmonotonic effect on Akt^{Ser473} in gastrocnemius muscle ↑ GLUT 2 in liver ↓ GLUT 4 in gastrocnemius muscle ↑ PPARγ expression	Shobana et al. (2017)
Oxidative stress and apoptosis in the placenta				
Timed pregnant Sprague-Dawley rats	Oral (drinking water)	50 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5. Euthanasia on GD 18.5	↑ hypertrophy, basal zone thickness, pyknotic nuclei (not quantitated) Hemorrhagic lesions observed w/treatment ↑ apoptosis (TUNEL) in various regions/cell types (AI%) ↑ Casp-3 in yolk sac and metrial gland (maternal compartment), nondetectable in basal and NS in labyrinth zones (fetal) ↑ AIF, Bax, ATM, p53, NOXA, PUMA, p27 all areas (Casp-3 indep) ↓ Bcl-2, Bcl-XL, XIAP	Banu et al. (2017a) (appears to be the same experiment as Banu et al. (2017b))
Timed pregnant Sprague-Dawley rats	Oral (drinking water)	50 mg/L $K_2Cr_2O_7$, GDs 9.5–14.5. Euthanasia on GD 18.5	↓ fetal weight, cytokeratin (TC marker), Cyclin D1 in metrial gland, basal and labyrinth zones ↓ markers for TGCs in basal and labyrinth zones, glycogen cells in basal zone, syncytial trophoblast in labyrinth zone ↑ marker for uterine NK cells in labyrinth zone ↑ LPO, H_2O_2 ↓ Gpx, SOD activity in whole extracts ↓ Prdx3, Txn2 mitochondrial expression all areas samples	Banu et al. (2017b)

System	Route	Exposure[a]	Results	Reference
Human placental tissues	Ex vivo	0.02 to 1.2 mg/L Cr detected in placental tissue	Placenta from male birth (results from higher Cr concentrations): ↑ CytoC, Casp-3, apoptosis inducing factor (AIF), vBAX, and p53, Bcl-2, Bcl-XL ↓ XIAP (x-linked apoptosis inhibitor) Placenta from female birth (results from higher Cr concentrations): ↑ CytoC, Casp-3, AIF, BAX, Bcl-2, Bcl-XL Null p53, XIAP	Banu et al. (2018)
Human trophoblastic cell line BeWo	In vitro	5, 15, 30 µM $K_2Cr_2O_7$ for 12 and 24 h	↑ GPX1 mRNA with 5 mM Cr(VI) treatment after 12 h, dose-dependent; decreased after 24 h ↓ GPX1 and SOD1 expression, 15 and 30 µM, 12 and 24 h ↓ Catalase and SOD2 mRNA, 5, 15, and 30 µM, after 12 and 24 h, dose-dependent ↓ PRDX3 and TXN2, 5 µM, after 24 h only ↓ PRDX3 and TXN2 mRNA, 15 and 30 µM, 12 and 24 h	Banu et al. (2018)
Primary human erythrocytes and mitochondria from placenta tissue	In vitro	0.05, 0.5, 1, 5 µg/mL $K_2Cr_2O_7$	↑ lipid peroxidation level (TBARS); decreased with coadministration of estrogen metabolite 4-OHE2 ↓ SOD and GST activity; SOD increased with coadministration of estrogen metabolite 4-OHE2; GST increased with coadministration of estrogen metabolite 16α-OHE1 ↓ nitric oxide levels in blood; estrogen metabolites caused further reduction	Sawicka et al. (2017; 2017)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.3. SUPPORTING EVIDENCE FOR CARCINOGENIC MODE OF ACTION

C.3.1. Meta-analysis of Cr(VI) and Cancer of the GI Tract

This section describes the methods for the review and meta-analysis of GI cancer risk reported by occupational studies of workers with inhalation exposure to Cr(VI) (toxicological review, Section 3.2.1). Occupational studies that analyzed cancer risks related to Cr(VI) exposure were identified as part of the overall assessment search strategy process as described in the Cr(VI) Protocol (U.S. EPA, 2019b). This search strategy, which was conditioned on terms for Cr(VI), identified 35 potentially relevant citations. Since these searches only identified references that mentioned chromium or related terms in the title or abstract, an additional search strategy was developed to identify studies of occupational groups with routine exposure to Cr(VI). Our list of

occupational groups with potential substantial exposure to Cr(VI) included those in categories I or II identified by the Occupational Safety and Health Administration (OSHA; see Table C-42) (Shaw Environmental, 2006). Group I industries are "primary industry sectors where the majority of occupational exposures occur to hexavalent chromium" while Group II industries "represent industries with limited potential for occupational exposure to hexavalent chromium; consequently, fewer data were available on occupational exposures and controls for these industries." This search resulted in 2,341 references.

Titles and abstracts for the second set of the references were screened by seven individuals using Distiller imposing a rule that each study be screened by two reviewers; conflicts were resolved by discussion. Screening decisions were guided by a PECO (population, exposure, comparator, outcome) statement designed to capture studies examining associations of cancers of the GI tract with Cr(VI)-exposed occupations (Table C-42). For our initial screening stage, we included all cancer sites along the digestive tract. Different studies used different naming conventions, partially due to the use of differing International Classification of Disease (ICD) coding versions.

Table C-42. PECO for screening occupational studies relevant to Cr(VI)

PECO Element	Evidence	
Population	Human including epidemiological studies, case-control studies, cohort/prospective studies, follow-up studies, occupational mortality studies	
Exposure	Industries including any in group I or group II. Include analyses of cancer in relation to occupation (e.g., stomach cancer and occupation in Sweden).	
	Group I	Group II
	Chromate or chromium production, ferrochrome production	Chromium dye production
	Chromated copper arsenate producers	Chromium catalyst users
	Chromium catalyst production	Chromium dioxide producers
	Chromium metal production	Chromium sulfate producers
	Chromium plating, chrome plating, electroplating	Leather work and tanning, tanners
	Stainless steel production	Portland cement work
	Welding, Stainless steel (carbon steel welding low prevalence of exposure to generally low levels)	Producers of refractory brick
	Chromium pigment production	Nonferrous superalloy producers and users
	Paint and coatings production	Producers of precase concrete products

PECO Element	Evidence	
	Printing ink producers	Textile dying
	Plastic colorant producers and users	Producers of colored glass
	Plating mixture production	Printing – if working with pigments
	Grinders, polishers (stainless steel)	Aircraft manufacturing; aerospace
	Wood preserving	Brick masons, bricklayers
	Painters – if in industry like shipbuilding, automobile manufacture; painting metals	Metal casting, cutting
	Steel and iron foundry workers	
	Steel mills	
Comparator	Analyses of mortality due to cancer or incidence of cancer and associations with occupational groupings (industries; professions)	
Outcome	Gastrointestinal tract cancers (incidence, prevalence, mortality)[a]	
	Specific GI cancers identified by ICD-10, -9, -8 or -7 codes, including: Oral cavity [ICD 140–149 (includes cancers of the mouth, lip, tongue, gum, or oropharynx)] Esophagus (ICD 150) Stomach (ICD 151) Small intestine [ICD 152 (includes the duodenum)] Colon (ICD 153) Rectum [ICD 154 (includes the rectosigmoid junction and anus)	

[a]As noted above, nomenclature for cancer sites varied across studies. Some of the alternative designations included: buccal cavity, oral cavity; salivary glands; pharynx; hypopharynx; cardia, corpus, gastric, gastric cardia; bowel, intestine, large intestine; colorectal; digestive tract, digestive system, digestive organs (and peritoneum), gastrointestinal tract.

A total of 199 references were identified during title and abstract screening, and these underwent full-text screening by three reviewers who resolved conflicts via discussion. Of these 199 references, 97 references were retained; the majority (93) were uniquely identified references. A snowball search was conducted by cross-checking the reference lists identified using the two search strategies with the studies included in the three recent meta-analyses, which resulted in identification of an additional 20 references. In total, 35 references from the previous literature searches, 93 references from the subsequent occupationally focused search, and 20 references from the snowball search of the reference lists in the three most recent meta-analyses were included in this review. Of these, 21 studies were not included because they were earlier follow-ups, the cohorts were not exposed to Cr(VI), or they did not contain results for site-specific GI tract cancers.

C.3.1.1. *Study evaluation criteria*

Studies were evaluated with respect to population selection; exposure and outcome evaluation; confounding; analysis; selective reporting; sensitivity; and overall confidence, following the framework outlined in the IRIS Handbook (U.S. EPA, 2020b). Criteria were developed for the exposure domain to identify those studies that used exposure assessment definitions that identified groups with higher certainty and prevalence of exposure to Cr(VI) (U.S. EPA, 2019b). For the evaluation of selected outcomes, we had higher confidence in studies of cancer incidence compared to mortality. Cancer deaths ascertained from death certificates were considered a valid outcome ascertainment method, acknowledging the potential for misdiagnosis of the underlying cause of death and subsequent underascertainment, particularly for cancers with longer survival periods. We had greater confidence in cancer incidence and mortality coding for stomach cancer compared with other sites in the gastrointestinal tract because the probability that the diagnosis on the death certificate is the same as that in the hospital medical records is higher (Percy et al., 1990; Percy et al., 1981).

With a few exceptions, most of the studies compared cancer incidence or mortality in an occupational group to that in the country or other geographical region in which the facilities were located, by calculating a standardized incidence ratio (SIR) or standardized mortality ratio (SMR). This study design can be subject to the healthy worker effect, a type of selection bias that results in an underestimate of the relative risk because individuals in the workforce are a healthier population than a general population that might be used for comparison. This limitation, and reduction in study sensitivity, is not generally present in studies using internal comparisons. Greater confidence was given to studies that considered major confounders of the association between Cr(VI) exposure and GI tract cancers. Risk factors for these cancers vary by site, but generally include sex, age, race/ethnicity, and geographic region. Individual-level information on other risk factors, such as smoking and alcohol consumption that could be risk factors for certain GI tract cancers and that might differ between the occupational groups and comparison populations, was not usually available to adjust the SMRs or SIRs, but the magnitude of bias likely differed across the occupational categories. Other risk factors such as obesity, *H. pylori* infection, dietary factors and family history of such cancers, likely were not differentially associated with chromium-exposed occupations or jobs and thus any differences would be expected to be random. Appropriate analysis methods were prioritized and largely included standardized ratios for mortality or incidence of cancer or relative risk estimates for comparisons of exposure groups within the study population; in a few studies, odds ratios were estimated for case-control study designs.

C.3.1.2. *Evaluation of exposure to Cr(VI)*

For the purposes of this meta-analysis, only occupational studies were considered, and studies were evaluated with respect to certainty of exposure to hexavalent chromium. Occupational groups were identified after inventorying the database of references, and specific

criteria developed for "good," "adequate," and "deficient" ratings for decreasing certainty of exposure within each one. Many of the identified studies were registry based, with occupation inferred based on a standardized set of occupation or industry codes. In the absence of further information on potential for Cr(VI) exposure, the certainty of exposure for these studies was deemed "deficient."

Since the focus of this meta-analysis was occupational exposure to Cr(VI), criteria to evaluate the certainty of exposure to Cr(VI) were developed specific to occupational groups. Exposure certainty was rated as "good," "adequate," or "deficient" using the guidelines in Table C-43. Potential bias in exposure assignments, and other domains of risk of bias and sensitivity, were evaluated using the methods described in the IRIS Handbook (U.S. EPA, 2020b). The results of the study evaluations with domain-specific ratings and overall confidence ("high," "medium," or "low") are available in HAWC for the cancer mortality studies with comparisons to external populations and studies with comparisons within the target study population and are shown in Table C-44.

Table C-43. Occupational group-specific criteria for rating certainty of exposure to Cr(VI)

Occupation group	Potential coexposures	Good	Adequate	Deficient
Brick masons/stone masons/tile setters/brick layers/cement or concrete workers *The main source of Cr(VI) exposure in this group comes from exposure to Portland cement (production or use).*	Asbestos, cement dust, silica, fiberglass, talc, solvents, asphalt (US DHHS, 1990; Pedersen and Sieber, 1988; Seta et al., 1988)	Portland cement production, exposure assigned using task-related data from job histories and other industrial hygiene evidence	Cement production, exposure assigned using task-related data from job histories	Cohort studies of bricklayers or case-control studies, where occupation was assigned on the basis of standard codes for industry/ occupation
Chromate production, ferrochromium industry *The main source of Cr(VI) exposure in this group comes from exposure to chromate and related compounds (production or use).*	Asbestos, nickel, acid and alkali mists, nitrogen oxides, cyanide, solvents (IARC, 1990)	Cohort studies of chromate workers, including chromate production, ferrochromium industry, with categories based on tasks involving direct exposure to Cr(VI)	Cohort studies of chromate workers, including chromate production, ferrochromium industry, or case-control studies, with categories based on (1) ever employment or duration of employment, or (2) standard codes for industry/occupation.	Cohort studies of chromate workers, including chromate production, ferro-chromium industry, or case-control studies, where the exposure assessment description was not sufficient to determine the prevalence or frequency of exposure to Cr(VI).
Building construction/carpenters/ wood workers	Asbestos, silica, wood dust, formaldehyde, wood	Cohort studies of construction workers, carpenters, or woodworkers with categories based on	Cohort studies of construction workers, carpenters or woodworkers with categories based on	Cohort studies of construction workers, carpenters or woodworkers, or case-control studies,

Occupation group	Potential coexposures	Good	Adequate	Deficient
The main source of Cr(VI) exposure in this group comes from exposure to refractory brick or Portland cement (construction, building) and from wood treated with chromated copper arsenate (CCA).	preservatives, solvents (Robinson et al., 1996)	tasks in Portland cement mixing or wood preservation or working with treated wood	tasks in cement mixing (nonspecific) or broader wood working categories.	where occupation was assigned on the basis of standard codes for industry/occupation
Automotive workers *The main source of Cr(VI) exposure in this group comes from exposure to metalwork (e.g., welding) and to automotive paint.*	Solvents, welding fumes, asbestos in brakes and clutches, metal welding fluids (Gibel et al., 1985) (OSHA, 2006a)	Cohort studies with task-specific exposure assignments based on job histories, specifically spray painting, welding, or metal cutting (see criteria for painting, welding or metal work) with supplemental industrial hygiene evidence	Cohort studies with task-specific exposure assignments based on job histories, specifically spray painting, welding, or metal cutting (see criteria for painting, welding or metal work, but with no supplemental information	Cohort studies of automotive workers, or case-control studies, where occupation was assigned on the basis of standard codes for industry/occupation
Aircraft manufacturing workers *The main source of Cr(VI) exposure in this group comes from exposure to metalwork (e.g., welding) and to aircraft paint.*	Solvents, heavy metal salts, welding fumes, epoxy resins, asbestos, other fibers, ionizing radiation (Lipworth et al., 2011; Costa et al., 1989)	Cohort studies with task-specific exposure assignments based on job histories, specifically spray painting, welding, or metal cutting (see criteria for painting, welding or metal work), with supplemental industrial hygiene evidence; sprayers and hosemen	Cohort studies with task-specific exposure assignments based on job histories, specifically spray painting, welding, or metal cutting (see criteria for painting, welding or metal work, but with no supplemental information	Cohort studies of aircraft manufacturing workers or case-control studies, where occupation was assigned on the basis of standard codes for industry/occupation
Painter/paint product/paint, and coating manufacturers *The main source of Cr(VI) exposure in this group comes from exposure to plaster and chromium-based pigments (usually used in marine, automotive, aircraft, etc. paints).*	Solvents, pigments, aromatic azo dyes, PAHs, resins (IARC, 2010)	Cohort studies with task-specific exposure assignments based on job histories; spray painting or coating in the marine, automotive or aircraft manufacturing industries, with supplemental industrial hygiene evidence	Cohort studies with task-specific exposure assignments based on job histories; spray painting or coating in the marine, automotive or aircraft manufacturing industries, but with no supplemental information	Cohort studies of painters, plasterers, or paint manufacturing workers, or case-control studies, where occupation was assigned on the basis of standard codes for industry/occupation
Printers	Solvents, dyes, lead salts	Cohort studies with task-specific exposure	Cohort studies with task-specific exposure	Cohort studies of printing workers or case-control studies,

Occupation group	Potential coexposures	Good	Adequate	Deficient
The main source of Cr(VI) exposure in this group comes from exposure to chromium-based pigments in ink.	(Lynge et al., 1995)	assignments based on job histories; photoengravers, press operators, with supplemental industrial hygiene evidence	assignments based on job histories; photoengravers, press operators, but with no supplemental information	where occupation was assigned on the basis of standard codes for industry/occupation
Textiles *The main source of Cr(VI) exposure in this group comes from exposure to chromium-based pigments in fabric dyes.*	Solvents, textile dusts and fibers, formaldehyde, dyes (IARC, 1998)	Cohort studies with task-specific exposure assignments based on job histories (e.g., textile dying), with supplemental industrial hygiene evidence	Cohort studies with task-specific exposure assignments based on job histories (e.g., textile dying), but with no supplemental information	Cohort studies of textile workers or case-control studies, where occupation was assigned on the basis of standard codes for industry/occupation
Welder/metal fumes *The main source of Cr(VI) exposure in this group comes from welding on stainless steel, and intensity of exposure varies by specific welding technique. For welding, highest exposure during shielded metal arc welding, less for gas metal arc welding and tungsten inert gas welding (Pesch et al., 2018).*	Nickel and other metals, arsenic asbestos, formaldehyde, silica dust (IARC, 1990) (IARC, 2018)	Cohort studies with task-specific exposure assignments based on job histories; stainless steel welding: shielded metal arc welding, or stainless steel welding: unspecified technique but with monitoring data or other Cr(VI)-specific information	Cohort studies with task-specific exposure assignments based on job histories; stainless steel welding (unspecified technique)	Cohort studies with task-specific exposure assignments based on job histories; gas metal arc welding, tungsten inert gas welding; or cohort studies of welders or case-control studies, where occupation was assigned on the basis of standard codes for industry/occupation
Tanners *The main source of Cr(VI) exposure in this group comes from the "two bath" tanning process which uses hexavalent chromium salts as the tanning material (Stern, 2003).*	Benzidine-based azo dyes, aromatic organic solvents, formaldehyde, airborne leather dust (IARC, 1981)	Work processes involving leather tanning and cohort description supports that at least 50% of cohort first employed as leather tanners when two-bath process was still used (pre 1940s in United States) and before mechanization was introduced.	Work processes involving leather tanning and cohort description supports that a large portion of cohort first employed as leather tanners when two-bath process was still used (pre 1940s in United States) and before mechanization was introduced	Work processes involving leather tanning and cohort description supports that most of the cohort (>70%) first employed as leather tanners when one bath process was used (post 1940s in United States); or occupation was assigned based on standard codes for industry/occupation
Metal Workers *The main source of Cr(VI) exposure in this group comes from work with chrome plating, stainless steel and steel alloys (tasks include: plating, melting,*	Nickel (electroplating), polynuclear aromatic hydrocarbons, silica, carbon monoxide, nickel, phenol,	Cohort studies analyzing stainless steel categories/tasks with some monitoring data or industrial hygiene documentation. Stainless steel	Cohort studies involving steel foundries with subgroup analyses. Cohort studies analyzing stainless steel categories with	Iron or steel foundries; If occupation was assigned on the basis of standard codes for industry/occupation

Occupation group	Potential coexposures	Good	Adequate	Deficient
pouring, cutting, grinding and welding operations).	formaldehyde, isocyanates, amines (IARC, 1990)	machining, production of stainless steel products (grinding, polishing) (based on job histories), stainless steel production (based on job histories), steel foundries (by work area/task)	no or minimal monitoring data.	

The meta-analyses focused on the studies considered to be "medium" or "high" overall confidence for which EPA had greater certainty in the exposure assessment for Cr(VI) and minimal concern for other sources of bias. These studies reported a variety of effect estimates, including standardized incidence or mortality ratios, standardized risk ratios, odds ratios, and proportionate mortality ratios. Studies that calculated proportionate mortality ratios were not included. In some instances, multiple risk estimates were reported—for example, for men or women separately, for exposure or occupational subgroups, or by latency period. A priori, we selected risk estimates (1) that were adjusted for potential confounders including age, sex, time period, and geographic region; (2) for the longest latency period; (3) from the most recent follow-up of a specific study cohort; and (4) for the most highly exposed subgroup of the study population. A comparison of the studies included in the three most recent meta-analyses and this analysis, with our rationale for decisions to exclude, are in Table C-44**.** The table indicates the citations included in our meta-analysis and those in the three most recent meta-analyses. The studies included in each meta-analysis comprised an overlapping but different set of studies reflecting the various time periods used for the literature searches, the inclusion criteria, and the results of the evaluations of study "quality" used in the studies. In this analysis, the primary reason for considering a study "low" confidence was that exposure to Cr(VI) in the population was too uncertain.

When reviewing the studies captured by our literature search and evaluation of studies, some cancer sites or groupings were difficult to reconcile across studies due to differences in ICD codes included, for example, or changes in coding practices and diagnostic naming conventions over time and across geographical sites. Consequently, determining whether common cancer sites were contained within some of the groupings was difficult. Further, in some cases, the number of studies for a given cancer site was small enough (and heterogenous enough) that a meta-analysis seemed unlikely to yield useful information. Consequently, we performed quantitative meta-analysis to derive summary risk estimates for a subset of GI tract cancers by site: esophagus, stomach, rectum, and colon. For each of these four sites, more studies were available to include in a summary effect estimate, and these studies used relatively consistent definitions for these specific cancer sites.

Separate meta-analyses were performed to obtain summary estimates from studies reporting odds ratios (stomach cancer, esophageal cancer), and from studies reporting SMR, SIR, or SRR estimates (all four sites). All analyses were performed using the "metafor" package in R, with a random effects model. This package was also used to generate forest plots. The potential for publication bias was evaluated using the Egger's test (Egger et al., 1997) for funnel plot asymmetry. The I2 statistic value is used to represent the percentage of variation across studies that is due to heterogeneity rather than chance.

Table C-44. Comparison of studies included in meta-analyses or that met PECO, with search phase, study evaluation rating, and rationale for exclusion in EPA meta-analysis

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Andersson et al. (2010)	x				PECO_1	Medium	
Birk et al. (2006)	x		x	x	PECO_1	Medium	
Davies et al. (1991)	x	x		x	PECO_1	Medium	
Franchini et al. (1983)	x	x		x	PECO_1	Medium	
Gibb et al. (2015)	x		x		PECO_1	Medium	
Hayes et al. (1989)	x	x	x	x	PECO_1	Medium	
Huvinen and Pukkala (2013)	x		x		PECO_1	Medium	
Huvinen and Pukkala (2016)	x	x			PECO_1	Medium	
Koh et al. (2013)	x	x			PECO_1	Medium	
Korallus et al. (1993)	x	x	x	x	PECO_1	Medium	
Langard et al. (1990)	x	x		x	PECO_1	Medium	
Rafnsson et al. (1997)	x				PECO_1	Medium	
Rosenman and Stanbury (1996)	x	x			PECO_1	Medium	
Silverstein et al. (1981)	x	x		x	PECO_1	Medium	
Sorahan and Harrington (2000)	x	x		x	PECO_1	Medium	

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Sorahan et al. (1987)	x	x	x		PECO_1	Medium	
Hayes et al. (1979)	x				PECO_1	Medium	
Kano et al. (1993)	x	x		x	PECO_1	Medium	
Becker (1999)	x	x		x	PECO_2	Medium	
Boice et al. (1999)	x		x	x	PECO_2	Medium	
Dalager et al. (1980)	x			x	PECO_2	Medium	
Danielsen et al. (1996)	x				PECO_2	Medium	
Delzell et al. (2003)	x				PECO_2	Medium	
Edling et al. (1986)	x	x			PECO_2	Medium	
Garabrant and Wegman (1984)	x	x			PECO_2	Medium	
Garabrant et al. (1988)	x				PECO_2	Medium	
Hansen et al. (1996)	x				PECO_2	Medium	
Iaia et al. (2006)	x		x	x	PECO_2	Medium	
Jakobsson et al. (1993)	x	x	x		PECO_2	Medium	
Jakobsson et al. (1997)	x	x	x		PECO_2	Medium	
Kaerlev et al. (2000)	x				PECO_2	Medium	
Kusiak et al. (1993)	x				PECO_2	Medium	
Lipworth et al. (2011)	x	x	x		PECO_2	Medium	
Lynge et al. (1995)	x				PECO_2	Medium	

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Mikoczy and Hagmar (2005)	x	x			PECO_2	Medium	
Montanaro et al. (1997)	x	x	x	x	PECO_2	Medium	
Morgan et al. (1981)	x				PECO_2	Medium	
Moulin et al. (1990)	x	x	x	x	PECO_2	Medium	
Moulin et al. (1993a)	x	x	x	x	PECO_2	Medium	
Park et al. (2005)	x		x		PECO_2	Medium	
Polednak (1981)	x				PECO_2	Medium	
Ramanakumar et al. (2008)	x				PECO_2	Medium	
Santibanez et al. (2008)	x				PECO_2	Medium	
Sciannameo et al. (2019)	x				PECO_2	Medium	
Sjögren et al. (1987)	x				PECO_2	Medium	
Sorahan et al. (1994)	x		x	x	PECO_2	Medium	
Tarvainen et al. (2008)	x				PECO_2	Medium	
Veyalkin and Gerein (2006)	x				PECO_2	Medium	
Xu et al. (1996)	x	x			PECO_2	Medium	
Olsen et al. (1988)	x				PECO_2	Medium	
Simonato et al. (1991)	x	x	x	x	PECO_2	Medium	
Axelsson et al. (1980)	x	x			Snowball ID	Medium	
Costantini et al. (1989)	x	x		x	Snowball ID	Medium	

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Dab et al. (2011)	x		x		Snowball ID	Medium	
Hara et al. (2010)	x	x		x	Snowball ID	Medium	
Horiguchi et al. (1990)	x	x	x	x	Snowball ID	Medium	
Pippard et al. (1985)	x	x	x	x	Snowball ID	Medium	
Smailyte et al. (2004)	x	x	x		Snowball ID	Medium	
Deschamps et al. (1995)	x	x		x	Snowball ID	Medium	
Aragones et al. (2002)					PECO_1	Low	*Low* confidence due to exposure assessment, which was based on self-reported occupation at one timepoint. Concern that occupation at one point in time does not represent etiologically relevant time window.
Guberan et al. (1989)			x	x	PECO_1	Low	*Low* confidence related to nonspecific exposure definition.
Koh et al. (2011)			x		PECO_1	Low	Main limitation is uncertain potential for exposure (highest likelihood for production and maintenance, but duration unknown and use of last held job could introduce misclassification) and low numbers of cases.
Parent et al. (1998)		x			PECO_1	Low	*Low* confidence due to the nonspecific nature of the exposure assignments.
Satoh et al. (1981)		x		x	PECO_1	Low	Although potential for chromium exposure seems clear, there is little information to inform potential for selection bias or outcome ascertainment, and low number of cases (n = 11).
Sweeney et al. (1985)		x			PECO_1	Low	Main limitations are uncertain potential for chromium exposure and low number of deaths for certain cancer sites.
Walrath et al. (1987)		x			PECO_1	Low	Main limitation is unclear potential for chromium exposure.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Andjelkovich et al. (1992)					PECO_2	Low	*Low* confidence study due to lack of information on likelihood of Cr(VI) exposure.
Andersen et al. (1999)					PECO_2	Low	*Low* confidence study due to lack of information on potential for Cr(VI) exposure, lack of consideration of latency.
Bertazzi and Zocchetti (1980)					PECO_2	Low	Main limitation is lack of certainty regarding potential for chromium exposure.
Bethwaite et al. (1990)					PECO_2	Low	*Low* confidence study due to lack of certainty regarding Cr exposure.
Bouchardy et al. (2002)					PECO_2	Low	Main limitation is lack of certainty for occupation in general and for chromium exposure potential.
Brown et al. (2002)					PECO_2	Low	Main limitation is the lack of certainty regarding chromium exposure, and potential healthy worker effect.
Brownson et al. (1989)					PECO_2	Low	Main limitation is lack of certainty regarding exposure (and occupation only at time of diagnosis).
Bulbulyan et al. (1999)					PECO_2	Low	Main limitation is lack of certainty regarding chromium exposure.
Chiazze et al. (1980)					PECO_2	Low	Main limitations are lack of certainty regarding chromium exposure, and uncertainty due to missing data. Further limitations are small sample size and use of PMR analysis.
Chow et al. (1994)					PECO_2	Low	Main limitation is the lack of certainty regarding chromium exposure and potential healthy worker effect.
Chow et al. (1995)					PECO_2	Low	Main limitation is the lack of certainty regarding chromium exposure and potential healthy worker effect.
Cocco et al. (1998)					PECO_2	Low	Main limitation is lack of certainty regarding chromium exposure.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Costa et al. (1989)					PECO_2	Low	Main limitation is lack of specificity about which workers might be exposed to chromium and inclusion of short-term workers, lack of information on longest held or usual occupational group.
Danielsen et al. (1993)					PECO_2	Low	*Low* confidence study, given short time period (1977 onward) that stainless steel was in use during the overall study period from 1940–1979.
Divine and Barron (1986)					PECO_2	Low	*Low* confidence primarily due to uncertainties in exposure domain. Type of welding metal was not reported so there is low certainty about the extent of exposure to chromium in the industry.
Dubrow and Wegman (1984)					PECO_2	Low	*Low* confidence due to uncertainties in the exposure domain due to likely misclassification in exposure assignments; usual occupation on death certificate and broad exposure categories.
Dubrow and Gute (1988)					PECO_2	Low	Primary limitation is the nonspecific nature of the exposure assignments and low sensitivity.
Engel et al. (2002)					PECO_2	Low	Although the greater specificity in the incident cancer ascertainment is a strength, the nonspecific nature of the exposure assignments based on occupational and industry codes constrained any conclusions regarding any associations with Cr(VI).
Finkelstein and Verma (2005)					PECO_2	Low	Exposure based on membership in the bricklayers union is nonspecific with large uncertainties in the prevalence, frequency and intensity of exposure to Cr(VI).
Golka et al. (2012)					PECO_2	Low	In addition to the nonspecific occupational and exposure group definitions for Cr(VI), the numbers of cases in the chromium VI relevant groups was small.
Greene et al. (1979)					PECO_2	Low	The lack of specificity in the exposure assignments is the major limitation, and the number of deaths was small.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Huebner et al. (1992)					PECO_2	Low	Although design and analysis are appropriate, main limitation is uncertain potential for chromium exposure.
Jansson et al. (2015)					PECO_2	Low	*Low* confidence study due to lack of information on potential for Cr(VI) exposure and lack of consideration of latency.
Ji and Hemminki (2006)					PECO_2	Low	*Low* confidence study due to lack of information on potential for Cr(VI) exposure.
Kaerlev et al. (2002)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Kang et al. (1997)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Keller and Howe (1993)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Kraus et al. (1982)					PECO_2	Low	Certainty regarding chromium exposure is low and it is unclear how census data were used to calculate expected number of deaths.
Lindsay et al. (1993)					PECO_2	Low	Main limitation is lack of certainty regarding chromium exposure.
Macleod et al. (2017)					PECO_2	Low	*Low* confidence study due to lack of certainty regarding chromium exposure.
Malker and Gemne (1987)					PECO_2	Low	Main limitation is lack of certainty regarding chromium exposure.
Matanoski et al. (1986)					PECO_2	Low	Main limitation is lack of information on potential for chromium study.
Mcmillan and Pethybridge (1983)					PECO_2	Low	Low numbers of deaths, uncertain potential for chromium exposure, and questionable statistical analysis.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Melkild et al. (1989)					PECO_2	Low	Main limitation is small sample size and uncertainty regarding chromium exposure.
Minder and Beerporizek (1992)		x			PECO_2	Low	Main limitation is lack of certainty for chromium exposure potential.
Park et al. (1994)					PECO_2	Low	*Low* confidence due to the nonspecific nature of the exposure assignments.
Pukkala et al. (2009)		x			PECO_2	Low	*Low* confidence study due to lack of information on potential for Cr(VI) exposure, lack of consideration of latency.
Richiardi et al. (2012)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Robinson et al. (1995)		x			PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Salg and Alterman (2005)		x			PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Silverstein et al. (1985)					PECO_2	Low	Main limitation is unclear potential for chromium exposure. The welding conducted at the plant was not likely to have involved exposure to Cr(VI).
Sjödahl et al. (2007)		x			PECO_2	Low	The large size of the cohort, almost complete ascertainment, number of cancer cases, and analysis of cancer incidence is a strength, allowing for analyses of relatively rare cancer types. The nonspecific nature of the exposure definition, however, reduced certainty that prevalence of Cr(VI) exposure was adequate.
Stellman and Garfinkel (1984)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Stern (2003)			x		PECO_2	Low	Main limitation is low potential for chromium exposure during study period.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Sun et al. (2002)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Urbaneja Arrúe et al. (1995)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Wang et al. (1999)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Westberg et al. (2013)					PECO_2	Low	Main limitation is unclear potential for chromium exposure.
Yuan et al. (2011)					PECO_2	Low	Main limitation is lack of information on case and control selection and use of a single biomarker measurement of total chromium of unclear timing after diagnosis.
Ahn et al. (2006)		x			Snowball ID	Low	There is some likelihood of Cr(VI) exposure in certain process areas, but industrial hygiene measures indicate levels could be fairly low. Combined with rather short follow-up and low numbers of cases, it may be difficult to infer cancer associations with Cr(VI).
Amandus (1986)		x			Snowball ID	Low	Main limitation is uncertainty regarding likelihood of Cr(VI) exposure.
Blair (1980)				x	Snowball ID	Low	*Low* confidence study due to lack of certainty regarding Cr exposure.
González et al. (1991)		x			Snowball ID	Low	Exposure definitions were not specific to Cr(VI).
Järvholm et al. (1982)		x			Snowball ID	Low	Main limitations are small sample and unclear potential for chromium exposure.
Kneller et al. (1990)		x			Snowball ID	Low	Main limitation is lack of uncertainty for chromium exposure potential.
Krstev et al. (2005)		x			Snowball ID	Low	Main limitation is lack of certainty regarding potential for chromium exposure.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Mallin et al. (1989)		x			Snowball ID	Low	Main limitation is uncertain potential for chromium exposure.
Mcdowall (1984)		x			Snowball ID	Low	Main limitation is lack of information on potential for chromium exposure. Classification by tasks within this cohort of cement workers allowed adequate exposure contrast for dust exposure, but whether the exposures were to Portland cement is unclear. Therefore there is less certainty about exposure to Cr(VI).
Santibañez et al. (2012)		x			Snowball ID	Low	Main limitation is unclear potential for chromium exposure.
Stern et al. (2001)		x			Snowball ID	Low	Main limitation is unclear potential for chromium exposure.
Becker et al. (1991)			x		PECO_1	Exclude	Earlier study of the cohort reported by Becker (1999).
Gibb et al. (2000b)				x	PECO_1	Exclude	Earlier study of the cohort reported by Gibb et al. (2015).
Luippold et al. (2003)			x	x	PECO_1	Exclude	No GI tract cancer results.
Park et al. (2004)			x		PECO_1	Exclude	Lung cancer only.
Proctor et al. (2016)			x		PECO_1	Exclude	Lung cancer only.
Rafnsson and Jóhannesdóttir (1986)					PECO_1	Exclude	Earlier study of the cohort reported by Rafnsson et al. (1997).
Sorahan et al. (1998)			x		PECO_1	Exclude	No analyses for GI tract cancer.
Steenland et al. (1991)			x		PECO_1	Exclude	Cohort was not exposed to Cr(VI).
Steenland (2002)			x		PECO_1	Exclude	Cohort was not exposed to Cr(VI).
Takahashi and Okubo (1990)			x		PECO_1	Exclude	Earlier study of the cohort reported by Hara et al. (2010).
Moulin (1995)		x			PECO_2	Exclude	Letter to the editor focused on lung cancer.

All included	EPA included	Welling included	Deng included	Suh included	Search	Overall rating	Rationale for exclusion
Becker et al. (1985)					PECO_2	Exclude	Earlier study of the cohort reported by Becker (1999).
Delzell et al. (1993)					PECO_2	Exclude	Earlier study of the cohort reported by Delzell et al. (2003).
Iaia et al. (2002)					PECO_2	Exclude	In Italian. Same analyses as Iaia et al. (2006).
Mastrangelo et al. (2002)					PECO_2	Exclude	Meta-analysis.
Mikoczy et al. (1994)			x		PECO_2	Exclude	Earlier study of the cohort reported by Mikoczy and Hagmar (2005).
Moulin et al. (2000)			x		PECO_2	Exclude	Focus of the study is on lung cancer.
Sorahan and Cooke (1989)					PECO_2	Exclude	Earlier study of the cohort reported by Sorahan et al. (1994).
Stern et al. (1987)					PECO_2	Exclude	Earlier study of the cohort reported by Stern (2003).
Svensson et al. (1989)					PECO_2	Exclude	Earlier study of the cohort reported by Jakobsson et al. (1997).
Veyalkin and Milyutin (2003)					PECO_2	Exclude	Earlier study of the cohort reported by Veyalkin and Gerein (2006).

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C.3.1.3. *Results*

As shown in Table 3-13 in the toxicological review, the summary effect estimates showed small increases in risk for each cancer site associated with Cr(VI) exposure, although only the estimate for rectal cancer was statistically significant. Few studies reported odds ratios, but in each case (esophagus and stomach), summary effect estimates based on these studies were somewhat higher compared with summary estimates based on other relative risk measures (although neither odds ratio-based estimate was statistically significant). No evidence of funnel plot asymmetry was found based on Egger's regression test, indicating that publication bias was not likely to be present.

Summary effect estimates were also derived for each cancer site, stratified by occupational grouping (see Table C-45 and Figures C-15 to C-20). This separation by occupational grouping did show some expected patterns for colon cancer risk estimates (see Figure C-19) in that the occupations with a higher certainty of exposure to Cr(VI) (i.e., ferrochromium, chromate production, stainless-steel workers, chromium pigment-exposed workers) showed higher summary effect estimates. Inconsistencies remained among the studies overall, however, and the results for cancer of the rectum did not show a similar pattern of risk (see Figure C-20).

All risks were either slightly above or close to the null (RRs ranging from 1.01 to 1.45) with the exception of stomach cancer among tannery workers [relative risk (RR) of 0.72]. For example, when looking at stomach cancer, there was a (nonsignificant) decreased risk for tannery workers, and a (nonsignificant) increased risk for those working with metal coatings and metal platers (RRs of 0.72 and 1.26, respectively). Risks for other occupational groups were close to the null, ranging from 1.01 to 1.10. Similarly, variation within occupational groups occurred—the group "ferrochromium, chromate production, stainless-steel workers," had modestly elevated risks for esophageal and colon cancer (RRs of 1.22 and 1.26), while risks were very close to 1 for stomach or rectal cancer (RRs of 1.01 and 1.04). Looking across cancer sites, for the occupational groups with four or more estimates, those with a higher certainty of exposure prevalence (i.e., ferrochromium, chromate production and stainless-steel workers, and chromium pigment exposed workers) had higher relative risk estimates for esophageal and colon cancers but not stomach or rectal cancers. The number of studies within another category with more certainty in the probability of Cr(VI) exposure, "estimated or measured chromium exposure," was too small to calculate a summary estimate. For esophageal cancer, the two studies in this category indicated elevated, but not significant, effect estimates. For colon cancer, this category included two analyses within one study of chromate production workers with exposure prior to and after work process changes that reduced Cr(VI) concentrations. Effect estimates are not consistent with what would be expected, however, since higher risk was observed for the post-change workers. A small number of colon cancer cases contributed to the effect estimates (pre-change n = 7, post-change n = 4), and there was evidence of bias from the healthy worker effect with consequent impacts on sensitivity. Heterogeneity in effect estimates (magnitude and direction) also was evident within occupational groups for a specific cancer site, as shown in the forest plots (Figures C-15 to C-20).

Table C-45. Summary effect estimates from random effects meta-analysis, by cancer site and occupational group, where four or more estimates are included

Cancer site	Occupational group	Number of individual effect estimates	Summary effect estimate (95% confidence interval)	I^2
Esophagus	Ferrochromium, chromate production, stainless-steel workers[a]	6	1.22 (0.90, 1.64)	0
	Chromium pigment-exposed workers	5	1.42 (0.87, 2.32)	10.6
Stomach	Ferrochromium, chromate production, stainless steel workers	13	1.01 (0.75, 1.35)	49.9
	Welders	5	1.10 (0.76, 1.60)	19.7
	Tannery workers	6	0.79 (0.56, 1.12)	12.7
	Portland cement workers, masons	4	1.02 (0.65, 1.61)	59.0
	Chromium pigment-exposed workers	6	1.07 (0.80, 1.42)	0
	Metal coatings, metal platers	6	1.26 (0.81, 1.98)	54.8
Colon	Ferrochromium, chromate production, stainless steel workers	4	1.26 (0.82, 1.91)	44.0
	Portland cement workers, masons	4	0.88 (0.61, 1.27)	0
	Chromium pigment-exposed workers	4	1.45 (0.68, 3.09)	41.7
Rectum	Ferrochromium, chromate production, stainless steel workers[a]	10	1.04 (0.78, 1.38)	0
	Welders	5	1.28 (0.69, 2.41)	39.2
	Tannery workers	4	1.32 (0.80, 2.21)	25.3
	Chromium pigment-exposed workers	4	1.11 (0.63, 1.98)	16.7

[a]Warning displayed during estimation of the summary estimate indicates that "Ratio of largest to smallest sampling variance extremely large. May not be able to obtain stable results."

These results could be due to misclassification and heterogeneity of Cr(VI) exposure among and within the included studies. Although this analysis included studies that analyzed associations among occupational groups or subgroups with greater certainty of exposure to Cr(VI), variation in the prevalence, frequency, and magnitude of exposure is likely within the exposure groups, which could decrease the ability to detect an association if it existed. Other factors that could contribute to the observed heterogeneity of risk estimates include presence of coexposures and bias due to the

use of occupational cohorts. Cancer risk in these industries is likely affected by prevalent exposures to other carcinogens in addition to Cr(VI), which would vary both within and across occupational groupings. As noted in Appendix Table C-43, two industry groupings with higher certainty of Cr(VI) prevalence, ferrochromium, chromate production, and stainless-steel workers, and chromium pigment-exposed workers, had occupational settings characterized by different coexposures, which argues against a strong common confounder. In some cases, authors did attempt to adjust for coexposures or restrict the study population to minimize their effect. Most of the studies estimated relative risk using SMRs, which also are subject to a bias toward the null due to the healthy worker effect. The summary effect estimates for esophageal and stomach cancers calculated using odds ratios from the few case-control studies were not subject to this bias and indicated a higher risk. These odds ratio estimates are based on very few studies, however, and are highly uncertain.

Previous meta-analyses reported summary effect estimates for stomach cancer that ranged between 0.93 (Deng et al., 2019) to 1.27 (Welling et al., 2015). A statistically significant increase in risk of stomach cancer was reported from two of the previous five estimates (Welling et al., 2015; Cole and Rodu, 2005). This assessment's finding of no increased risk (summary RR of 1.01) is within the range of these previous estimates. Two of the five previous meta-analyses included estimates for cancers of the esophagus, colon, and rectum (Deng et al., 2019; Gatto et al., 2010). This assessment's summary estimate of 1.08 for esophageal cancer was not significantly elevated, and was slightly less than that from Gatto et al. (2010). The effect estimate for colon cancer of 1.10 (95% CI: 0.97, 1.25), was close to the estimate reported by Deng et al. (2019). Finally, this assessment's estimate of rectal cancer risk was significantly elevated, and very similar to those previously reported (1.18, 95% CI: 1.01, 1.37), compared with 1.17 (Gatto et al., 2010) and 1.14 (Deng et al., 2019).

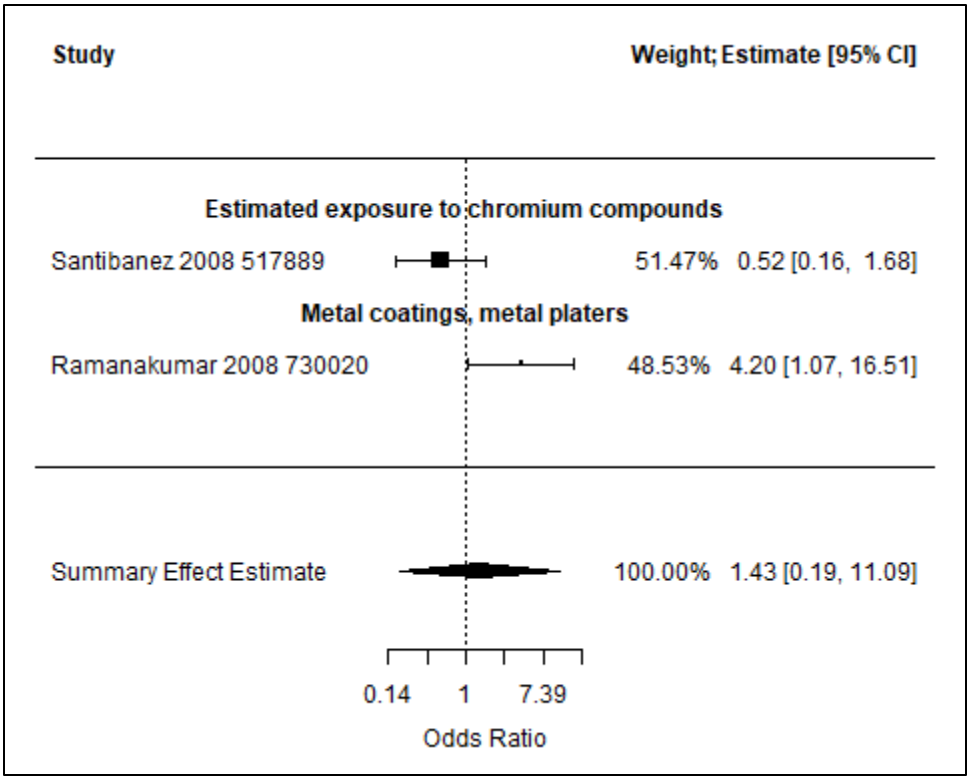

Figure C-15. Forest plot displaying summary measures for esophageal cancer risk from studies reporting odds ratios.

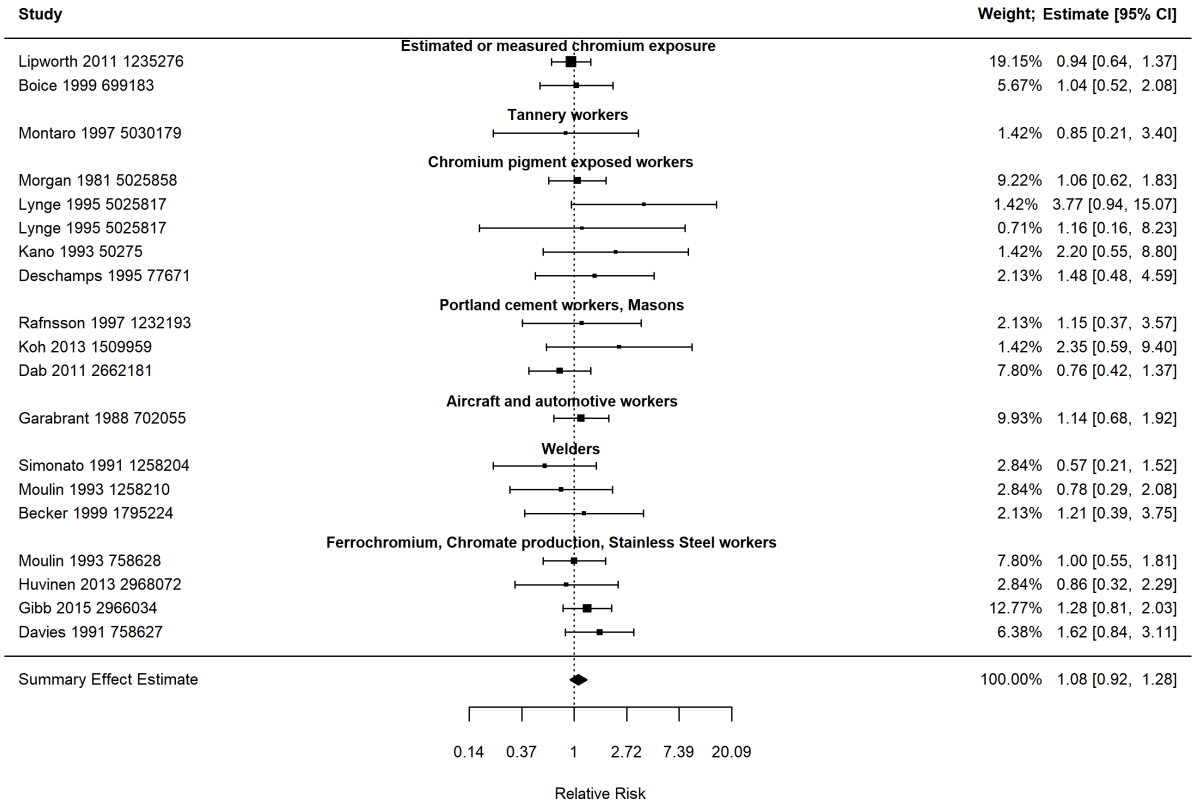

Figure C-16. Forest plot displaying summary measures for esophageal cancer risk from studies reporting standardized mortality or incidence ratios.

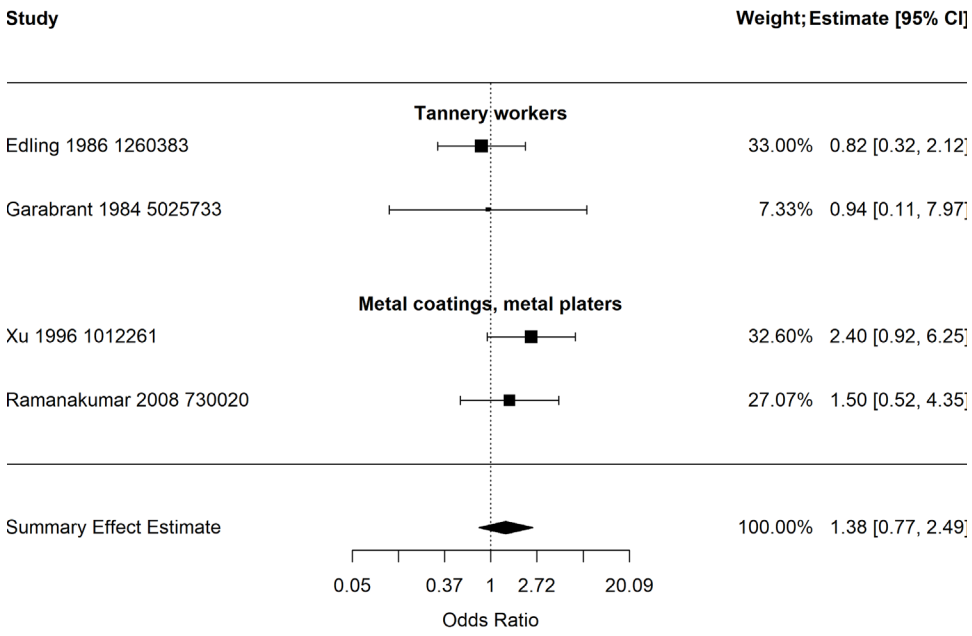

Figure C-17. Forest plot displaying summary measures for stomach cancer risk from studies reporting odds ratios.

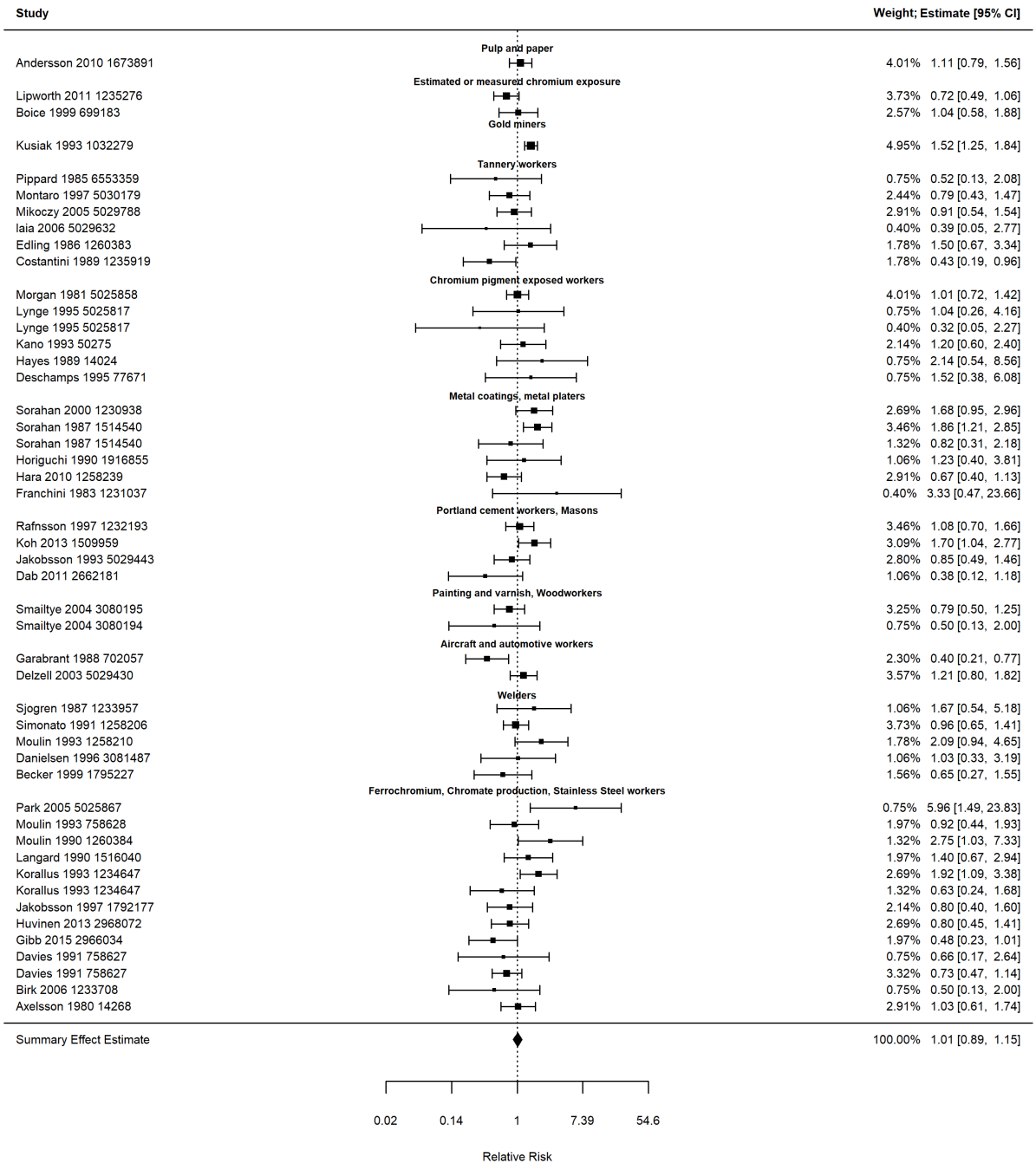

Figure C-18. Forest plot displaying summary measures for stomach cancer risk from studies reporting standardized mortality or incidence ratios.

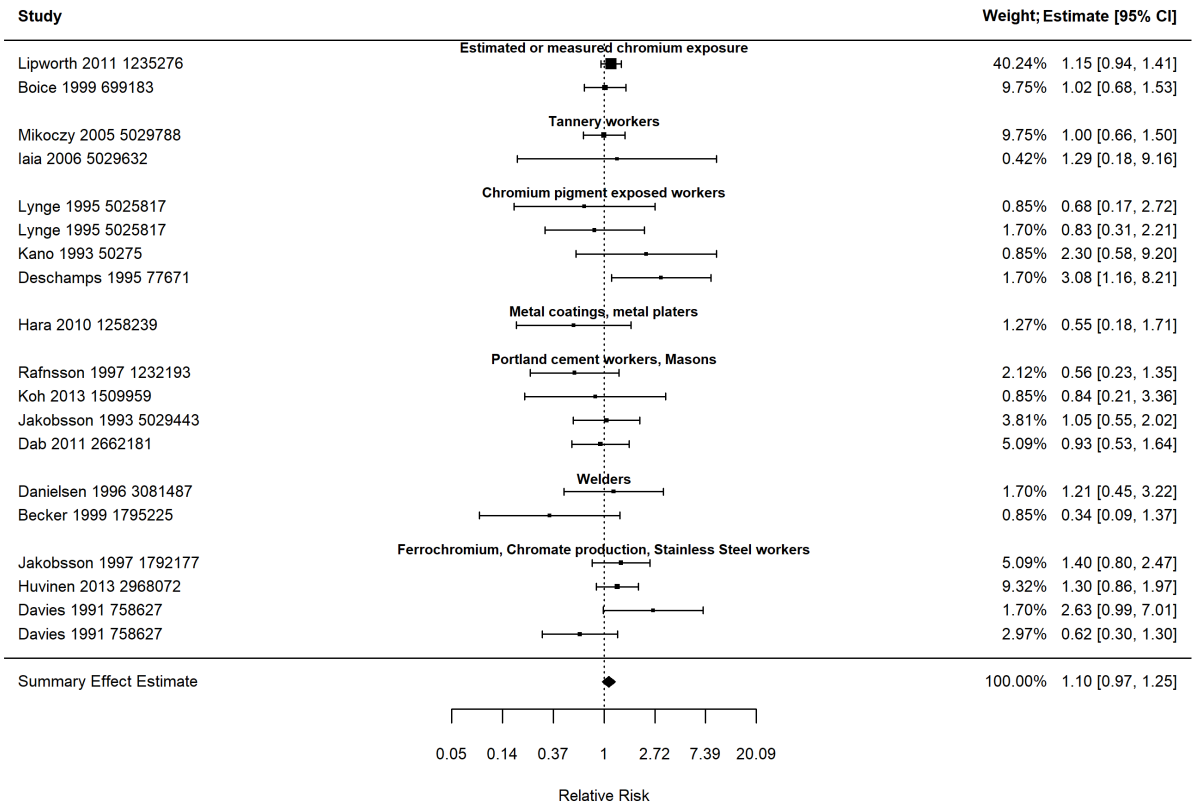

Figure C-19. Forest plot displaying summary measures for colon cancer from studies reporting standardized mortality or incidence ratios.

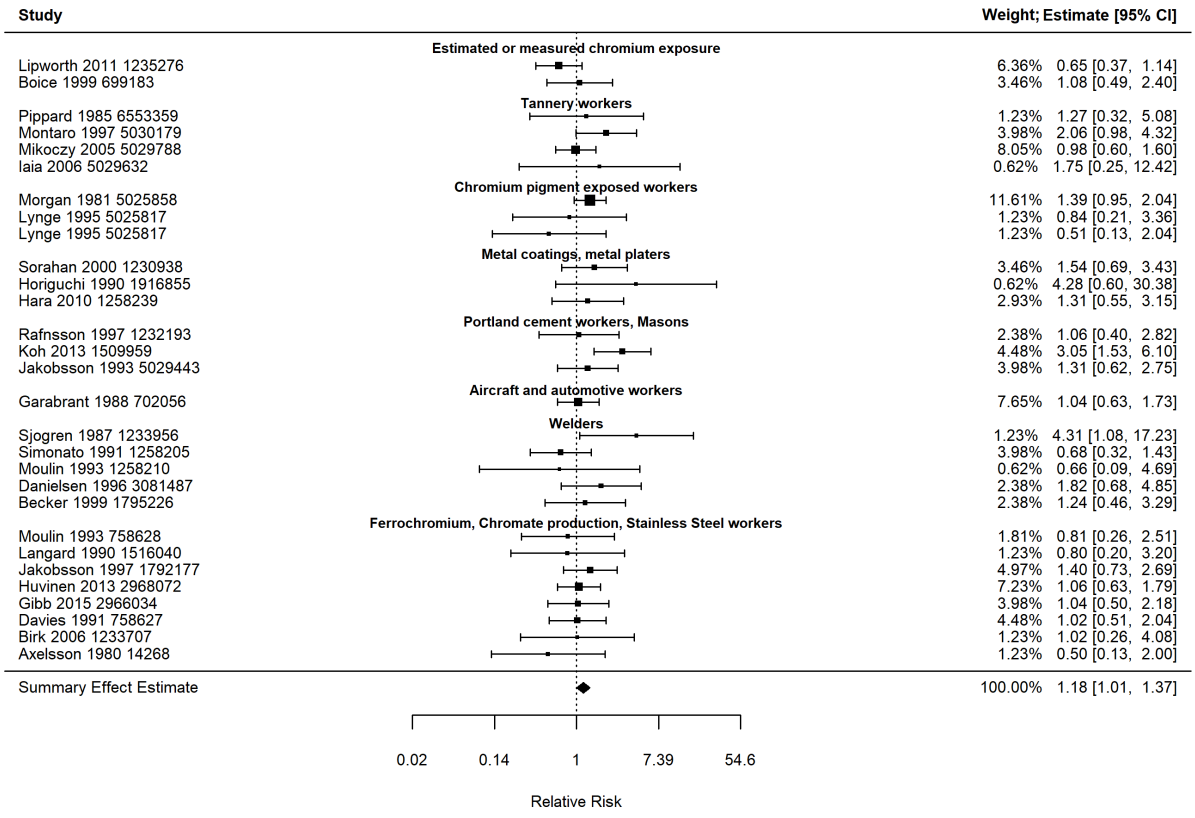

Figure C-20. Forest plot displaying summary measures for rectal cancer risk from studies reporting standardized mortality or incidence ratios.

C.3.2. Mechanistic Evidence Organized by the 10 Key Characteristics of Carcinogens

The hazard identification of cancers of the lung and GI tract include an analysis of whether a mutagenic mode of action (MOA) could be involved in Cr(VI)-induced carcinogenesis. Because a large and diverse set of mechanistic studies was identified that has potential relevance for informing Cr(VI)-induced carcinogenicity in the GI tract and lung, several prioritization factors have been considered to identify the most informative evidence for the MOA analysis for cancer of the GI tract and lung following Cr(VI) exposures.

The first phase of the identification and screening of literature pertinent to the MOA analysis is described in Appendix B.1. Mechanistically relevant studies are not included in the initial PECO criteria, which are intended to identify studies in humans and animals reporting apical health effects data that will be evaluated for reporting quality, risk of bias, and sensitivity. Instead, studies reporting mechanistic data are initially screened and categorized to provide a clearer view of the proposed biological pathways and processes involved in the toxicity of the chemical and to identify critical research gaps. The initial broad literature search for Cr(VI) identified 1,522 Cr(VI)

mechanistic studies, which were screened for relevance and sorted into groups primarily based on the 10 key characteristics (KCs) of carcinogens (Smith et al., 2016). These studies, summarized in Appendix Sections C.3.3–C.3.12, were generally prioritized if they measured mechanistically relevant biomarkers in humans exposed to Cr(VI) or were experimental studies conducted in mammals exposed to Cr(VI) or in human primary cells or cell lines.

Because of the importance of determining whether Cr(VI) is mutagenic, it was determined that the evidence that could be most informative for the mutagenic potential of Cr(VI) would be subject to study evaluation for reporting, risk of bias, and sensitivity. This includes test systems in animals that measure mutations (e.g., transgenic rodent assays) and structural and numerical chromosomal aberrations (e.g., the micronucleus assay). The studies identified as most informative for mutagenic risk and evaluated in HAWC are summarized separately below for the GI tract and the lung. All other evidence for genotoxicity and other characteristics of carcinogens are summarized and synthesized as supporting evidence for biological pathways and processes related to carcinogenesis.

C.3.2.1. *Electrophilicity and DNA reactivity (KC#1)*

Studies informing the ability of Cr(VI), the reductive intermediates Cr(V) and Cr(IV), and the final form Cr(III) to bind DNA and proteins, forming adducts and crosslinks, are summarized in Table C-46, followed by a summary of the major findings.

Table C-46. Mechanistic studies informing the intracellular reduction of Cr(VI) and reactivity of Cr species with DNA and proteins

Study findings	Reference
Formation and stabilization of intracellular Cr species and reactive oxygen species	
Cr(V) complexes characterized by elemental analyses, electrospray mass spectrometry (ESMS), and electron paramagnetic resonance (EPR) spectroscopy	Bartholomäus et al. (2013)
Reduction of Cr(VI) generates Cr(V), superoxide and hydroxyl radicals in purified human cytochrome b(5) and NADPH:P450 reductase in reconstituted proteoliposomes (PLs)	Borthiry et al. (2007)
Two Cr(V) electron spin resonance (ESR) signals, g = 1.979 (nonthiol dependent) and 1.985 (thiol-dependent) in human bronchial epithelial cells (BEAS-2B) Signals blocked by suppressing NAD(P)H	Borthiry et al. (2008)
ESR spectroscopy and electrospray mass spectrometry measured long-lived Cr(V) complexes formed by reduction of Cr(VI) with p-bromobenzenethiol (RSH)	Levina et al. (2010)
Cr-DNA adducts in acellular/in vitro test systems	
Cr(VI) reduction by glutathione produces 2 Cr(V) complexes and glutathione thiyl radical, correlated with Cr-DNA adduct formation; no DNA strand breaks Cr(VI) reduction by H_2O_2 produces hydroxyl radical, DNA strand breaks, and 8-OHdG adducts with no Cr(V) generation	Aiyar et al. (1991, 1990; 1989)
Cr(VI) showed weak complexation with DNA at high molar ratios of CrO_4^{2-} to nucleotides (r > 1) but not at low molar ratios (r = 1:20 to r = 1:1).	Arakawa et al. (2000)

Study findings	Reference
Calf thymus DNA and defined DNA polynucleotides	Borges and Wetterhahn (1989)
DNA-chromium adducts cause guanine-specific arrests of DNA replication in calf thymus DNA using mammalian polymerases alpha and beta	Bridgewater et al. (1998)
Low, nonphysiological levels of ascorbate lead to GSH reduction of Cr(VI) that produce weakly mutagenic glutathione-Cr(III)-DNA adducts and no oxidative damage in human fibroblasts	Guttmann et al. (2008)
↑ ATM activation by Cr(VI) in ascorbate-deficient cells; no ATM activation when ascorbate levels are restored in human lung H460 cells and normal human lung fibroblasts	Luczak et al. (2016)
DNA-protein crosslinks formed in human lung A549 cells in 3 steps: Cr(VI) reduction to Cr(III), Cr(III)-DNA binding, and capture of proteins by DNA-bound Cr(III)	Macfie et al. (2010)
Interstrand DNA crosslinks formed in XPA-null (GM04312), FANCD2-null (GM16633), and FANCD2-complemented (GM16634) human fibroblasts with ascorbate (1.3% of total adducts, dose-dependent) and glutathione (<1%, sublinear) Absence of FANCD2 and XPF-ERCC1 endonuclease produced no hypersensitivity to Cr(VI) with restored ascorbate levels Authors interpreted as evidence that DNA crosslinks are more commonly formed in vitro	Morse et al. (2013)
↑ ascorbate-Cr(III)-DNA crosslinks in human lung A549 cells with restored ascorbate levels (25% of total Cr-DNA adducts) Ascorbate-Cr(III)-DNA crosslinks inhibited by Mg^{2+} ions suggests predominant binding of ascorbate-Cr(III) to DNA through phosphate oxygen	Quievryn et al. (2002)
Cr-DNA adducts, and not oxidative strand breaks, responsible for mutation and replication fork stalling in SV40-immortalized human HF/SV fibroblasts Ternary adducts more mutagenic than binary Mutation spectra equally deletions and point mutations targeting G/C	Quievryn et al. (2003)
Reduction of Cr(VI) by ascorbate produced stable adducts in supercoiled ϕX174 DNA that could be disrupted only by phosphate treatment at high concentrations of ascorbate (1 mM) and not at lower concentrations of ascorbate (0.2 mM)	Quievryn et al. (2006)
Cr(III) forms adducts with DNA via formation of Cr-protein crosslinks with amino acids in intact cell cultures.	Salnikow et al. (1992)
Fanconi anemia cells (hypersensitive to DNA crosslinking agents) are hypersensitive to Cr(VI)-induced apoptosis, clonogenic lethality, and DNA DSBs (gH2AX foci).	Vilcheck et al. (2006; 2002)
In human fibroblasts, ternary adducts glutathione-Cr(III)-DNA and histidine-Cr(III)-DNA are more mutagenic than cysteine-Cr(III)-DNA; binary Cr-DNA adducts were weakly mutagenic	Voitkun et al. (1998)
Cr(VI) reduction by cysteine forms Cr-DNA and Cys-Cr-DNA adducts and interstrand DNA-DNA crosslinks that increase with Cr(VI) concentration but did not produce DNA breaks or oxidative DNA damage	Zhitkovich et al. (2000)
In human fibroblasts, binding of Cr(III) and the formation of Cr(III)-DNA adducts induces structural distortions of DNA Ascorbate-Cr(III)-DNA and cysteine-Cr(III)-DNA adducts were found to be 31-fold and 5.3-fold more mutagenic than the binary Cr(III)-DNA adducts, respectively	Zhitkovich et al. (2001)
Cysteine-dependent Cr(VI) reduction led to Cr-DNA adducts (54%), cysteine-Cr-DNA adducts (45%), and interstrand DNA crosslinks (1%)	Zhitkovich et al. (2002)

Study findings	Reference
Cr(III)-DNA binding: • To backbone phosphates through reversible electrostatic interactions • To nucleobases with the preference G>C>T~A, generating stable crosslinks resistant to dissociation by EDTA; this binding is slow due to slow ligand exchange in Cr(III) complexes	Zhou et al. (2016)
In vivo test systems	
Exposed: Four human adult volunteers *Referents:* Preingestion background DNA-protein crosslink levels for each individual served as the controls Ingestion of a single bolus dose of 5,000 µg Cr(VI) as $K_2Cr_2O_7$ alone (Cr(VI) or reduced to Cr(III) with orange juice; approximately equivalent to 71 µg Cr(VI)/kg, assuming a body weight of 70 kg. Blood samples were collected at 0, 60, 120, 180, and 240 min after ingestion. • No significant changes in DNA protein cross-linking after ingestion • Very small sample size limits confidence in the results • The only known ingestion study in humans; all other human studies evaluate inhalation in occupational cohorts	Kuykendall et al. (1996)
Rat, Fischer 344, male, exposed to 100 or 200 mg/L $K_2Cr_2O_7$ in drinking water, 3 or 6 wk • ↑ DNA-protein crosslinks in liver; not in splenic lymphocytes • No cytotoxicity detected	Coogan et al. (1991a)
Rat, exposed to 20 mg/kg by i.p. injection, 40 h • ↑ Cr binding to DNA, nonhistone proteins, and cytoplasmic RNA-protein fraction in liver	Cupo and Wetterhahn (1985)

DNA reactivity of Cr species

Formation of Cr(V) and free radicals generated by these species is considered to play an important role in Cr(VI)-induced DNA damage. Cr(V) intermediates have been shown to induce direct oxidative DNA damage through abstraction of H atoms at the deoxyribose sugar moiety, resulting in the generation of abasic sites (Sugden and Wetterhahn, 1997). Cr(V) can also induce oxidative damage indirectly through the generation of reactive oxygen species, causing oxidative damage at dG sites and formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) residues, presumably via production of hydroxyl radicals generated through a Fenton-like reaction (i.e., $Cr(V)+H_2O_2 \rightarrow Cr(VI) + \cdot OH + OH^-$) (reviewed in Levina and Lay (2005) and Sugden and Stearns (2000)).

Cr(IV) is the major transient form of intracellular reduction of Cr(VI) in cells with physiological levels of ascorbate. An in vitro study using synthetic compounds of Cr(VI) reduction

intermediates showed significantly increased mutation frequencies in cells exposed to Cr(IV) compared to Cr(V) (Wakeman et al., 2017). In the presence of hydrogen peroxide, Cr(IV) is a more potent Fenton-like reagent than Cr(V) and generates hydroxyl radicals, which has been shown to cause DNA strand breaks and oxidative damage at dG positions that are preventable by hydroxyl radical scavengers (Luo et al., 1996). In addition, this process generates Cr(V), leading to further oxidative DNA damage.

Cr(III) is a thermodynamically stable species produced by the reduction of Cr(VI) through the intermediary species Cr(V) and Cr(IV), which transiently exist in variable amounts during the intracellular reduction of Cr(VI). The interaction of Cr(III) with DNA is responsible for the formation of DNA lesions, the most common of which are the binary Cr(III)-DNA adducts (Floro and Wetterhahn, 1984). Two different forms of Cr(III)-DNA adducts have been suggested by a study investigating the reation of DNAzyme Ce13d with $CrCl_3$. The results showed that Cr(III) first binds to the DNA phosphate backbone through weak electrostatic interactions, then slowly coordinates with all four nucleobases, forming highly stable DNA interstrand crosslinks (Zhou et al., 2016). A more recent study concluded instead that Cr(III) is coordinated with N7 of dG as a $[Cr(H_2O)_5]^+$ complex located within the major groove of the DNA double helix structure without the direct participation of neighboring bases of phosphate groups (Brown et al., 2020), but also supported the formation of interstrand crosslinks. It is likely that the existing evidence of the reactions of Cr(III) complexes with DNA do not provide a full model of all possible Cr-DNA interactions that occur during Cr(VI) reductions with variable amounts of intracellular reducers.

Binary Cr(III)-DNA adducts can further conjugate proteins and form DNA-protein cross-links (DPCs). The DPCs represent ternary protein-Cr(III)-DNA adducts generated by a rate-limiting reaction of binary Cr(III)-DNA adducts with proteins. The formation of DPCs in cultured cells exposed to Cr(VI) is decreased by the depletion of glutathione and is facilitated by the restoration of physiological levels of ascorbate (Macfie et al., 2010). Overall, the biological significance of the DPCs is still incompletely understood. In addition to their genotoxic potential, some studies demonstrated their ability to inhibit specific gene expression (Macfie et al., 2010).

Other ternary adducts have been identified in cells exposed to Cr(VI), including ascorbate-Cr(III)-DNA, glutathione-Cr(III)-DNA, cysteine-Cr(III)-DNA, and histidine-Cr(III)-DNA. Ascorbate-Cr(III)-DNA adducts were detected in Cr(VI)-treated human A549 lung cancer cells with restored ascorbate levels, accounting for approximately 6% of the total DNA-bound chromium (Quievryn et al., 2002). In addition, the binding of Cr(III) and the formation of Cr(III)-DNA adducts induces structural distortions in DNA (Zhitkovich et al., 2001).

Biological effects of Cr-DNA interactions

Binary Cr(III)-DNA adducts formed by the reaction of Cr(III) aqua complexes and DNA are reportedly weakly mutagenic lesions, with a considerably lower mutagenic potential when compared to any ternary ligand-Cr-DNA adduct (Quievryn et al., 2003). Indeed, ascorbate-Cr(III)-DNA and cysteine-Cr(III)-DNA adducts were found to be 31-fold and 5.3-fold more mutagenic than

the binary Cr(III)-DNA adducts, respectively (Holmes et al., 2008; Zhitkovich et al., 2001). Consequently, ascorbate appears to be the most important intracellular reducer of Cr(VI) that forms highly mutagenic DNA adducts. The ternary adducts glutathione-Cr(III)-DNA and histidine-Cr(III)-DNA were also found to be mutagenic, and their mutagenicity exceeded that of cysteine-Cr(III)-DNA (Voitkun et al., 1998). Ternary adducts are also more genotoxic than binary Cr(III)-DNA adducts, demonstrated through more prominent DNA replication fork stalling by ternary adducts in comparison to binary adducts (e.g., (Quievryn et al., 2003; Snow and Xu, 1991).

Under lower, non-physiological levels of ascorbate, reduction of Cr(VI) by glutathione in vitro produced mutagenic glutathione-Cr(III)-DNA adducts (Guttmann et al., 2008). This finding implies that lesions produced at physiological concentrations of GSH in ascorbate-depleted cells are less mutagenic and suggests that studies employing standard cell cultures with low intracellular ascorbate could have underestimated the mutagenicity of Cr(VI). Taken together, studies performed under non-physiological, low ascorbate levels favored the production of Cr(V) and a lower amount of highly mutagenic ternary species, which did not accurately reflect the genotoxic and mutagenic effects of Cr(VI) *in vivo* (Quievryn et al., 2006).

Cells with restored ascorbate levels display considerably different cell signaling responses to Cr(VI) than in ascorbate-depleted cells. As previously discussed, reduction of Cr(VI) by glutathione in vitro and in cells with depleted ascorbate leads to an appreciable formation of Cr(V), which can act as an oxidant (Quievryn et al., 2003), while reduction of Cr(VI) by ascorbate is a low oxidant generating process (Wong et al., 2012). Treatment with Cr(VI) also induces double-strand breaks in cells with restored ascorbate; however, these are formed selectively in euchromatin and their signaling is dependent on ATR rather than on ATM kinase (Deloughery et al., 2015).

C.3.2.2. *Genotoxicity (KC#2)*

In vivo studies

Inhalation route of exposure

Mutagenic MOA studies

Studies considered most relevant to a mutagenic MOA analysis for lung cancer are studies of occupationally or environmentally exposed humans or studies in experimental animals exposed via inhalation or intratracheal instillation and include measures of gene mutation (prior to tumorigenesis), micronuclei induction, and chromosomal aberrations. Occupational studies were considered only if they included a comparison or referent population exposed to Cr(VI) at lower levels (or no exposure/exposure below detection limits) or for shorter periods of time. Animal studies were considered if they included a concurrent control group exposed to vehicle-only treatment or an untreated control.

Twenty-nine studies in humans occupationally exposed and one study in transgenic mice were identified. These were evaluated in HAWC using criteria specific to the mutational assay used

in the study to judge the outcome ascertainment domain. The overall confidence judgments and summaries of the study findings can be found in the Cr(VI) Toxicological Review in Section 3.2.3 Cancer—Mechanistic Evidence; more extensive summaries of the human studies are in Table C-47 below. Human studies reporting other outcomes informative to genotoxicity are summarized in the following sections.

Table C-47. Chromosomal mutation studies in humans exposed to Cr(VI) via inhalation (evaluated in HAWC)

Study overview	Exposure[a]	Results	Comments	Reference
Chromosomal aberrations				
Cross-sectional study, South India. *Exposed*: n = 72 (n = 36 directly exposed via work in a tannery, n = 36 indirectly exposed via residence in proximity to tanneries) *Referent*: n = 36 unexposed controls ("normal and healthy individuals who had not exposed themselves to any kind of chemicals or radiation")	*Assessment*: Exposure to Cr(VI) inferred based on occupation and residence. In addition, Cr was measured in urine and air samples (unclear where air samples were collected) *Levels:* There was a gradient in levels of both, there were detectable chromium levels in both air and urine for "controls" Direct exposure (n = 36) (mean ± SD): Total Cr in air (1 mg/m^3): 0.101 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.021 ± 0.003 Cr content in urine: 2.11 ± 1.01 Indirect exposure (n = 36): Total Cr in air (1 mg/m^3): 0.089 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.013 ± 0.005 Cr content in urine: 1.81 ± 0.88 Controls (n = 36): Total Cr in air (1 mg/m^3): 0.014 ± 0.004 Cr(VI) in air (0.001 mg/m^3): 0.006 ± 0.001 Cr content in urine: 0.54 ± 0.39 *Duration:* Directly exposed subjects were "selected based on the duration of their exposure (0–5; 6–10; 11–15; 16–20; 21–25 years) and were known to be exposed to Cr(VI) for a minimum of 8 h/day," while indirect exposure was inferred from residence of at least 30 yr duration, "in and around the tanneries."	↑ chromosomal aberrations in DE group compared to IE group and controls Also observed ↑ mean tail length for comet assay in DE group compared to IE group and controls and ↑ MN among directly exposed subjects compared to indirectly exposed & controls; further elevated in those with longer duration of exposure	*Low* confidence. There is evidence of a gradient of chromium exposure across the three study groups, but inference is limited by small sample size and lack of description. Some of the controls also had detectable chromium in urine, suggesting this is not really a true "control" group. Concerns with chromosomal aberrations assay—culture of 72 h may have missed first in vitro cell division. Very limited evaluated of confounders.	Balachandar et al. (2010)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Bulgaria. *Exposed:* Chromium plate workers (n = 15) *Referents 1:* age, gender, smoking-matched controls (n = 15) *Referents 2:* individuals of similar age from unpolluted rural region (n = 8)	*Assessment*: Blood samples and buccal mucosal cells taken from exposed group; exposure to Cr(VI) inferred based on occupation. Also measured Cr with personal air samplers and in urine samples. *Levels*: There was a gradient of chromium in air and urine across groups, although there was detectable Cr in urine of rural controls. Mean air concentration of total chromium was 0.0075 mg Cr/m^3 in the low-exposure group (n = 4) and 0.0249 mg Cr/m^3 in the high-exposure group (n = 7). (4 workers in the exposed group temporarily discontinued exposures and were considered separately.) Mean concentrations of Cr in urine were 18.63 µg/L (low) and 104.22 µg/L (high). Results reported for combined groups (0.0075 and 0.0249 mg Cr/m^3). *Duration:* Duration of exposure ranged from 2 to >20 yr; mean duration of exposure was not reported.	In exposed workers compared to referent 1: Buccal cells: No difference in frequencies of chromosomal aberrations or SCEs Study also reported significantly increased MN in buccal cells and lymphocytes in referent 1 compared to referent 2	*Low* confidence. Although exposed and unexposed workers were matched on age, sex, and smoking habit, the two unexposed (worker and rural) groups were combined, resulting in lower confidence in comparability of exposed and unexposed group comparisons. Inference is further limited by small sample size and lack of description. Similar proportion of centromere-positive and -negative micronuclei indicate both clastogenic and aneugenic effects occurring.	Benova et al. (2002)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study of workers at a single facility in China. *Exposed*: n = 7 electroplating workers exposed to chromium *Referent*: n = 10 office workers Note: also included n = 7 electroplating workers exposed to nickel	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr in personal air samples from work room, hair, and stool samples. *Levels*: Authors note that there seemed to be little cross-contamination of nickel and chromium in respective work areas based on air samples, but stool samples showed similar levels of both compounds between exposure groups. Hair levels of chromium were higher in chromium compared with nickel workers. The mean chromium (total) air concentration (by random air collection) was 8.1 µg/mm^3, the mean chromium concentration in stool samples was 8.5 µg/g stool, and the mean chromium concentration in hair was 35.68 µg/g. (The exposure level of 8.1 µg chromium/mm^3 is as reported by Deng et al. (1988); however, this appears to be a reporting error, as this concentration is equivalent to 8,100,000 mg chromium/m^3.) *Duration:* Mean duration of occupational exposure was 12.8 yr.	↑ chromosomal aberrations in chromium workers compared to nickel workers & controls ↑ SCE in chromium & nickel workers compared to controls	*Low* confidence. Although controls were age and sex matched to exposed subjects and were stated to have similar socioeconomic status, the sample size is quite small and the analysis limited. Also unclear how well differentiated chromium exposure is by group—analyses of chromium in hair suggest a delineation with controls, but no information on stool samples that showed similarities between nickel and chromium workers.	Deng et al. (1988)
Cross-sectional study, Slovak Republic. *Exposed*: n = 73 male welders *Referent*: n = 71 male controls (administrative officers and hospital employees)	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr in blood. *Levels*: Exposed workers had average values about twice as high as referent group (stated to be significantly different). Mean ± SE was 0.07 ± 0.04 vs. 0.03 ± 0.007 µmol/L. *Duration:* Mean ± SD duration of occupational exposure was 10.2 ± 1.7 yr.	No differences in CAs, CTAs, and CSAs between exposed and control groups ↑ CAs in individuals with Gln/Gln genotype compared to Arg/Gln or Arg/Arg genotypes in XRCC1 Arg299Gln; more pronounced in Cr-exposed workers	*Medium* confidence. Main limitations are related to lack of description (e.g., for participant selection) and lack of evaluation of confounders aside from smoking.	Halasova et al. (2012)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Slovak Republic. *Exposed*: n = 39 male welders *Referent*: n = 31 male controls (source not given)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr in blood. *Levels:* Exposed workers had average values about twice as high as referent group. Mean ± SE was 0.07 ± 0.04 vs. 0.03 ± 0.007 µmol/L. *Duration*: Mean ± SD duration of occupational exposure was 10.2 ± 1.7 yr.	No significant differences in frequencies of CTAs between exposed and control groups; only minor differences in CAs between groups ↑ CSAs in exposed compared to control groups ↑ CAs & CTAs in individuals with Gln/Gln genotype compared to Arg/Gln or Arg/Arg genotypes in XRCC1 Arg299Gln	*Low* confidence. Main limitations are related to sample size, unclear differentiation between exposure groups, and lack of description (e.g., for participant selection).	Halasova et al. (2008)
Cross-sectional study, Finland. *Exposed*: n = 23 male welders *Referent*: n = 22 male office employees at a printing company	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Welders were chosen due to "exposure to MMA/SS welding fumes with little or no exposure to other agents in their occupational history." Also measured total Cr in urine. *Levels:* Urine levels are not discussed in text (table shows values ranging from 0.20 to 1.55 µmol/L). *Duration:* Welders likely had Cr(VI) exposure due to history of manual metal arc welding for at least 4 yr and most for much longer (mean ± SD = 21 ± 10 yr).	No significant differences (frequency of chromosome aberrations or SCEs)	*Low* confidence. Although Cr(VI) exposure seems likely to occur among these welders, the analysis is limited by small sample size when stratifying by smoking (found to be related to the outcome).	Husgafvel-Pursiainen et al. (1982)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Japan. *Exposed*: n = 51 male stainless steel welders *Referent*: n = 33 male office or research workers in the same factory	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Total Cr also measured in urine samples. *Levels:* Mean urinary Cr was 9.8 and 4.2 µg/L among exposed and referent group, respectively. *Duration:* Welders had been "constantly engaged" in stainless steel welding for 5–20 yr (mean 12 yr) and thus are presumed to have high potential for Cr(VI) exposure.	↑ chromosomal aberrations and SCEs in welder compared to controls	*Low* confidence. The main limitations are related to the outcome evaluation and to poorly described and reported data analysis and lack of consideration of potential confounders.	Koshi et al. (1984)
Cross-sectional study, Sweden. *Exposed*: n = 24 stainless steel welders from six industries *Referent*: n = 24 matched referents who "had no occupational (or other) experience with the handling of stainless steel (or other known mutagenic/carcinogenic agents)"	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in air (welders only) and urine (all). *Levels:* Mean urinary Cr was 47 and 1.5 µmol/mol creatinine among exposed and referent group, respectively. Mean air Cr level 81 µg/m^3. *Duration:* Welders were selected for their "long and intense" welding on stainless steel (mean work duration of 19 yr).	No significant differences (frequency of breaks or fragments; gaps and isogaps; interchanges, dicentrics, rings, and markers; structural aberrations, hyperdiploidy; SCEs)	*Low* confidence. Main limitations are related to outcome ascertainment and statistical analysis, as well as limited description of results.	Littorin et al. (1983)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, South Korea. *Exposed*: n = 51 male chrome plating and buffing workers *Referent*: n = 31 male office workers from "industrial areas" in South Korea	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr measured in air samples (total and VI), blood, and end-shift urine samples (See Table 1). *Levels*: Concentrations in blood and urine were significantly higher in exposed workers, indicating adequate delineation between groups. For example, the geometric mean blood level of Cr was 0.9 and 0.2 µg/dL in exposed and referent workers, respectively. Differently, while air measures were higher for exposed workers the difference was not statistically significant. *Duration:* Mean duration of occupational exposure was 9.1 yr (range: 1 mo to 40 yr).	↑ frequency of chromatid exchange; chromosome/chro-matid breaks and exchanges; and of translocations, with higher blood Cr ↑ frequency of translocations in exposed compared with unexposed.	*Low* confidence. Main limitations are related to lack of description for analysis and results reporting.	Maeng et al. (2004)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Italy. *Exposed*: n = 38 male plating factory workers (two groups from factories using nickel and chromium for bright plating, and two groups from factories using only chromium for hard plating) *Referent*: n = 35 "healthy male sanitary workers" not known to have chromium exposure Note: Analysis of SCEs only included n = 21 workers from factories using only chromium, and n = 14 "healthy blood donors" with similar selection as unexposed worker control group	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Exposed group was stratified based upon coexposure to nickel ("bright" plating, vs. "hard" plating). Also measured Cr in urine. *Levels:* Urinary Cr levels were lowest in controls (mean ± SD = 1.9 ± 1.4 µg/g crt), intermediate in bright plating (6.1 ± 2.8 µg/g crt), and highest in hard plating groups (10.0 ± 7.5 µg/g crt), indicating adequate delineation between groups. *Duration:* Mean (SD) yr of exposure: bright plating = 9 (11); hard plating = 7 (3)	↑ frequency of total aberrations, chromosome-type aberrations in all exposed. Also ↑ chromatid-type aberrations in bright platers. ↑ SCEs for some worker compared to blood donors.	*Low* confidence. Main limitations are related to outcome ascertainment, small sample size for certain analyses, and lack of description (e.g., for participant selection and statistical analysis).	Sarto et al. (1982)

Study overview	Exposure[a]	Results	Comments	Reference
Micronuclei				
Cross-sectional study, South India. *Exposed*: n = 72 (n = 36 directly exposed via work in a tannery, n = 36 indirectly exposed via residence in proximity to tanneries) *Referent*: n = 36 unexposed controls ("normal and healthy individuals who had not exposed themselves to any kind of chemicals or radiation")	*Assessment*: Exposure to Cr(VI) inferred based on occupation and residence. In addition, Cr was measured in urine and air samples (unclear where air samples were collected) *Levels*: There was a gradient in levels of both urine and air, there were detectable chromium levels in both air and urine for "controls." Direct exposure (n = 36) (mean ± SD): Total Cr in air (1 mg/m^3): 0.101 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.021 ± 0.003 Cr content in urine: 2.11 ± 1.01 Indirect exposure (n = 36): Total Cr in air (1 mg/m^3): 0.089 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.013 ± 0.005 Cr content in urine: 1.81 ± 0.88 Controls (n=36): Total Cr in air (1 mg/m^3): 0.014 ± 0.004 Cr(VI) in air (0.001 mg/m^3): 0.006 ± 0.001 Cr content in urine: 0.54 ± 0.39 *Duration:* Directly exposed subjects were "selected based on the duration of their exposure (0–5; 6–10; 11–15; 16–20; 21–25 years) and were known to be exposed to Cr(VI) for a minimum of 8 h/day" while indirect exposure was inferred from residence of at least 30 year's duration, "in and around the tanneries."	↑ micronuclei peripheral lymphocytes among directly exposed subjects compared to indirectly exposed & controls; and further elevated in those with longer duration of exposure	*Low* confidence. There is evidence of a gradient of chromium exposure across the three study groups, but inference is limited by small sample size and lack of description. Some controls also had detectable chromium in urine, suggesting this is not really a true "control" group. Very limited evaluation of confounders.	Balachandar et al. (2010)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Bulgaria. *Exposed:* Chromium plate workers (n = 15) *Referents 1:* age, gender, smoking-matched controls (n = 15) *Referents 2:* individuals of similar age from unpolluted rural region (n = 8)	*Assessment:* Blood samples and buccal mucosal cells taken from exposed group; exposure to Cr(VI) inferred based on occupation. Also measured Cr with personal air samplers and in urine samples. *Levels:* There was a gradient of chromium in air and urine across groups, although there was detectable Cr in urine of rural controls. Mean air concentration of total chromium was 0.0075 mg Cr/m^3 in the low-exposure group (n = 4) and 0.0249 mg Cr/m^3 in the high-exposure group (n = 7). (4 workers in the exposed group temporarily discontinued exposures and were considered separately.) Mean concentrations of Cr in urine were 18.63 µg/L (low) and 104.22 µg/L (high). Results reported for combined groups (0.0075 and 0.0249 mg Cr/m^3). *Duration:* Duration of exposure ranged from 2 to >20 yrs; mean duration of exposure was not reported.	↑ micronuclei per peripheral blood leukocytes (PBLs) & ↑ overall number of PBLs with micronuclei in exposed workers compared to controls ↑ micronuclei in buccal cells in exposed workers compared to controls No significant difference between proportion of C+ and C− micronuclei in buccal or PBLs in exposed workers compared to controls	*Low* confidence. Positive results reported for combined groups (0.0075 and 0.0249 mg chromium/m^3). Although exposed and unexposed workers were matched on age, sex, and smoking habit, the two unexposed (worker and rural) groups were combined, resulting in lower confidence in comparability of exposed and unexposed group comparisons. Inference is further limited by small sample size and lack of description.	Benova et al. (2002)
Cross-sectional study, India. *Exposed*: n = 102 male welders *Referent*: n = 102 male controls selected from the general population "with no history of exposure to welding fumes or any known physical or chemical agent in the workplace, but belonged to the same age group and socio-economic status as the welders."	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Welders used shielded metal arc welding and were working with stainless steel electrodes. Also measured Cr in blood for a sample (~50%) of subjects. *Levels:* Welders had much higher chromium compared with controls, indicating delineation of exposure. Mean Cr was 151.65 and 17.86 µg/L in exposed and referent, respectively. DNA damage was measured by comet assay in all 204 subjects; frequency of micronuclei was measured in 58 welders and 53 controls. *Duration:* The duration of exposure varied widely (range: 1–24 yr). (Overall mean not presented)	In buccal cells of exposed welders compared to referent: ↑ micronuclei ($p < 0.001$); correlated with duration of work ($p = 0.0001$), age ($p = 0.007$), and Cr level in blood	*Low* confidence. Limitations related to outcome evaluation, such as the use of outdated methods no longer recommended, could lead to inaccurate scoring. A description/details on participant selection (e.g., concern for potential selection bias) is lacking. Study also reported ↑ mean comet tail length in whole blood cells ($p < 0.001$).	Danadevi et al. (2004)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Egypt. *Exposed*: n = 41 male electroplating workers exposed to chromium and nickel *Referent*: n = 41 male administrative workers at the same facility	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr (and nickel) in serum. *Levels:* Serum Cr significantly higher in exposed compared with controls. Mean Cr was 3.30 and 0.23 µg/L in exposed and referent, respectively. *Duration:* Exposed workers were required to have worked in electroplating section at least 2 yr, but most worked for considerably longer with mean ± SD = 26.68 ± 11.21 yr.	In buccal cells of exposed electroplaters compared to referent: ↑ micronucleus induction ($p < 0.001$) ↑ serum Cr correlates with ↑ micronuclei ($p < 0.05$)	*Medium* confidence. Exposed and unexposed groups are delineated, although limited description of methods (e.g., participant selection) and known coexposure to nickel could limit inference. Study also reported ↑ serum 8-OHdG.	El Safty et al. (2018)
Cross-sectional study, China. *Exposed*: n = 87 workers from a single factory in China, who had "occupational exposure to chromate from different work sections" *Referent*: n = 30 working in administrative offices without chromate exposure	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in air samples and in blood. *Levels:* Authors state "The concentration of Cr in the air and blood of subjects in the exposure group were significantly higher than the control group ($p < 0.001$)," which increases confidence in delineation of exposure groups. Geometric Mean ± SD of Cr in blood was 8.5 ± 1.3 µg/L in exposed vs. 4.1 ± 1.4 µg/L in referent group, while median (IQR) of air concentrations were 15.5 (19.0) vs. 0.2 (0.4) mg/m^3. *Duration*: Median duration of employment was 5 yr in both exposed and referent.	↑ MN in peripheral lymphocytes in exposed workers compared with referent	*Medium* confidence. Main limitations are related to lack of description (e.g., for participant selection). Study also reported ↑ hypermethylation of CpG sites and 8-OHdG adducts.	Hu et al. (2018) Related studies: Li et al. (2014a; 2014b)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed 1: male welders working in areas without collective protections (n = 27) *Exposed 2:* male welders working in locations with smoke extraction systems (n = 33) *Referents:* office workers with no history of occupational exposure to welding fumes or other physical/chemical agent in workplace (n = 30)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in blood and urine. *Levels:* Cr levels in blood and urine were higher among both groups of welders compared with controls (means 129 to 145, compared with 92 µg/L), and urinary chromium was higher among welders working without smoke extraction systems. *Duration:* Welders exposed for 0.5–45 yr	↑ mean BN % in lymphocytes of welder compared to controls	*Low* confidence. Main limitations are related to lack of description (e.g., for participant selection, analysis), unknown contribution of Cr(VI) to Cr exposure (states that <5% of welding was done on stainless steel, which raises concern that total Cr measured in blood and urine may be attributed to Cr(III) exposure) and known coexposures to other metals.	Iarmarcovai et al. (2005)
Cross-sectional study, China. *Exposed:* n = 29 "healthy" chrome platers employed for at least one yr at two facilities *Referent*: n = 29 subjects "randomly selected from the healthy workers in the same enterprises and been engaged in public security, support services, or administration work for more than one yr, and had no specific chromate exposure history"	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr in blood. *Levels:* Blood Cr levels were significantly higher among exposed compared with unexposed workers, indicating adequate delineation between groups. Mean (range) values were 15.2 (2.1, 42) in exposed vs. 4.6 (0.2, 28) in referent group. *Duration*: Chrome platers had been employed for at least one yr.	↑ micronuclei frequencies in peripheral lymphocytes of Cr-exposed workers compared to controls, but no correlation between blood Cr concentration and micronuclei	*Low* confidence. Limitations are the limited and poorly described statistical analysis and limited description (e.g., for participant selection). Small sample size. Inconsistent results could indicate the influence of other occupational hazards on micronuclei concentrations.	Linqing et al. (2016)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Sweden. *Exposed*: n = 24 stainless steel welders from six industries *Referent*: n = 24 matched referents who "had no occupational (or other) experience with the handling of stainless steel (or other known mutagenic/carcinogenic agents)"	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in air (welders only) and urine (all). *Levels:* Mean urinary Cr was 47 and 1.5 µmol/mol creatinine among exposed and referent group, respectively. Mean air Cr level 81 µg/m^3. *Duration:* Welders were selected for their "long and intense" welding on stainless steel (mean work duration of 19 yr).	No significant differences in micronuclei between exposed and referent groups	*Uninformative* (for micronucleus only). Main limitations are primarily due to extended culture times and the lack of a measure of cell replication, which could result in bias toward the null. Other limitations are related to outcome ascertainment and statistical analysis, as well as limited description of results.	Littorin et al. (1983)
Cross-sectional study, China. *Exposed*: n = 120 chromate-exposed workers working at a chromate production facility *Referent*: n = 97 unexposed workers at same facility ("without contact history of harmful substances")	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr in whole blood. *Levels:* Cr levels were significantly higher among exposed compared with controls, indicating delineation of exposure. Median (interquartile range) of Cr in whole blood was 2.81 (3.86) and 0.99 (1.21) µg/L in exposed and referent groups, respectively. *Duration:* Mean (SD) yr of exposure in chromate group = 14.57 (5.85).	↑ MN frequency ratio in lymphocytes of exposed; results of exposure-SNP interaction on MN presented as well	*Medium* confidence. Main limitations are related to lack of description (e.g., for participant selection and statistical analysis).	Long et al. (2019)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Portugal. *Exposed 1*: n = 5 stainless steel welders exposed to Cr(VI) *Exposed 2:* n = 33 tannery workers exposed to Cr(III) *Referent*: n = 20–30 unexposed controls ("not known to be exposed to either environmental or occupational carcinogens")	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr in plasma and in urine (mid-shift for welders). *Levels:* Urinary and plasma chromium levels were higher in both exposed groups compared with controls. For example, mean ± SD levels in plasma were 2.43 ± 2.11 in tanners, 1.55 ± 0.67 in welders, and 0.41 ± 0.11 µg/L. *Duration:* Not reported	↑ micronuclei in lymphocytes among tanners compared to control group; (there was also a marginal increase in the welders group, but not statistically significant)	*Low* confidence. Main limitation is small number of welders, lack of description for participant selection, analysis, and confounders. Study also reported ↑ formation of DNA protein crosslinks in welders compared to controls.	Medeiros et al. (2003)
Cross-sectional study, Italy. *Exposed*: n = 17 tannery finishing workers with potential exposure to Cr(VI) *Referent* (2 groups): n = 21 and n = 17 workers "from different industries" Note: also evaluated n = 21 tannery workers with potential exposure to Cr(III)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. State that tannery finishing workers had potential for exposure to Cr(VI) but with no supporting description or evidence. Although unclear from the text, workers might have been from several different tanneries with differing potential for exposure to Cr(VI) containing dyes. *Levels:* Not reported *Duration:* Not reported	No significant associations	*Low* confidence. Main limitation is unclear potential for Cr(VI) exposure for tannery finishing workers.	Migliore et al. (1991)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, India. *Exposed*: n = 100 male electroplaters exposed to Cr(VI) and nickel. Group II: exposed <10 yr, n = 50; Group III: exposed for ≥10 yr, n = 50 *Referent*: n = 50 unexposed controls (Group I)	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr in plasma. *Levels*: Concentrations were significantly higher in exposed (and higher for longer exposed) workers compared with unexposed. Mean + SD levels for longer exposed and shorter exposed workers were 2.9 + 0.8 and 1.7 + 0.55 µg/L, respectively, while values for referent were 0.55 + 0.08 µg/L. *Duration:* Group II exposed 1−9 yr; Group III exposed 10−25 yr.	In buccal cells of Group II compared to Group I, and in Group III compared to Group II: ↑ micronucleus frequency ($p < 0.05$), correlated with Cr levels in plasma ($p < 0.01$)	*Low* confidence. Main limitations are related to outcome ascertainment, limited statistical analysis, and lack of description (e.g., for participant selection). Coexposure to nickel is also a concern. Study also reported ↑ nuclear anomalies (karyorrhexis, karyolysis, pyknosis) ($p < 0.05$).	Qayyum et al. (2012)
Cross-sectional study, India. *Exposed*: n = 66 welders *Referent*: n = 60 controls ("selected from the general population with no history of occupational exposure to welding fumes or any known physical or chemical agent in the workplace, but belonged to the same age group and socio-economic status as the welders")	*Assessment:* Exposure to Cr(VI) inferred based on occupation. State that welders were engaged in SMA welding, working with electrodes containing 20% chromium. *Levels:* Not reported. *Duration:* Duration of welding ranged from 5 to 20 yr.	In buccal cells of exposed welders compared to referent: ↑ micronucleus frequency and mean comet tail length (DNA damage) that increased with duration of work ($p < 0.05$)	*Medium* confidence. The overall sample size is adequate but might not be sufficient for analyses stratified by smoking and alcohol consumption (and might need to consider both simultaneously). Potential for chromium exposure seems high given occupational context, but lack of measurements in environmental or biological media are lacking.	Sudha et al. (2011)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Bulgaria. *Exposed 1*: n = 30 male workers at a hydraulic machinery plant. Of these, n = 16 had low level exposure to chromium (various occupations, did not work close to electroplating tanks), while n = 14 had higher exposure to chromium due to work as electroplaters *Exposed 2*: n = 10 hospitalized electroplaters from different plants were recruited from an occupational health clinic *Referent 1:* n = 5 male administrative workers from the hydraulic machinery plant *Referent 2*: n = 13 administrative workers (workplace not described)	*Assessment*: Exposure to Cr(VI) inferred based on occupation. The workers were split into two groups based on levels of exposure. Also measured Cr in air, erythrocytes, and urine for exposed workers only. *Levels:* Mean air chromium (total) concentrations were 43 and 83 µg/m^3 in the low- and high-exposure groups, respectively. Mean chromium concentrations in erythrocytes and urine of the low-exposure group were 4.31 and 3.97 µg/L, respectively. The mean chromium concentrations in erythrocytes and urine of the high-exposure group were 8.4 and 5.0 µg/L, respectively. *Duration:* Duration of employment ranged from 4 to 25 yr with mean durations of 10.44 and 11.63 yr in the low- and high-exposure groups, respectively.	↑ MN and binucleated cells carrying MN in lymphocytes of exposed compared to control; also found correlations of Cr measured in air, erythrocytes and urine, with higher MN.	*Low* confidence. Limitations are due to small sample size, questionable pooling of various exposed and control groups, lack of consideration of confounding, and limited description of analysis.	Vaglenov et al. (1999)

Study overview	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Austria. *Exposed*: n = 22 bright chrome plating workers exposed to chromium and cobalt *Referent*: n = 22 jail wardens	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Welders used mainly TIG process (95%) with smaller proportions of electric arc and very little autogenous welding. Also measured Cr in whole blood. *Levels*: Blood levels were higher in welders compared with controls. Mean + SD levels for exposed workers at the beginning and end of the work week were 1.4 + 0.9 and 2.3 + 1.5 µg/L, respectively, while values for referent were 0.2 + 0.2 µg/L. *Duration:* All welders worked 8 h/d, 3 wk before and during the collection of the samples.	In exfoliated cells of exposed chrome platers compared to referent: Buccal cells: ↑ micronucleus frequency by 23% that was not quite statistically significant (p = 0.516) Nasal cells: ↑ micronucleus frequency by 97% (p = 0.005) ↑ nuclear anomalies in both cell types	*Low* confidence. Limitations are due to small sample size and presence of coexposures, which precluded more detailed analysis to separate effects.	Wultsch et al. (2014)
Cross-sectional study, China *Exposed*: n = 79 chromate production workers *Referent*: n = 112 peasant volunteers without occupational chromate exposures	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr in blood, urine, and air. *Levels:* Concentrations were higher in all media among exposed (mean (range); air: 13.01 (1.03−56.60) µg/m^3; blood: 9.19 (1.17−51.88) µg/L; urine: 17.03 (2.78−97.23) µg/g) creatinine compared to controls (air: 0.073 (0.023−0.235) µg/m^3; blood: 3.44 (0.25−22.51) µg/L; urine: 1.42 (0.39−26.82) µg/g. *Duration:* Mean (SE) yr of work among chromate group = 14.89 (8.65).	↑ MN in binucleated cells among exposed compared to control group. Moderate correlations (0.353−0.517) between Cr in blood, urine, air, and MN	*Low* confidence. Limitations include unclear recruitment processes (leaving potential for selection bias), potential exposure to chromium in control group reducing sensitivity, and limited analysis (including unclear approach to address confounding).	Xiaohua et al. (2012)

The following studies were found to be *uninformative* due to critical deficiencies in the exposure or outcome domain: Cid et al. (1991), Coelho et al. (2013), Hilali et al. (2008), Sarto et al. (1990), Sellappa et al. (2010), and Wultsch et al. (2017).

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Supporting genotoxicity studies in lung tissue

In addition to the studies measuring gene and chromosomal mutation summarized above, other mechanistic evidence investigating genotoxicity specific to lung tissues following exposures to Cr(VI) was identified in preliminary title and abstract screening. These studies were tagged as "mechanistic" and further screened and tagged as "inhalation" and "cancer" if they were epidemiological studies of humans exposed to Cr(VI) via inhalation or studies conducted in lung tissues or cells that were relevant to carcinogenic processes. Four additional genotoxicity studies of lung tumor tissue in occupationally exposed humans were identified. Genotoxicity evidence from in vitro studies conducted in human primary or immortalized lung cells examining genotoxicity endpoints relevant to lung cancer are also summarized below. The evidence is summarized in Table C-48.

Table C-48. Supporting genotoxicity studies in lung tissues and cells following Cr(VI) exposures

Study overview	Exposure[a]	Results	Comments	Reference
Gene mutation or gene expression in tumor tissue				
20 lung tumor & normal tissue samples from 19 individuals undergoing surgery for lung cancer or at autopsy	*Assessment:* Based on occupation *Levels:* Not reported *Duration:* Male workers exposed to chromate for average 21.7 ± 9.1 (8–38) yr	P53 mutations found in 4 (20%) of 20 chromate-exposed lung samples ↓ occurrence of p53 mutations in chromate exposed workers Key differences in chromate exposed workers: no G-to-T transversions; 50% point mutations had changes in AT base pairs; 50% of those with point mutations had double missense mutations	P53 mutations in chromate-exposed workers with lung cancer; the pattern of p53 mutations in lung cancer patients exposed to chromate differed from that of common lung cancers in 3 respects. No adjustments for potential confounders; no information on smoking provided; small sample size; limited information on selection.	Kondo et al. (1997)
Exposed 1: exocrine pancreatic cancer cases with K-ras mutated tumors (n = 83) *Exposed 2:* exocrine pancreatic cases without K-ras mutated tumors (n = 24)	*Assessment:* Finnish job-exposure matrix (Finjem): Inhalation exposure to chromium dust or fumes from welding, smelting, grinding, or related processing of steel or other materials containing chromium (including metallic chromium, Cr(III), Cr(VI), and other chromium compounds) Industrial hygiene evaluation: inhalation and dermal exposure to Cr(III) and Cr(VI) *Levels:* Not reported *Duration:* Not reported	↑ OR of K-ras codon 12 mutated pancreatic cancer with inhalation exposure to chromium ↑ proportion of glycine to valine mutations (G-to-T transversions) with inhalation exposure to chromium	PCR-RFLP analysis of formalin-fixed and paraffin-embedded tumor specimens for point mutations at codon 12 of the K-ras gene. Very few individuals actually exposed to Cr; wide confidence intervals indicate model instability.	Alguacil et al. (2003)
Exposed: Chromium workers diagnosed with lung cancer (n = 67 males)	*Assessment*: Total and hexavalent Cr measured in soil and air samples taken "in the vicinity of the workplace" using atomic absorption spectrometry	In lung cancer tissues (preserved in paraffin blocks): ↓ surviving (anti-apoptotic) ↑ p53 (pro-apoptotic)	The information regarding potential exposure is sparse. There were also differences in the type of lung cancer between	Halasova et al. (2010)

Study overview	Exposure[a]	Results	Comments	Reference
Referent: male controls with lung cancer but without known exposure to chromium (n = 104)	*Levels*: Mean values of Cr(VI) in air of smelting plants was 0.019–0.03 mg/m^3. Soil chromium had a value of 137 mg/kg. *Duration:* Mean exposure time 16.7 ± 10.0 (SD) yr (range 1−41 yr)		exposed and referent which may impact results. No information on smoking, which could be important to consider given all participants had lung cancer. In addition, P53 detection by IHC is nonspecific and will include nonfunctional P53 protein.	
Exposed: lung cancer specimens from ex-chromate workers (n = 19) *Referents 1:* lung cancer specimens from individuals never exposed to chromate, silica, or other occupational compounds (n = 52) *Referents 2:* lung cancer specimens from nonasbestos pneumoconiosis (n = 63)	*Assessment:* Based on occupational history *Levels:* Not reported *Duration:* Not reported	In lung cancer tissues (squamous cell carcinomas) from chromate-exposed patients compared to nonexposed or pneumoconiosis patients: ↑ cyclin D1 expression ($p < 0.001$) No difference in bcl-2 or p53 expression	No assessment of exposure; reliance on work history alone. Minimal details on case/control selection. No consideration of confounders, except smoking status.	Katabami et al. (2000)
Mouse, transgenic C57BL/6 Big Blue® mice	Intratracheal instillation (single administration): 0, 1.7, 3.4, or 6.8 mg/kg Cr(VI) Measured mutation frequency in lung at 1, 2, or 4 wk postexposure	Significantly increased mutation frequency at all doses; increased with dose and duration posttreatment Mutation spectrum: increased frequency of G:C to T:A transversions, associated with oxidative damage	Preliminary experiment identified doses >6.75 mg/kg were lethal. Potentially underpowered with 4 mice per dose group. Positive control not concurrently tested with Cr(VI)-treated group.	Cheng et al. (2000; 1998)

Study overview	Exposure[a]	Results	Comments	Reference
			Inconsistent/low numbers of PFUs scored per animal. Spontaneous mutations primarily G:C to A:T transitions.	
In vitro genotoxicity in primary and immortalized human lung cells				
A549 (human lung adenocarcinoma)	10 µM K_2CrO_4, 1–24 h	Distribution of bulky DNA adducts and oxidative DNA damage and mutational signature of p53 mutations following exposure to Cr(III), Cr(VI), and Cr(V).		Arakawa et al. (2012)
HLF human lung fibroblasts (LL-24 cell line)	3, 6, and 9 µM Na_2CrO_4, 24 h	↑ Cr-DNA adducts	Pretreatment with 1 mM ascorbate or 20 µM tocopherol had no ameliorative effects. Also ↑ cytotoxicity, duration- and dose-dependent (stat. sig. ≥6 µM). ↑ apoptosis ↑ p53 (4- to 6-fold)	Carlisle et al. (2000a)
A549 (human lung adenocarcinoma) and BEAS2B (human bronchial epithelial) cells	0.1, 0.5, 1.0, and 10 µM Na_2CrO_4, 0.5, 1, and 4 h	↑ oxidative DNA damage (Fpg-modified comet assay)	Oxidative role in DNA damage decreased with time at lower Cr(VI) concentrations and increased with time at higher concentrations. A549 more sensitive than BEAS2B. Also ↑ apoptosis at 10 µM (caspase-3 activity and morphology).	Cavallo et al. (2010)

Study overview	Exposure[a]	Results	Comments	Reference
H460 human lung epithelial cells, IMR90 normal human lung fibroblasts, and normal mouse embryonic fibroblasts	0, 5, 10, 15, and 20 µM K_2CrO_4	DNA damage response to Cr(VI)-induced DNA double-strand breaks (phosphorylation of γH2AX) dependent on ATR kinase and not ATM in ascorbate-restored cells DNA DSBs only formed in euchromatin	Involvement of ATR and DSBs forming in actively transcribed regions increases the probability that Cr(VI) can generate carcinogenic mutations.	Deloughery et al. (2015)
Human bronchial epithelial cells and IMR-90 embryonic lung fibroblasts	K_2CrO_4, 25–200 µM, 1–12 h	↑ DNA-protein crosslinks, dose-dependent, persistent at 12 h		Fornace et al. (1981)
A549 human lung adenocarcinoma cells	10−500 µM $Na_2Cr_2O_7$, 1 or 16 h	↑ DNA strand breaks, dose-dependent (comet assay) that were 10× higher with FAPY ↑ 8-OHdG	Authors conclude that Cr(VI)-induced oxidative DNA damage might partly be due to a reduced capacity to repair endogenous and Cr(VI)-induced 8-OHdG lesions. Also ↓ OGG1 mRNA, dose-dependent (RT-PCR and RNase protection assay); not affected by adding H_2O_2. No effect on hAPE or GAPDH.	Hodges et al. (2002; 2001)
HeLa and human lung bronchial epithelial cells	0.25 µM Na_2CrO_4, 30 d, or 10 µM, 16 or 48 h	↑ chromosomal aberrations with acute or chronic exposures	Chromosomal instability caused in part by suppressed activation of BubR1 and expression of Emi1, causing activation of APC/C, following nocodazole-induced mitotic arrest activation.	Hu et al. (2011)

Study overview	Exposure[a]	Results	Comments	Reference
Human U2OS osteosarcoma cells, Werner syndrome (WS) skin fibroblasts (AG03141), WI-38 fetal lung fibroblasts, telomerase-immortalized cell lines (hTERT GM01604, (hTERT AMIE15010, AG03141, hTERT BJ skin fibroblasts)	0–4 µM Cr(VI), 6–48 h	↑ γH2AX foci in S-phase ↑ WRN colocalization at γH2AX foci ↑ telomere defects exacerbated by lack of telomerase Lack of WRN slowed Cr(VI)-induced DNA DSB repair	Cr(VI) induces DNA DSBs and stalled replication forks; WRN helicase plays a role in the cellular recovery from Cr(VI)-induced replicative stress.	Liu et al. (2010a, 2009)
A549 (human lung adenocarcinoma) and BEAS2B (human bronchial epithelial) cells	0, 0.5, 1, 2, 3, 5 µM Cr(VI), 2–72 h	↓ Gene 33 (Mig6, ERRFI1), dose- and time-dependent (≥1 µM, 24 h); reversed by NAC ↑ DNA DSBs (γH2AX), dose-dependent (≥2 µM) Suppression of Gene 33 increases DNA damage (γH2AX, micronuclei) and cell transformation	Cr(VI) suppresses Gene 33, inhibiting the Cr(VI)-induced DNA damage response mediated in part by Gene 33-induced cell signaling pathways.	Park et al. (2016)
Human lung epithelial A549 and colon HCT116 (MLH-/-) and DLD1 (MSH6-/-) cells	1–20 µM K_2CrO_4, 3–12 h	↑ survival, ↓ apoptosis in mismatch repair (MMR)-deficient cells ↑ DNA DSBs (γH2AX) and apoptosis in MMR-proficient cells γH2AX foci occur in G2, but no G2 cell cycle arrest No p53 induction in either cell type at subtoxic levels	MMR responsive to Cr-DNA adducts, not oxidative damage or crosslinks. In MMR+ cells, apoptosis induced by Cr-DNA adducts independently of p53.	Peterson-Roth et al. (2005); Zhitkovich et al. (2006)
S-9 fraction from pulmonary alveolar macrophages or S-12 fraction of peripheral	10–30 µg sodium dichromate dihydrate per plate	↓ mutagenicity in the Ames assay when Cr(VI) was preincubated with lung fractions		Petrilli et al. (1986), De Flora et al. (1987b)

Study overview	Exposure[a]	Results	Comments	Reference
lung parenchyma of human patients				
Primary human lung IMR90 fibroblasts, H460 human lung epithelial cells, and XPA- and XPF-human fibroblasts	1–5 µM K_2CrO_4, 3 h	Cr-DNA adducts are substrate for nucleotide excision repair (NER) ↑ mutagenicity of these adducts and ↑ apoptosis with NER deficiency	NER efficiently removes Cr-DNA adducts.	Reynolds et al. (2004)
Human colon HCT116 (MLH1-/-) and DLD1 (MSH6-/-), lung epithelial H460, and lung fibroblast IMR90 cell lines	2–10 µmol/L K_2CrO_4, 3 h	Ternary ascorbate-Cr-DNA adducts are substrate for error-prone mismatch repair (MMR) MSH2-MSH6 dimer, leading to ↑ DNA DSBs and ↑ apoptosis Cells deficient in MMR have higher survival and lower DNA DSBs	Colon cells deficient in MMR have increased survival following Cr(VI) exposures, increasing probability of clonal selection of these cells.	Reynolds et al. (2009)
Primary human lung IMR90 fibroblasts H460 human lung epithelial cells	0.2–8 µM K_2CrO_4, 3 h	↑ DNA DSB with ascorbate caused by aberrant mismatch repair ↑ cytotoxicity and apoptosis with ascorbate; effects reversed by suppressing DNA mismatch repair but p53 status had no effect ↑↑ cytotoxicity and cell cycle delay in cells deficient in oxidative DNA damage repair (XRCC1 knockdown); effects reversed by ascorbate Chromosomal aberrations not affected by XRCC1 status	By restoring intracellular ascorbate to physiological levels via DHA (max intracellular 0.9 mM), it was shown that ascorbate can suppress Cr(VI)-induced oxidative damage but promotes Cr-DNA lesions that are either repaired by mismatch repair, independently of p53, or lead to cytotoxicity and apoptosis.	Reynolds et al. (2012; 2007; 2007)

Study overview	Exposure[a]	Results	Comments	Reference
Primary human bronchial epithelial cells; p53+ and p53− H358 bronchoalveolar carcinoma isogenic cells	200 µM K_2CrO_4, 2 h	↑ DNA strand breaks ↑ apoptosis in p53+ cells Apoptosis mediated by p53-upregulated modulator of apoptosis (PUMA), BAX, cytochrome C and caspase-3		Russo et al. (2005)
Primary human bronchial fibroblasts (PHBFs)	1–10 µM Na_2CrO_4, 24 h	Relative survival of 74% (1 µM), 57% (2.5 µM), 13% (5 µM) and 0% (10 µM) Chromosomal damage in 18% (1 µM) and 33% (2.5 µM) of metaphases		Wise JP et al. (2002)
Human SV40 transformed fibroblasts, Werner syndrome fibroblasts, primary human lung IMR90 fibroblasts, and human colon HCT116 MLH1-/- and MLH1+ cells	0–30 µM K_2CrO_4, 3 h	↑ nuclear relocalization of WRN in response to Cr(VI) ↓ cell survival, ↑ DNA DSBs and ↓ RAD51 foci in cells lacking WRN ↓ DNA DSBs in cells lacking mismatch repair	Error-prone mismatch repair of Cr-DNA adducts generates DNA DSBs and repair of persistent DNA DSBs is dependent on WRN helicase.	Zecevic et al. (2009)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Supporting inhalation exposure genotoxicity studies

Another set of genotoxicity studies was identified that was informative for interpretations of genotoxic risk in humans but did not specifically measure genotoxicity in lung tissues. These studies were also identified in preliminary title and abstract screening as "mechanistic" and were further screened and tagged as "inhalation," "cancer," and "genotoxicity" if they were epidemiological studies of humans or experimental animal studies exposed to Cr(VI) via inhalation that measured genotoxicity endpoints. After removal of endpoints already considered that reported gene and chromosomal mutation measures and studies specific to lung tissues (see above), 29 genotoxicity studies of humans occupationally exposed and 1 study in animals exposed via intratracheal instillation were identified. The evidence is summarized in Table C-49.

Table C-49. Supporting genotoxicity studies in humans and animals exposed to Cr(VI) via inhalation or intratracheal instillation

Study overview	Exposure[a]	Results	Comments	Reference
DNA strand breaks				
Exposed 1: directly exposed (DE) to Cr(VI) for >8h/d in tannery industry (n = 36) *Exposed 2:* indirectly exposed (IE) to Cr(I) for >30 yr based on residence near tannery industry (n = 36) *Referents:* age-matched controls, unexposed to chemicals or radiation (n = 36)	*Assessment*: Exposure to Cr(VI) inferred based on occupation and residence. In addition, Cr was measured in urine and air samples (unclear where air samples were collected). *Levels:* There was a gradient in levels of both, there were detectable chromium levels in both air and urine for "controls." Direct exposure (n = 36) (mean ± SD): Total Cr in air (1 mg/m^3): 0.101 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.021 ± 0.003 Cr content in urine: 2.11 ± 1.01 Indirect exposure (n = 36): Total Cr in air (1 mg/m^3): 0.089 ± 0.003 Cr(VI) in air (0.001 mg/m^3): 0.013 ± 0.005 Cr content in urine: 1.81 ± 0.88 Controls (n = 36): Total Cr in air (1 mg/m^3): 0.014 ± 0.004 Cr(VI) in air (0.001 mg/m^3): 0.006 ± 0.001 Cr content in urine: 0.54 ± 0.39 *Duration:* Directly exposed subjects were "selected based on the duration of their exposure (0–5; 6–10; 11–15; 16–20; 21–25 years) and were known to be exposed to Cr(VI) for a minimum of 8 h/day" while indirect exposure was inferred from residence of at least 30 year's duration, "in and around the tanneries."	↑ mean tail length for comet assay in DE group compared to IE group and controls	Some of the controls also had detectable chromium in urine, suggesting this is not really a true "control" group. Very limited evaluation of confounders. Small sample size. Study also reported ↑ CAs & MN in DE group compared to IE group and controls.	Balachandar et al. (2010)
Exposed: male welders (n = 102) *Referents:* male general population controls	*Assessment*: Blood samples from 51 welders & 49 controls, selected randomly, on 4th day of the work week. Cr and Ni content measured with ICP-MS.	↑ DNA mean tail length in welders	Limitations are related to outcome evaluation, such as the use of outdated methods no longer	Danadevi et al. (2004)

Study overview	Exposure[a]	Results	Comments	Reference
(n = 102), age and SES-matched to exposed	*Levels:* Welders had higher Cr and Ni compared to controls [(Cr, 151.65 versus 17.86 mg/L; Ni, 132.39 versus 16.91 mg/L; $p < 0.001$)]. *Duration:* The duration of exposure varied widely (range: 1–24 yr). (Overall mean not presented).		recommended, which could lead to inaccurate scoring. Also a lack of description/details on participant selection (e.g., concern for potential selection bias). Comet assay conducted in all subjects, but micronucleus test conducted only in 58 welders and 53 controls, selected randomly from population (study reported ↑ MN in welders compared to controls and with increased duration of welding work).	
Exposed: Chrome-plating workers (n = 19) *Referents 1*: hospital workers (n = 18) *Referents 2:* university personnel (n = 20)	*Assessment:* Total Cr measured in urine, erythrocytes, and lymphocytes using graphite furnace atomic absorption. *Levels:* Total Cr was higher in exposed workers compared with hospital workers (see Table 3; for example, postshift mean urine levels were 7.31 [SD = 4.33] in exposed vs. 0.12 [SD = 0.07] µg/g crt in referent). *Duration:* Mean (SD) yr of exposure among chrome-plating workers = 6.3 (4.3).	In peripheral blood lymphocytes: ↑ comet tail moment correlated with Cr lymphocyte concentrations Null apoptotic nuclei	Did not exclude smokers (high prevalence) although did present results stratified by smoking (small numbers). Unclear whether exposure was to Cr(VI) specifically (possible with chrome plating workers but measured total Cr in urine). State that previous air monitoring for total chromium showed levels of 0.4 to 5.6 µg/m^3, which is fairly low. The comet assay is an insensitive method for measuring apoptosis.	Gambelunghe et al. (2003)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: chromium exposed workers (n = 10) *Referents:* nonexposed workers (n = 10)	*Assessment:* Urine and blood samples were taken from workers at the end of a work week. *Levels*: Chromium concentrations in the factory ranged from 0.001 to 0.055 mg Cr(VI)/m^3 (obtained from personal and area samplers). Mean chromium concentrations in urine (5.97 µg/g creatinine), whole blood (5.5 µg/L), plasma (2.8 µg/L), and lymphocytes (1.01 µg/10^{10} cells) of exposed workers were significantly higher than in nonexposed workers. *Duration*: The mean duration of exposure was 15 yr.	No difference in DNA strand breaks (alkaline elution assay) between groups	Very small sample and low exposure levels, which probably limited power. Study also reported no increased incidence in 8-OHdG.	Gao et al. (1994)
Exposed 1: male welders working in areas without collective protections (n = 27) *Exposed 2:* male welders working in locations with smoke extraction systems (n = 33) *Referents:* office workers with no history of occupational exposure to welding fumes or other physical/chemical agent in workplace (n = 30)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in blood and urine. *Levels:* Cr levels in blood and urine were higher among both groups of welders compared with controls (means 129 to 145, compared with 92 µg/L), and urinary chromium was higher among welders working without smoke extraction systems. *Duration:* Welders exposed for 0.5–45 yr.	↑ OTM_X^2 distribution (measure of DNA damage) in welders at the end of the work week compared to beginning ↑ DNA strand breaks at end of work week in welders	Main limitations are lack of description (e.g., for participant selection, analysis), unknown contribution of Cr(VI) to Cr exposure, and known coexposures to other metals. Study also reported ↑ frequency of chromosomal damage in welders.	Iarmarcovai et al. (2005)
Exposed: welders (n = 93) *Referents*: general population controls with no history of occupational exposure to welding fumes; age and SES-matched to exposed group (n = 60)	*Assessment*: Exposure determined by occupation. *Levels:* Not reported. *Duration:* 5–15 yr.	↑ DNA mean tail length in welders compared to controls *Study was not included due to a critically deficient rating in the exposure domain when evaluated in HAWC for the micronucleus frequency endpoint.*	Study also reported ↑ frequency of MN in welders compared to controls and in welders with increased duration of work.	Sellappa et al. (2010)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: male welders (n = 66) *Referents:* male individuals from the general population with no history of occupational exposure to welding fumes or other physical/chemical exposure in workplace; age and SES-matched to welders (n = 60)	*Assessment*: Exposure determined by occupation. *Levels:* Not reported. *Duration:* Duration of welding ranged from 5–20 yr.	↑ DNA mean tail length in welders compared to controls, and in welders with increased duration of work	Study also reported ↑ frequency of MN in welders compared to controls and in welders with increased duration of work.	Sudha et al. (2011)
Exposed: individuals (n = 115; 29 female, 86 male) with exposure to sodium dichromate for at least 6 mo *Referents:* healthy volunteers (n = 60; 15 female, 45 male) in the same city without chromate exposure history.	*Assessment:* Air-Cr concentration collected with point dust sampler and measured with electrothermal atomic absorption spectrometry. Personal air samples collected through full-shift (8h) sampling to calculate cumulative dose postshift blood samples collected; chromium measured with ICP-MS. *Levels*: Mean (SD) chromium in blood of exposed workers = 12.45 (20.28) µg/L.↑ accumulation of Cr in peripheral red blood cells in chromate-exposed workers. *Duration:* Mean (SD) yr of employment among exposed group: 12.86 (6.02); range: 1–33.	↑ urinary 8-hydroxy-2-deoxyguanosine, DNA strand breaks and global DNA hypomethylation in chromate-exposed workers	Urinary 8-hydroxy-2'-deoxyguanosine, DNA strand breaks and global DNA hypomethylation. No adjustment for diet or other nonfolate supplements. ↓ serum folate in chromate-exposed workers.	Wang et al. (2012)
Exposed: electroplating workers (n = 157) *Referents:* individuals without exposure to chromium or known physical/chemical genotoxic agents (n = 93)	*Assessment:* Air-Cr and blood Cr determined by graphite furnace atomic absorption spectrophotometer. *Levels*: median (range) Cr in erythrocytes (µg/L) among exposed: 4.41 (0.93–14.98); among controls: 1.54 (0.14–4.58). Median (range) short-term concentrations of Cr in air: 0.060 (0.016–0.531) mg/m^3. *Duration:* Median (min–max) yr of exposure among exposed group: 5.3 (0.5–23).	↑ 8-OHdG adducts among exposed compared to referents ↑ Olive tail moment, tail length, & tail DNA% among exposed compared to referents	Limited adjustment for confounders (including diet). Potential coexposures to other metals in the workplace.	Zhang et al. (2011)

Study overview	Exposure[a]	Results	Comments	Reference
Rat, Wistar	Intratracheal instillation, 1.3 and 2.5 mg/kg $Na_2Cr_2O_7$, 24 h.	↑ DNA strand breaks in peripheral lymphocytes	Fluorometric analysis of DNA unwinding (FADU) assay.	Gao et al. (1992)
DNA-protein crosslinks				
Exposed 1: Full-time tannery workers, directly involved in chromium tanning or finishing process (n = 33) *Exposed 2:* Full-time manual metal arc stainless steel welders (n = 5) *Referents:* Control individuals with no known exposure to environmental or occupational carcinogens (n = 30)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr in plasma and in urine (mid-shift for welders). *Levels:* Urinary and plasma chromium levels were higher in both exposed groups compared with controls. For example, mean ± SD levels in plasma were 2.43 ± 2.11 in tanners, 1.55 ± 0.67 in welders, and 0.41 ± 0.11 µg/L. *Duration:* Not reported.	↑ DNA-protein crosslinks in tannery workers & welders compared to controls	Main limitation is small number of welders, lack of description for participant selection, analysis, and confounders. Study also reported ↑MN in tannery workers & welders compared to controls.	Medeiros et al. (2003)
Exposed: residents living near Hudson County, New Jersey chromium-containing landfills and with urinary chromium ≥0.5 µg/L (n = 33) *Referents:* individuals living in noncontaminated areas (n = 49)	*Assessment*: No description of exposure assessment protocol. *Levels:* Based on recruitment, exposed group had urinary chromium ≥0.5 µg/L. *Duration:* Not reported.	↑ DNA-protein crosslinks in exposed compared to controls, after adjustments for covariates	Control for the covariates (age, gender, race, smoking, weight) increases confidence in results. Unclear whether chromium measures were also assessed in the control population and whether unexposed status was confirmed.	Taioli et al. (1995)
Exposed: male stainless steel welders working in open environment (n = 5) *Referents:* age-matched male control blood	*Assessment:* Based on occupation. Welders worked in stainless steel industry using acetylene flame method in open environment without protective masks over nose or mouth. *Levels:* Not reported.	↑ DNA-protein crosslinks in lymphocytes of welders ↓ excess of glutathione over cysteine in welders	Comparisons of reduction rates and extent of DNA damage and DNA-protein adducts to levels of intracellular reductants glutathione and cysteine.	Quievryn et al. (2001)

Study overview	Exposure[a]	Results	Comments	Reference
samples obtained from local blood center (n = 22)	*Duration*: Not reported.		Small sample size limits confidence in results.	
Exposed: Chrome-platers from metallurgic plant (n = 14) *Referents:* residents of the same town, not living in vicinity of the factory and not known to be exposed to chromium or other metals (n = 12) and additional unexposed individuals living in nearby coastal town (n = 6)	*Assessment*: Personal breathing sampling pump with sampling flow of 21 min^{-1} for all workers over the course of one 8-h shift; collection using Millipore filters; analyzed with atomic absorption flame method for total chromium. 11 workers also fitted with pumps with medium range flow (1.21 min^{-1}); collection with 5-mm PVC filters; analyzed with visible absorption spectrophotometer for Cr(VI), with portion of each sample analyzed for total chromium by flame atomic absorption. Blood samples collected post work shift; analyzed with flameless atomic absorption spectrometry. Urine samples collected pre & post work shift *Levels:* Ambient levels of total chromium in chrome-plating plant ranged from 0.009 to 0.327 mg/m^3 (median = 0.041 mg/m^3) as measured with Millipore filters and from 0.008 to 0.19 mg/m^3 (median = 0.027 mg/m^3) measured by Higitest filters. Cr(VI) levels in ambient air ranged from 0.0005 to 0.13 mg/m^3 (median = 0.003 mg/m^3). *Duration:* Workers had been continually employed at metallurgic plant for 8-h work shifts for 1.5–15 yr (mean: 9.5 ± 4.0).	↑ chromium in pre-& postshift urine, erythrocytes, and lymphocytes elevated in exposed compared to referents No difference in DNA-protein crosslinks between exposed and referents; however, there were + associations between DNA protein crosslinks and chromium in erythrocytes at low and moderate exposures with saturation at higher exposure levels	Small sample size limits confidence. No consideration of covariates. Potential confounding by other occupational exposures.	Zhitkovich et al. (1996)
Exposed: railroad arc welders (n = 21) *Referents:* unexposed controls (office workers, supervisors, janitors, laboratory technicians) (n = 26)	*Assessment:* Chromium and nickel measured in blood of controls and welders with atomic absorption. *Levels*: No difference in nickel levels between groups; small but not statistically significant difference in chromium between groups (numbers not provided).	↑ DNA-protein cross-links in welders compared to controls	Unclear how an effect detected was when there was no overall/ meaningful difference in chromium or nickel between groups – could possibly be due to an unmeasured confounder.	Costa et al. (1993)

Study overview	Exposure[a]	Results	Comments	Reference
	Duration: Welders had been exposed full time to welding fumes for at least 6 mo, but not stainless-steel welding.		The exposed group did not actually experience high levels of Cr exposure, which might have limited power to detect effects. Small sample size limits confidence.	
Sister chromatid exchange				
Exposed: Chromium plate workers (n = 15) *Referents 1:* age, gender, smoking-matched controls (n = 15) *Referents 2:* individuals of similar age from unpolluted rural region (n = 8)	*Assessment:* Blood samples and buccal mucosal cells taken from exposed group; exposure was estimated with personal air samplers and in urine samples. *Levels:* Mean air concentration of total chromium was 0.0075 mg chromium/m^3 in the low-exposure group and 0.0249 mg chromium/m^3 in the high-exposure group (number of workers in each exposure group was not reported). Mean concentrations of chromium in urine were 18.63 µg/L (low) and 104.22 µg/L (high) *Duration:* Duration of exposure ranged from 2 to >20 yr; mean duration of exposure was not reported.	No difference in SCE/cell between exposed and controls	Although exposed and unexposed workers were matched on age, sex, and smoking habit, the two unexposed (worker and rural) groups were combined, resulting in lower confidence in comparability of exposed and unexposed group comparisons. Inference is further limited by small sample size and lack of description. Study also reported ↑ micronuclei in peripheral lymphocytes and buccal cells in workers compared to controls.	Benova et al. (2002)
Exposed: chromium electroplating workers (n = 7) *Referents:* age and sex-matched nonexposed office employees (n = 10)	*Assessment:* Air samples from the electroplating room were collected, along with stool and hair samples to determine exposure. *Levels:* The mean chromium (total) air concentration (by random air collection) was 8.1 µg/mm^3, the mean chromium concentration in stool samples was 8.5 µg/g stool, and the mean chromium concentration in hair was 35.68 µg/g. The valence of	↑ chromosomal aberrations and sister chromatid exchanges (SCE) in exposed group	Although controls were age and sex matched to exposed subjects and were stated to have similar socioeconomic status, the sample size is quite small and the analysis limited. Also unclear how well differentiated chromium exposure is by group—	Deng et al. (1988)

Study overview	Exposure[a]	Results	Comments	Reference
	chromium that workers were exposed to was unspecified. *Duration:* Mean employment period of 12.8 yr among exposed groups.		analyses of chromium in hair suggest delineation with controls, but no information on stool samples, which showed similarities between nickel and chromium workers. Also reports coexposure to nickel.	
Exposed: male stainless steel welders (n = 23) *Referents:* men employed in office of printing company (n = 22)	*Assessment:* Urine sampling at end workday to evaluate chromium concentration. *Levels:* Urinary chromium levels ranged from 0.20 to 1.55 µmole/L. *Duration:* Welders had been employed in manual metal arc (MMA) welding for at least 4 yr; mean (SD) length of employment = 21 (10). Welders worked in poorly ventilated areas.	No differences in SCE between exposure groups	Although Cr(VI) exposure seems likely to occur among these welders, the analysis is limited by small sample size when stratifying by smoking (found to be related to the outcome). Study also reported no differences in CA between exposure groups.	Husgafvel-Pursiainen et al. (1982)
Exposed: male stainless steel welders (survey 1 n = 17; survey 2 & 3 n = 44) *Referents:* male office workers (survey 1 n = 6; survey 2 n = 7; survey 3 n = 20)	*Assessment:* Classification based on occupation. Spot urine samples collected during workday; analyzed with direct flameless atomic absorption spectrometer. *Levels:* Mean urinary Cr was 9.8 and 4.2 µg/L among exposed and referent group, respectively. *Duration:* Stainless steel welders employed for 5–20 yr (mean 12.1).	No differences in sister chromatid exchanges (SCE) in exposed compared to controls	The main limitations are related to the outcome evaluation and to poorly described and reported data analysis and lack of consideration of potential confounders. Study also reported ↑ chromosomal aberrations in exposed compared to controls.	Koshi et al. (1984)
Exposed 1: chromium exposed electroplating male workers (n = 14) *Exposed 2:* nickel-chromium exposed	*Assessment*: Urine and blood samples collected; analyzed with atomic absorption spectrophometry. Levels: Cr workers had the highest blood Cr (11.39 lg/L) and urine Cr concentrations (14.7 lg/g creatinine).	↑ sister chromatid exchanges and high frequency cells in Cr & Ni-Cr groups	Small sample size limits confidence. Observed synergistic effect with smoking.	Lai et al. (1998)

Study overview	Exposure[a]	Results	Comments	Reference
electroplating male workers (n = 34) *Referents:* male administrative workers free of exposure to heavy metals and solvents (n = 43)	*Duration:* At least 6 mo of electroplating experience at the start of the study. Mean (SD) yr of work among chromium workers = 6.6 (5.8); among nickel-chromium workers = 3.7 (4.6).			
Exposed: manual metal arc stainless steel welders (n = 24) *Referents:* matched controls (n = 24)	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in air (welders only) and urine (all). *Levels:* Mean urinary Cr was 47 and 1.5 µmol/mol creatinine among exposed and referent group, respectively. Mean air Cr level 81 µg/m^3. *Duration:* Welders were selected for their "long and intense" welding on stainless steel (mean work duration of 19 yr).	No difference in cytogenetic effects (i.e., chromosomal aberrations, sister chromatid exchanges, or micronuclei) between groups	Main limitations are related to outcome ascertainment and statistical analysis and to limited description of results.	Littorin et al. (1983)
Exposed: male chromium platers (n = 12) *Referents*: none	*Assessment:* Venous blood and urine sample were collected over a 5-yr period. *Levels:* Urinary chromium concentrations ranged from 1.2 to 57.0 µg/g with a mean urinary chromium concentration of 17.9 µg/g creatinine. *Duration*: Employment duration ranged from 6.6 to 25.1 yr, with mean employment duration of 15.5 yr.	No association between urinary Cr and sister chromatid exchanges	Small sample size and no control group used in study limits exposure comparisons and power for analysis; limited adjustment for confounders.	Nagaya et al. (1991)
Exposed: male chromium platers (n = 44) *Referents:* male controls unexposed to Cr or other harmful agents (n = 47) (further grouping by smoking within exposed and referents)	*Assessment:* Urinary collected during working hours; analyzed with direct flameless atomic absorption spectrophotometer. *Levels:* Mean among all chromium platers = 0.25 µmol/L. *Duration*: Duration of employment: 0.5–30.7 yr [mean (SD): 13.8 (8.7)].	No association between urinary Cr and sister chromatid exchanges	Limited adjustment of confounders: considered stratification only by smoking status.	Nagaya et al. (1989)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: male chromium platers (n = 24) *Referents*: sex, age, smoking-matched office worker controls, unexposed to Cr (n = 24)	*Assessment*: Urine samples analyzed with direct flameless atomic absorption spectrophotometer. *Levels:* The mean (SD) concentration of chromium in the urine was 13.1 (16.7) µg/L. *Duration:* Duration of employment ranged from 0.5 to 30.5 yr with a mean employment of 11.6 yr.	No difference in SCEs between exposed and unexposed groups; no association between urinary Cr and sister chromatid exchanges among exposed	Authors suggest that null results could be due to low exposures. Consideration of smoking but minimal other confounders.	Nagaya (1986)
Exposed: male welders (n = 39) *Referents:* unexposed men (n = 18)	*Assessment:* Chromium in urine samples (time of day unspecified) from workers analyzed with atomic absorption spectrometry. *Levels:* Mean (SD) chromium among welders = 28.4 (19.8) µg/L. *Duration:* Authors state that employees had been employed since 1983 (paper published in 1991); ~7–8 yr (?).	↓ sister chromatid exchange frequency in welders compared to controls	Only considered age and smoking as potential covariates. Authors note some concern with alkaline filter elution that might impact validity of results.	Popp et al. (1991)
Exposed: male chromium platers (n = 38) *Referents:* male sanitary workers unexposed to ionizing radiation for at least 5 yr & no mutagenic drugs (n = 35)	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Exposed group was stratified based upon coexposure to nickel ("bright" plating, vs. "hard" plating). Also measured Cr in urine. *Levels:* Urinary Cr levels were lowest in controls (mean ± SD = 1.9 ± 1.4 µg/g crt), intermediate in bright plating (6.1 ± 2.8 µg/g crt), and highest in hard plating groups (10.0 ± 7.5 µg/g crt), indicating adequate delineation between groups. *Duration:* Mean (SD) yr of exposure: bright plating = 9 (11); hard plating = 7 (3).	Association between urinary Cr and sister chromatid exchanges	Main limitations are related to outcome ascertainment, small sample size for certain analyses, and lack of description (e.g., for participant selection and statistical analysis). Study also reported ↑ chromosomal aberrations and sister chromatid exchanges in exposed groups.	Sarto et al. (1982)
Exposed: chromium platers (n = 12) *Referents*: controls (n = 10)	*Assessment:* Based on occupation. *Levels*: Cr(VI) exposure levels and blood concentrations were not reported. *Duration*: Exposure durations ranged from 0.5 to 18 yr (mean exposure duration was not reported).	↑ sister chromatid exchanges in exposed group	Very small sample size; no consideration of confounders; no exposure information on participants.	Stella et al. (1982)

Study overview	Exposure[a]	Results	Comments	Reference
			Results supported by in vitro findings (human lymphocytes cultured & treated with Cr(VI) and Cr(III).	
Exposed: chromium workers (n = 35) *Referents:* age and gender-matched controls (n = 35)	*Assessment:* Based on occupation. *Levels:* Not reported. *Duration:* Exposure duration ranged from 2 to 14 yr with a mean (SD) of 6.5 (4.2) yr.	↑ sister chromatid exchanges in exposed group; association with work duration; synergy with smoking ↑ high frequency cells in exposed group; synergy with smoking	No quantitative assessment of exposure; exposure based on work only; limited sample size. Only adjusted for smoking, no other confounding incorporated into Cr analysis.	Wu et al. (2000)
Exposed: chromium platers (n = 35) *Referents:* healthy subjects with no history of disease or previous exposure to chromium or other metals (n = 35)	*Assessment:* Personal exposure monitoring for 8 h working shift (1.71/min) on only 10 individuals in the exposed group. Blood and urine samples collected at end of shift and analyzed with atomic absorption spectrophotometry. *Levels:* Individual time-weighted average range: 0.049–1.130 mg/m^3. *Duration*: The mean duration of employment was 6.5 yr.	↑ sister chromatid exchange and percent high frequency cells in exposed group compared to controls	Personal air sampling only obtained for n = 10 individuals in the exposed group; SCE analysis conducted based on work group rather than measured exposure level. Unable to draw conclusions about effect of genotype due to small sample size.	Wu et al. (2001)
Exposed: male welders (n = 39) *Referents:* matched controls not substantially exposed to carcinogens (n = 39)	*Assessment:* Venous blood samples analyzed with atomic absorption spectrometry. *Levels*: Mean (SD) concentration of chromium in exposed group erythrocytes: 4.3 (7.0) µg/L. *Duration:* Not reported.	↑ sister chromatid exchange and DNA single strand breaks in exposed compared to controls	Only considered smoking status, no other covariates. Possible confounding by coexposure to other toxic metals, such as nickel, which was also measured in this study.	Werfel et al. (1998)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Oral route of exposure

Mutagenic MOA studies

Studies considered most relevant to a mutagenic MOA analysis for cancer of the GI tract are studies that measure gene mutation (prior to tumorigenesis), micronuclei induction, and chromosomal aberrations following oral exposures in experimental animals. This includes gavage exposures with the acknowledgment that this dosing regimen condenses the exposure time, inhibiting gastric reduction and potentially increasing Cr(VI) exposure. Human studies of occupationally exposed workers that tested GI tissues (i.e., buccal cells from the oral cavity) were also considered. Although these subjects were exposed via inhalation, this route of exposure is presumed to be relevant to tissues in the oral cavity given exposure when breathing and via mucociliary clearance.

No oral exposure studies in humans meeting these criteria were identified, but eight studies reporting occupational measures of mutagenic biomarkers in buccal cells were identified; these studies have already been summarized with the mutagenic MOA studies for inhalation exposures in the preceding section. Eighteen studies in animals exposed via drinking water, diet, or gavage were identified; some the findings reported in these studies are visualized in Figures C-21 to C-24. These studies were evaluated in HAWC; the evaluations and the study findings are summarized in Tables 3-18 and 3-19 in Section 3.2.3.3 of the toxicological review.

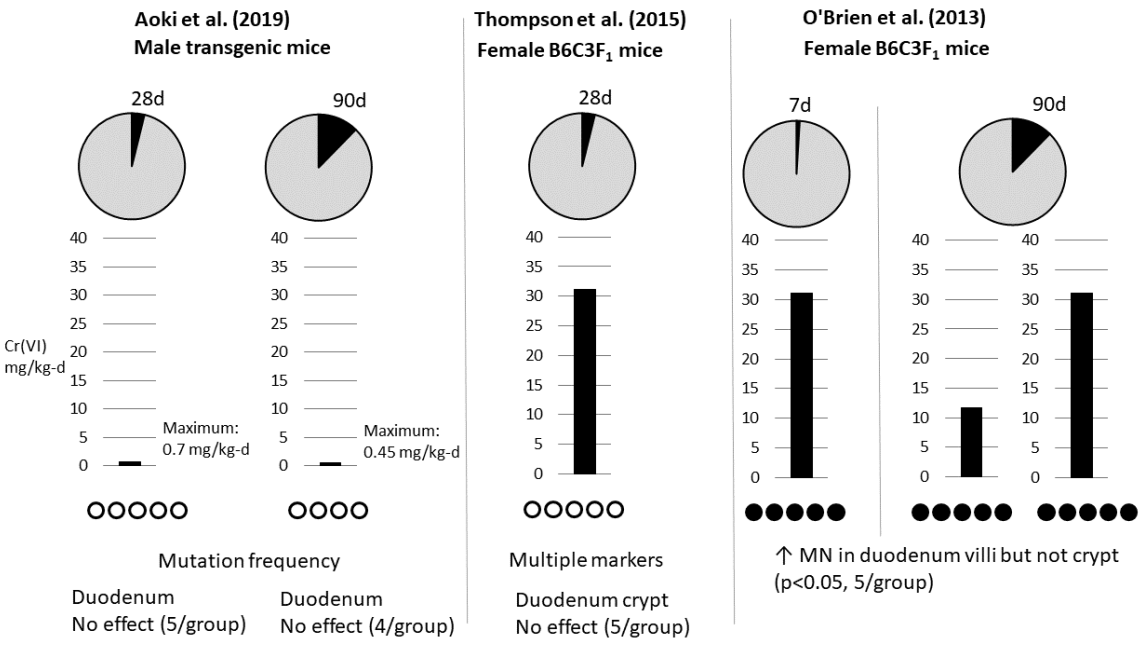

Figure C-21. Overview of selected studies evaluating mutagenic markers in the gastrointestinal tract of mice following ad libitum drinking water exposure. Full circle of a pie chart represents 2 years. Bar chart represents the maximum dose range or the dose where an effect is first observed (whichever is lower). Full or empty circles represent sample size per group (darkened if an effect was observed).

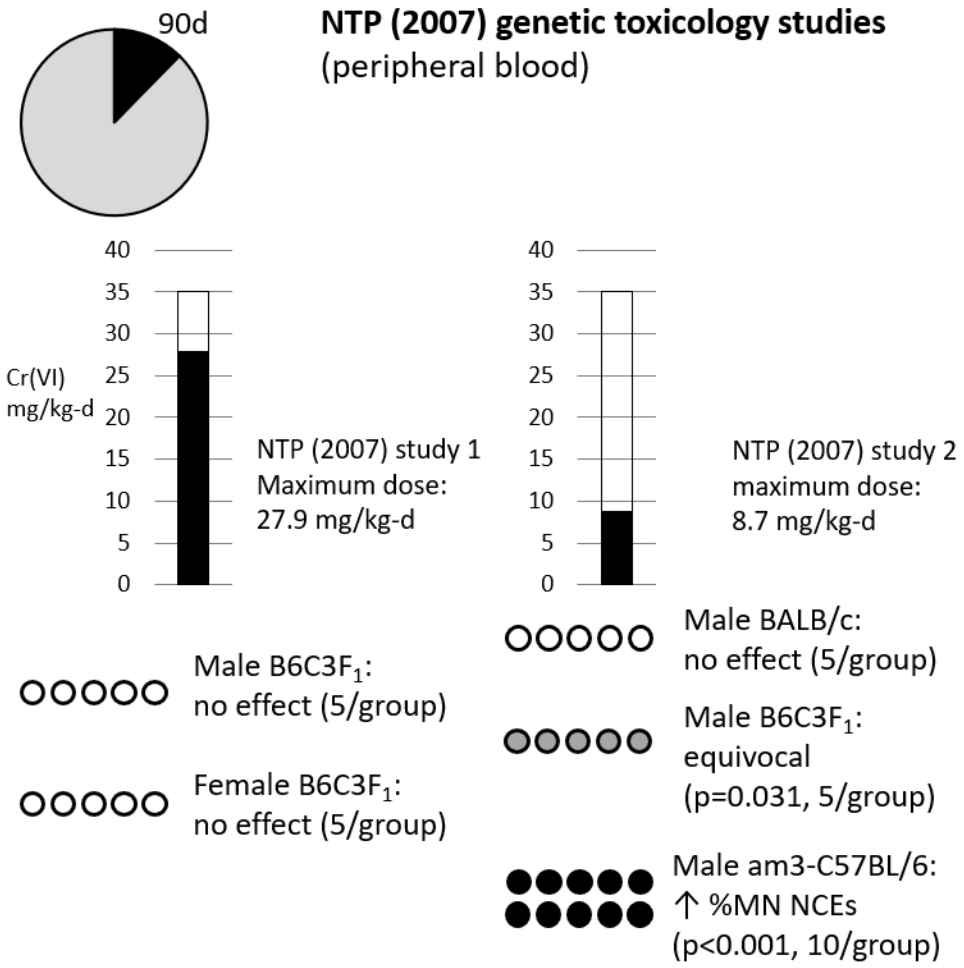

Figure C-22. Overview of the NTP (2007f) genetic toxicology (ad libitum drinking water exposure). Full circle of a pie chart represents 2 years. Bar chart represents the maximum dose range or the dose where an effect is first observed (whichever is lower). Full or empty circles represent sample size per group (darkened or shaded if an effect was observed).

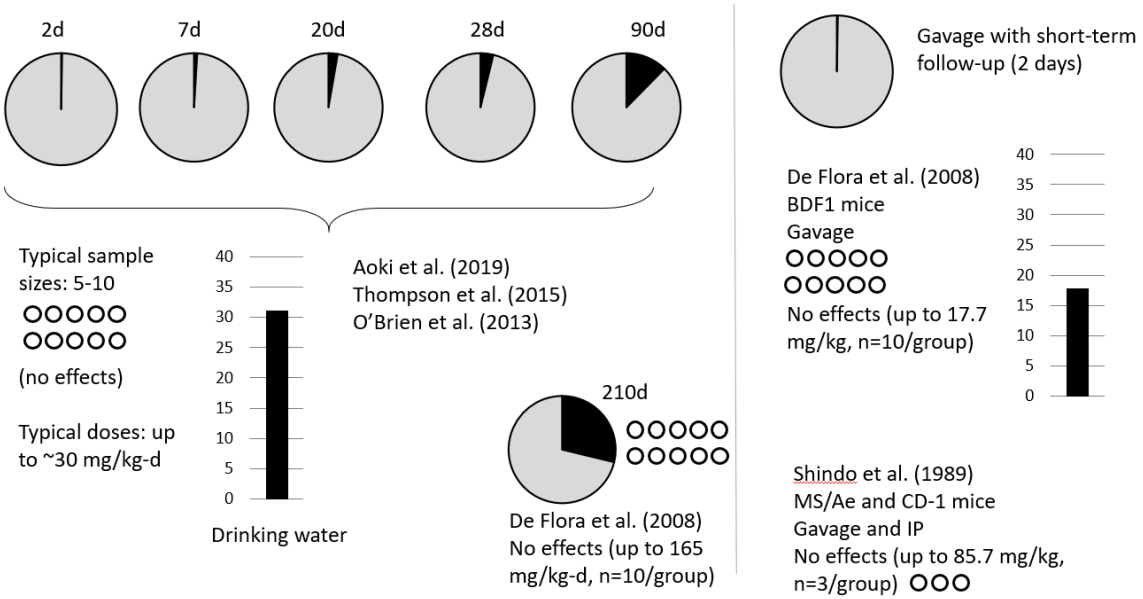

Figure C-23. Overview of selected studies evaluating mutagenic markers (but finding no effect) following ad libitum drinking water exposure (left) and oral gavage (right). Full circle of a pie chart represents 2 years. Bar chart represents the maximum dose range. Empty circles represent sample size per group.

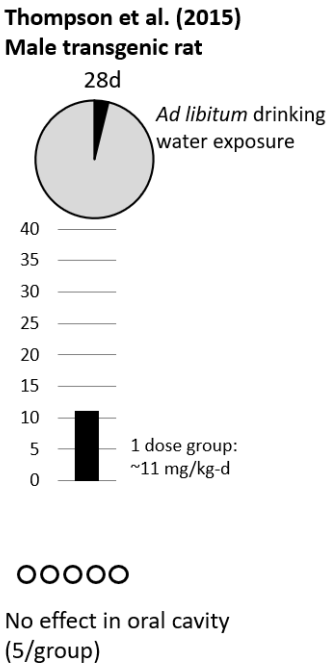

Figure C-24. Overview of the Thompson et al. (2015a) study evaluating mutagenic markers in rats (but finding no effect) following ad libitum drinking water exposure. Full circle of a pie chart represents 2 years. Bar chart represents the maximum dose range. Empty circles represent sample size per group.

Supporting genotoxicity studies in gastrointestinal tract tissue

In addition to the studies measuring gene and chromosomal mutation identified above, mechanistic evidence of genotoxicity in GI tract tissues or in cells isolated from the GI tract were identified in the preliminary title and abstract screening. These studies were tagged as "mechanistic" and further screened and tagged as "GI tract" and "cancer" if they were studies in humans or animals conducted in GI tissues or cells that were relevant to carcinogenic processes. Seven genotoxicity studies of GI tissues in experimental animals and 10 studies in cells derived from GI tissues were identified; no human studies were identified. This evidence is summarized in Table C-50.

Table C-50. Supporting genotoxicity studies in gastrointestinal tract tissues and cells following Cr(VI) exposures

System	Exposure[a]	Results	Reference
Mouse, B6C3F1, female Oral, drinking water	0, 0.1, 1.4, 4.9, 20.9, 59.3, and 181 mg/L Cr(VI) 0, 0.024, 0.32, 1.1, 4.6, 11.6, or 31.1 mg/kg-d Cr(VI) 7 d (n = 5) or 90 d (n = 10)	7 and 90 d: No increases in 8-OHdG adducts in any tissues	Thompson et al. (2011b)
Mouse, B6C3F1 & rat, F344, female Oral, drinking water	0 and 180 mg/L Cr(VI) 0 and 31.1 mg/kg-d Cr(VI) 13 wk	γH2AX elevated in duodenal villi but not crypts No aberrant foci indicative of transformation	Thompson et al. (2015a) Continued analysis of tissues from Thompson et al. (2011b)
Mouse, B6C3F1 Oral, drinking water	0, 1.4, 21, and 180 mg/L Cr(VI) 0, 0.32, 4.6, and 31.1 mg/kg-d Cr(VI) 7 d	No effect on γH2AX foci or on micronucleus induction in crypt enterocytes	Thompson et al. (2015b)
Mouse, SKH-1 hairless, female Oral, drinking water	0, 5, and 20 mg/L Cr(VI) 1.20 and 4.82 mg Cr(VI)/kg-d 9 mo	No effect on DNA-protein crosslinks or oxidative 8-OHdG adducts in forestomach, glandular stomach, duodenal cells, lung or skin No measure of cytotoxicity	De Flora et al. (2008)
Mouse, C57BL/6J Oral, drinking water	0, 0.019, 0.19, 1.9 mg/L Cr(VI) 150 d 2 animals per dose group	In proximal and distal sections of GI tract: Immunohistochemistry: 1.5-fold increase in γH2AX in distal sections	Sánchez-Martín et al. (2015)

System	Exposure[a]	Results	Reference
Rat Oral gavage	530 mg/kg-d Cr(VI), 3 d 106 mg/kg-d Cr(VI), 30 d Note: The administered gavage potassium dichromate doses (1,500 mg/kg and 300 mg/kg) are higher than the LD_{50} for rats listed in MSDS (130 mg/kg)	Intestinal epithelial cells, 3-d exposure: ↓ glucose-6-phosphate dehydrogenase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, superoxide dismutase and catalase ↓ glutathione and total thiols ↑ lipid peroxidation Intestinal epithelial cells, 30-d exposure: ↑ superoxide dismutase, glutathione peroxidase Null glucose-6-phosphate dehydrogenase, glutathione reductase and catalase ↓ glutathione-S-transferase	Sengupta et al. (1990)
Mouse, ddY, 4 per group Oral gavage	0 or 85.7 mg/kg Cr(VI) Single dose	p.o.: ↑ DNA damage (comet assay) in stomach, colon, and lung (also in brain, liver, kidney, bladder, but not in bone marrow) in cells collected 8 h after treatment Effects subsided at 24 h in all dose groups No clinical or microscopic signs of cytotoxicity	Sekihashi et al. (2001)
In vitro human primary and immortalized GI cells or gastric fluid			
Human primary lymphocytes and gastric mucosal cells	177 µM or 0.57 mM Cr(VI)	↑ DNA damage (comet assay) ($p < 0.001$)	Błasiak et al. (1999), Trzeciak et al. (2000)
Pre- and post-meal gastric fluid samples from healthy volunteers (n = 8)	0.021 mg/L Cr(VI)	↓ mutagenicity of Cr(VI) (assessed via Ames reversion test) as a function of time in human gastric juice	De Flora et al. (2016)
Human gastric cancer SGC-7901 cells	3.53 µM Cr(VI)	DNA damage (comet assay, γH2AX), oxidative stress, apoptosis and necrosis all increased when the Unconventional prefoldin RPB5 Interacting protein (URI) is knocked down	Luo et al. (2016)
Human primary gastric and nasal mucosa cells	0.087–0.349 µmoles/mL Cr(VI)	↑ DNA damage (comet assay) and cytotoxicity, equal sensitivity in human and rat primary gastric and nasal mucosal cells	Pool-Zobel et al. (1994)
Human lung epithelial A549 and colon HCT116 (MLH-/-) and DLD1 (MSH6-/-) cells	1–20 µM K_2CrO_4, 3–12 h	↑ survival, ↓ apoptosis in mismatch repair (MMR)-deficient cells ↑ DNA DSBs (γH2AX) and apoptosis in MMR-proficient cells γH2AX foci occur in G2, but no G2 cell cycle arrest No p53 induction in either cell type at subtoxic levels MMR responsive to Cr-DNA adducts, not oxidative damage or crosslinks In MMR+ cells, apoptosis induced by Cr-DNA adducts independently of p53	Peterson-Roth et al. (2005); Zhitkovich et al. (2006)

System	Exposure[a]	Results	Reference
Human colon HCT116 (MLH1-/-) and DLD1 (MSH6-/-), lung epithelial H460, and lung fibroblast IMR90 cell lines	2–10 µmol/L K_2CrO_4, 3 h	Ternary ascorbate-Cr-DNA adducts are substrate for error-prone mismatch repair (MMR) MSH2-MSH6 dimer, leading to ↑ DNA DSBs and ↑ apoptosis Cells deficient in MMR have higher survival and lower DNA DSBs Colon cells deficient in MMR have increased survival following Cr(VI) exposures, increasing probability of clonal selection of these cells	Reynolds et al. (2009)
Caco-2 human colorectal adenocarcinoma cells	0.1, 0.3, 1, 3, 10, 30, 100 µM Cr(VI)	Increase in 8-OHdG at nontoxic and cytotoxic concentrations, increase in γH2AX only at cytotoxic concentrations (24 h) No change in p53, annexin-V (apoptosis markers), LC3B (autophagy marker) Translocation of ATF6 to nucleus (ER stress response marker)	Thompson et al. (2012a)
Human SV40 transformed fibroblasts, Werner syndrome fibroblasts, primary human lung IMR90 fibroblasts, and and human colon HCT116 MLH1-/- and MLH1+ cells	0–30 µM K_2CrO_4, 3 h	↑ nuclear relocalization of WRN in response to Cr(VI) ↓ cell survival, ↑ DNA DSBs and ↓ RAD51 foci in cells lacking WRN ↓ DNA DSBs in cells lacking mismatch repair Error-prone mismatch repair of Cr-DNA adducts generates DNA DSBs and repair of persistent DNA DSBs is dependent on WRN helicase	Zecevic et al. (2009)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Supporting oral exposure genotoxicity studies

Besides the studies identified above that reported gene or chromosomal mutations or measured genotoxicity endpoints directly in GI tissues, a small set of in vivo experimental animal studies was identified that measured genotoxicity in tissues other than the GI tract following oral exposures to Cr(VI). These studies identified in the preliminary title and abstract screening as "mechanistic" were further screened and tagged as "oral exposure, "cancer," and "genotoxicity" if they were in vivo oral exposure studies that measured genotoxicity endpoints. After removal of endpoints already considered (see above), five genotoxicity studies in experimental animals were identified; no human studies were identified. This evidence is summarized in Table C-51.

Table C-51. Supporting genotoxicity studies in animals exposed via the oral route to Cr(VI)

System	Exposure[a]	Results	Comments	Reference
Rat, Fischer 344	Oral-drinking water, 0, 0.35, 1.77, 7.07 mg Cr(VI)/L, 48 h Comparison to single gavage doses (20 mL/kg) at same concentrations	No increase in unscheduled DNA synthesis in hepatocytes collected from the rat livers and analyzed in the in vivo-in vitro hepatocyte DNA repair assay	No measure of cytotoxicity RDS not determined	Mirsalis et al. (1996)
Rat, Sprague-Dawley	Oral-drinking water, 0, 10.6, 35.4, 106.1 mg/L Cr(VI) 0, 2.49, 7.57, 21.41 mg/kg-d Cr(VI) 4 wk	In plasma: no change in 8-OHdG levels	↑ MDA at two high doses ↓ GSH-Px ↓ global DNA methylation at two high doses No change in P16 methylation	Wang et al. (2015)
Mouse, ddY, 4 per group	Oral gavage, 0 or 85.7 mg/kg Cr(VI) Single dose Also i.p.: 0 or 32.1 mg Cr(VI)/kg	p.o.: ↑ DNA damage (comet assay) in stomach, colon, liver, kidney, bladder, lung, and brain, but not in bone marrow in cells collected 8 h after treatment i.p.: ↑ DNA damage (comet assay) in stomach, colon, and bladder (but not in liver, kidney, lung, brain, or bone marrow) at 8 h	Effects subsided at 24 h in all dose groups No clinical or microscopic signs of cytotoxicity	Sekihashi et al. (2001)
Mouse, Swiss albino	Oral gavage, 0, 0.21, 0.42, 0.84, 1.68, 3.37, 6.7, 13.5, or 26.9 mg/kg Cr(VI) Single dose	↑ DNA strand breaks (comet assay) in leukocytes at 24, 48, 72, and 96 h and 1 and 2 wk posttreatment Dose-response from 0.59–9.5 mg/kg. Peak response at 48 h. No cytotoxicity detected (trypan blue).		Dana Devi et al. (2001)
Mouse, Swiss albino	Oral gavage, 0, 8.8, 17.7, and 35.4 mg/kg Cr(VI) Single dose or 1×/d, 5 d	↑ DNA damage (comet assay) in lymphocytes (statistically significant); increasing with dose		Wang et al. (2006)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Injection studies

Supporting evidence of the genotoxic effects of Cr(VI) is provided by studies investigating mechanisms of genotoxic effects by more direct routes of administration in vivo, e.g., intraperitoneal (i.p.) injection. Twenty-three studies, summarized in Table C-52, were identified that measured genotoxic endpoints in animals exposed to Cr(VI) via i.p. injection.

Table C-52. Genotoxicity studies in animals exposed to Cr(VI) via i.p. injection

System	Exposure[a]	Results	Comments	Reference
Gene and chromosome mutation				
Mouse, CD-1, male	i.p., 0, 20, 30, 40, and 50 mg/kg K_2CrO_4 (0, 5.4, 10.6, 14.1, or 17.7 mg Cr(VI)/kg), single dose	↑ micronuclei in peripheral blood reticulocytes		Awogi et al. (1992)
Mouse, BDF_1, male Mouse, Swiss albino, pregnant females	i.p., 0 or 50 mg/kg $K_2Cr_2O_7$, 24 h	↑ micronuclei in bone marrow of males or dams ($p < 0.001$) and in peripheral blood and liver of fetuses ($p < 0.001$)	No effect on PCE/NCE ratios (no cytotoxicity) No effect on fetus body weights	De Flora et al. (2006)
Mouse, MS and ddY	i.p., 0, 12.5, 25, or 50 mg/kg K_2CrO_4 (0, 4.4, 8.8, or 17.7 mg Cr(VI)/kg), single dose	↑ micronuclei in bone marrow at 17.7 mg Cr(VI)/kg; statistically significant trend	Cytotoxicity not reported	Hayashi et al. (1982)
Mouse, ddY, male	i.p., 40 mg/kg K_2CrO_4 (14.1 mg Cr(VI)/kg), single dose	In peripheral blood reticulocytes sampled at 0, 24, 48, and 72 h and hepatocytes at 5 d post-partial hepatectomy: ↑ micronucleus frequency		Igarashi and Shimada (1997)
Mouse, Slc:ddY	i.p., 0, 30, 40, and 50 mg/kg K_2CrO_4 (0, 10.6, 14.1, or 17.7 mg Cr(VI)/kg), 1×/d, 2 d	↑ micronucleus frequency in bone marrow cells; statistically significant dose-response	%PCEs decreased at two highest doses	Itoh and Shimada (1996)
Mouse, lacZ transgenic (Muta Mouse)	i.p., 40 mg/kg K_2CrO_4 (0 or 14.1 mg Cr(VI)/kg), 1×/d, 2 d, or single dose sampled on d 1 and d 7	↑ micronucleus frequency in peripheral blood reticulocytes ↑ mutant frequency in liver at 1 d ↑ mutant frequency in bone marrow at 7 d	7 d postinjection is too long to detect MN in bone marrow Cytotoxicity not reported	Itoh and Shimada (1997), Itoh and Shimada (1998)

System	Exposure[a]	Results	Comments	Reference
Mouse, C57BL/6J/BOM, female, mated to T-stock male	i.p., 0, 10 or 20 mg/kg K_2CrO_4 (0, 2.7, or 5.4 mg Cr(VI)/kg)	+ mouse spot test in offspring	Decline in number of surviving offspring with dose	Knudsen (1980)
Rat, white outbred, male	i.p., 0 or 14 mg $K_2Cr_2O_7$/kg-body mass, single dose (4.9 mg/kg Cr(VI), 24 h	Rodent dominant lethal test: dominant lethal mutation frequency of 0.665 by comparing the number of live fetuses in the Cr(VI) treatment group to the control group Micronucleus test in bone marrow	Also exposed via gavage; was evaluated in HAWC for male repro and mutagenic outcomes	Marat et al. (2018)
Rat, Wistar	i.p. 21 mg $K_2Cr_2O_7$/kg-body mass, single dose (4.9 mg/kg Cr(VI), 48 h	↑ chromosomal aberrations in the bone marrow but not in lymphocytes unless dose reached toxic levels		Newton and Lilly (1986)
Mouse, CBA × C57Bl/6J hybrid male	i.p., 0, 0.5, 1.0, 2.0, 10, or 20 mg/kg $K_2Cr_2O_7$ (0, 0.18, 0.35, 0.70, 3.5, or 7.1 mg Cr(VI)/kg), single dose i.p., 0, 1.0, or 2.0 mg/kg $K_2Cr_2O_7$ (0, 0.35, 0.70 mg Cr(VI)/kg), 1×/d, 21 d	Rodent dominant lethal test Single dose: Statistically significant decrease in embryo survival at 7.1 mg Cr(VI)/kg Repeat dose: Statistically significant decrease in embryo survival at 0.7 mg Cr(VI)/kg		Paschin et al. (1982)
	i.p., 0, 1, 5, or 10 mg/kg $K_2Cr_2O_7$ (0.35, 1.77, or 3.54 mg Cr(VI)/kg), single dose	↑ micronucleus frequency in bone marrow at 24, 48, or 72 h; peak at 48 h	No measure of cytotoxicity	
Mouse, BALB/c, C57BL/6, and DBA/2	i.p., K_2CrO_4	↑ micronucleus frequency in PCEs in all mouse strains		Sato et al. (1990)
Mouse, MS/Ae and CD-1, male	i.p., 0, 10, 20, 40, or 80 mg/kg K_2CrO_4 (0, 3.5, 7.1, 14.1, or 28.3 mg Cr(VI)/kg), single dose	↑ micronuclei in bone marrow cells, dose-response	%PCEs decreased at highest dose	Shindo et al. (1989)

System	Exposure[a]	Results	Comments	Reference
Mouse, ddY, CD-1, BDF1, and ms, male	i.p., 0, 15, 30, or 60 mg/kg K_2CrO_4, single dose, 24 h	↑ micronucleus frequency in PCEs in all mouse strains		The Collaborative Study Group for the Micronucleus Test (1988)
Mouse, NMRI	i.p., 0, 12.12, 24.25, or 48.5 mg/kg K_2CrO_4 (0, 3.2, 6.49, or 13.0 mg Cr(VI)/kg), 2 doses 24 h apart	↑ micronuclei in bone marrow at 13 mg Cr(VI)/kg; statistically significant trend	Cytotoxicity not reported	Wild (1978)
Mouse, B6C3F1, male, 8–10/group	i.p., 0, 0.51, 5.1, and 51.0 µg Na_2CrO_4/d, 4 wk (5.5×10^{-5}, 0.055, 0.55 mg/kg Cr(VI))	No significant increase in micronucleated erythrocytes (PCEs or NCEs) per 1,000 cells analyzed from peripheral blood collected at the end of the treatment period.		Witt et al. (2000)
Mouse, BALB/c	i.p., 0 or 400 µmol $K_2Cr_2O_7$ (20.8 mg Cr(VI)/kg), single dose	↑ micronucleus frequency in bone marrow cells ($p < 0.001$) Significantly decreased %PCEs (PCE/NCE ratio = 0.64 ± 0.14) ($p < 0.01$)	In liver: ↑ lipid peroxidation ($p < 0.05$) ↑ heme oxygenase ($p < 0.001$) ↓ GSH-peroxidase activity ($p < 0.1$); slight but nonsignificant reduction in GSH levels	Wroñska-Nofer et al. (1999)
DNA damage				
Mouse, BDF1, female	i.p., 25mg/kg $Na_2Cr_2O_7$ – acute; 12.5mg/kg – subchronic, single injection for acute (1–14 d) or every 4 wk for 128 d	↑ changes in ploidy in acute group	N ranged from 3 to 5 per group. All regions of liver	Garrison et al. (1990)
Rat, Sprague-Dawley, male	i.p., 0, 2.5, 5.0, 7.5, and 10 mg/kg-d $K_2Cr_2O_7$, 5 d	In peripheral blood lymphocytes: ↑ DNA damage (comet assay)	In liver: ↑ ROS, MDA, SOD, CAT activity	Patlolla et al. (2009b)
Mouse	i.p., K_2CrO_4	DNA damage (comet assay) in liver, lung, kidney, spleen, and bone marrow		Sasaki et al. (1997)

System	Exposure[a]	Results	Comments	Reference
Rat, Sprague-Dawley, male	i.p., 20 or 50 mg/kg-d	1 h: DNA-DNA and DNA-protein crosslinks in liver, lung and kidney ↑ DNA strand breaks in liver 36–40 h: DNA-protein crosslinks in lung and kidney		Tsapakos et al. (1981), Tsapakos et al. (1983)
Mouse, albino male	i.p., 0 or 20 mg Cr(VI)/kg, single dose	DNA damage (comet assay), 15 min post-injection (all back to control levels at 3 h): ↑ liver, kidney No increases in spleen, lung, brain	Same pattern as Cr(V) complexes Cytotoxicity not reported DNA damage reduced with deferoxamine	Ueno et al. (2001)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Summary of supporting in vivo genotoxicity evidence

Human evidence

In addition to the studies of gene and chromosome mutation, other types of genotoxicity studies conducted among humans exposed occupationally or environmentally to Cr(VI) are considered supporting evidence for the ability of Cr(VI) to cause genetic damage in exposed workers. These are biomonitoring DNA damage assays conducted on peripheral blood that measure DNA strand breaks, adducts, crosslinks, or other DNA damage and repair-related endpoints (e.g., sister chromatid exchange). These studies are summarized in Table C-49. They did not undergo formal study evaluation unless they included other endpoints that met the mutagenic prioritization criteria.

DNA damage in exposed humans

Seven of eight studies of exposed chromium industry workers detected significant increases in DNA strand breaks in peripheral blood using the comet assay; seven of these studies also confirmed exposures by detecting higher Cr levels in air and/or biomarkers compared to referents (Wang et al., 2012; Sudha et al., 2011; Zhang et al., 2011; Balachandar et al., 2010; Iarmarcovai et al., 2005; Danadevi et al., 2004; Gambelunghe et al., 2003; Gao et al., 1994). These tests provide supporting evidence for increased genetic damage following Cr(VI) exposure, though they do not anticipate the proportion of DNA strand breaks that could lead to mutation. Five studies evaluated DNA-protein crosslinks, which are considered biomarkers for the genotoxic effects of Cr(VI) exposure in humans (Zhitkovich, 2005). Four of these studies documented increases among exposed groups compared to controls (Medeiros et al., 2003; Quievryn et al., 2001; Taioli et al., 1995; Costa et al., 1993). The fifth study did not document clear differences between exposed and controls but did identify positive associations between DNA-protein crosslinks and chromium in

erythrocytes at low and medium exposure levels, with a saturation of crosslink incidence at higher levels (Zhitkovich et al., 1996). Fifteen studies evaluated sister chromatid exchange (SCE). Elevated levels of SCEs following exposures are indicative of increased DNA repair and are considered biomarkers of exposure to potential genotoxic agents but do not correlate well with mutation frequency (Eastmond, 2014). Among these, six studies documented increased SCEs per cell among exposed groups of welders (Werfel et al., 1998) or electroplating workers (Wu et al., 2001; Wu et al., 2000; Lai et al., 1998; Deng et al., 1988; Stella et al., 1982) compared to control groups. Similarly, one study documented an association between urinary chromium and SCE (Sarto et al., 1982). Seven studies did not observe impacts on SCEs, either through comparing exposed and control groups (Benova et al., 2002; Nagaya, 1986; Koshi et al., 1984; Littorin et al., 1983; Husgafvel-Pursiainen et al., 1982) and/or through evaluating the association with urinary chromium directly (Nagaya et al., 1991; Nagaya et al., 1989; Nagaya, 1986). One study documented a decrease in SCE frequency among welders compared to controls, though the authors noted concerns with the alkaline filter elution that may have impacted the validity of the results (Popp et al., 1991).

Target tissue analyses of genotoxicity

A small number of studies conducting analyses of genotoxicity in human gastric fluid or primary human GI or lung cells were also identified. In a gastric reduction capacity experiment using pre- and post-meal gastric fluid samples from healthy volunteers (n = 8), higher reducing capacity and significantly decreased mutagenicity (evaluated by the Ames assay) were observed in post-meal samples compared to pre-meal samples. A 70% total Cr(VI) reduction was observed within 1 minute with a 98% reduction by 30 minutes (De Flora et al., 2016). Because gastric emptying occurs in vivo (reduction and emptying are competitive processes), a fraction of ingested Cr(VI) will empty to the small intestine prior to reduction (see Section 3.1 of the toxicological review and Appendix C.1). In a study of lung reduction capacity by the same group, the S-9 fraction from pulmonary alveolar macrophages (PAM) isolated from the lung of human subjects (n = 47) was capable of lowering Cr(VI)-induced mutagenicity in the Ames assay by approximately 25% when preincubated for 1 hour prior to plating (Petrilli et al., 1986). Similar results were obtained by the S-12 fractions of peripheral lung parenchyma isolated from healthy subjects and from patients with lung cancer on the mutagenicity of Cr(VI) in the Ames assay; samples from smokers had a significantly higher ability to reduce Cr(VI) (De Flora et al., 1987b).

Pool-Zobel et al. (1994) performed the comet assay for measuring DNA strand breaks on human mucosal cells from macroscopically healthy tissues of patients collected during biopsy treated with 0.087−0.349 µmoles/mL Cr(VI) in vitro. The results showed genotoxicity occurring at non-cytotoxic doses, with responses in the cells from humans paralleling those of cells from SD rats (see DNA damage section in synthesis of animal genotoxicity evidence). Similarly, a separate group reported statistically significant increases in DNA damage using the comet assay in two studies of

human primary gastric mucosal cells exposed to concentrations ≥177 μM Cr(VI), which underwent repair within an hour (Trzeciak et al., 2000; Błasiak et al., 1999).

Tumor genotyping

The study of mutations occurring in oncogenes or tumor suppressor genes in tumor tissues can help identify chemical-specific driver mutations that could be key for tumor progression, as well as signature mutations that can potentially establish a causal association between chemical exposure and tumors. One study, Alguacil et al. (2003), evaluated mutations in the KRAS oncogene in tumor tissues, comparing pancreatic cancer cases with and without KRAS mutated tumors in individuals with inhalation exposure to chromium (ascertained using occupational history and a job-exposure matrix). The exposed workers with pancreatic tumors had increased odds of KRAS mutations in these tumors. Study authors also documented an increased proportion of G-to-T transversions with inhalation exposure to chromium. However, very few individuals were identified as having occupational chromium exposure, resulting in wide confidence intervals around the effect estimates (Alguacil et al., 2003). In addition, because pancreatic tumors have not been associated with occupational Cr(VI) exposure, and nearly 100% of pancreatic tumors (pancreatic ductal adenocarcinomas) have mutations in the KRAS gene (Waters and Der, 2018), this evidence may have little biological relevance to Cr(VI)-induced cancer.

Three studies evaluated p53 mutations among chromate factory workers with lung cancer, comparing cases with and without chromium exposure. Kondo et al. (1997) identified fewer p53 mutations among chromate workers. Yet, study authors also identified specific patterns of p53 mutations among lung cancer cases with prior chromate exposure, including double missense mutations. However, lack of adjustment for confounding and small sample size limit confidence in these findings (Kondo et al., 1997). Similarly, Katabami et al. (2000) detected an upregulation in cyclin D1 protein expression but no differences in p53 or bcl-2 protein expression in lung cancer tissues from chromate-exposed patients compared to non-exposed or pneumoconiosis lung cancer patients, though this study also had a small sample size and only considered confounding due to smoking status. Cyclin D1 is involved in the regulation of cell cycle progression and is elevated in a number of human cancers (Alao, 2007), and when paired with the absence of a protective p53-induced apoptotic response, may indicate a factor in Cr(VI)-induced cancer development. The third study, Halasova et al. (2010), determined that expression of the apoptosis inhibitor survivin protein was decreased, concomitant with an increase in pro-apoptotic p53 levels, in former chromium workers with lung cancer compared to control lung cancer patients. However, little information was given regarding the potential exposures of these workers, and no information on confounders including smoking status was included. Although this finding is not surprising given these interconnected pathways of cell fate determination, the potential for co-exposures and co-morbidities precludes the ability to draw conclusions from these findings.

Overall, specific driver mutations or mutational signatures considered to be specific to Cr(VI) exposure have not been identified in exposed humans. However, there is evidence that

critical human cancer effector pathways are directly and indirectly impacted after Cr(VI) exposure. Cr-DNA adducts, well established to occur in controlled conditions in cell cultures and acellular test systems in vitro (see Section 3.2.3.4 of the toxicological review and Appendix C.3.2.1 for a broader discussion of Cr-DNA adduct formation), could potentially provide additional support connecting exposure to genotoxic chemicals with effect. However, due to their transient nature, they do not appear to have the potential to be used as biomarkers of genotoxicity following Cr(VI) exposure in humans; accordingly, no evidence of the recovery of Cr-DNA adducts has been identified in Cr(VI)-exposed humans or animals.

Animal evidence

DNA damage

Genotoxicity endpoints that did not meet the mutagenicity prioritization criteria have also been reported in animal studies. These include measures of DNA damage that may not reflect actual mutation frequency, as well as studies using less relevant routes of exposure (i.e., i.p. injection studies).

Only one animal study was identified that reported DNA damage measures following direct exposure to the lung. Gao et al. (1992) exposed Wistar rats to 0.45 and 0.87 mg/kg Cr(VI) via intratracheal instillation and detected a significant increase of DNA strand breaks in peripheral lymphocytes after 24 hours. Several drinking water exposure studies were identified that reported mostly negative findings for DNA damage. Thompson et al. (2015b; 2015a) conducted immunohistochemical staining for phosphorylated histone H2AX (γH2AX), a marker of DNA double-strand breaks, in the intestinal villi and crypts of mice after oral exposure. Immunohistochemical grading reported moderate staining in the crypts that was not treatment-related, and moderate staining in the villi after exposure to 31 mg/kg Cr(VI)-day (high dose) after 13 weeks (Thompson et al., 2015a). A 7-day follow-up study by the same group also reported no treatment-related increase in γH2AX foci in the crypts, although these results may have biased toward the null due to the 24 hour recovery period given the potentially rapid disappearance of γH2AX (Thompson et al., 2015b). Another group reported a 1.5-fold increase in γH2AX in the 'distal section' of the GI tract in C57BL/6J mice exposed to up to 1.9 mg/L Cr(VI) in drinking water for 150 days, although the low number of animals studied (2/group) make these findings less informative (Sánchez-Martín et al., 2015). A separate genotoxicity study reported no evidence of DNA-protein crosslinks in GI tissues (forestomach, glandular stomach, and duodenum) of female SKH-1 mice after 9 months of low dose oral exposure to 1.20 and 4.82 mg Cr(VI)/kg-day through drinking water (De Flora et al., 2008).

Three studies in mice administering Cr(VI) via gavage reported significant, dose-dependent increases in DNA damage, measured by the comet assay, in multiple tissues, including lymphocytes (Wang et al., 2006), leukocytes (Dana Devi et al., 2001), stomach, colon, liver, kidney, bladder, lung, and brain (Sekihashi et al., 2001). Single, bolus gavage doses greatly condense the exposure time,

inhibiting gastric reduction (ad libitum drinking water exposures are distributed over a 24-hour period, whereas gavage occurs over a very short period). This difference in pharmacokinetics could potentially explain the difference in genotoxicity results between gavage and drinking water observations. The only tissue Sekihashi et al. (2001) tested that did not find an increase in DNA damage was the bone marrow, and no indications of cytotoxicity were observed in the animals, indicating that Cr(VI) did not reach the bone marrow at sufficient concentrations to induce DNA damage (Dana Devi et al., 2001; Sekihashi et al., 2001).

Similarly, studies in rats and mice uniformly indicate Cr(VI) can cause gene and chromosomal mutations and DNA damage when injected intraperitoneally (i.p.); these are summarized in Table C-52. While less informative for GI tract cancers, intraperitoneal dosing experiments are considered supplemental to oral dosing studies in providing mechanistic evidence to inform mutagenic and genotoxic effects. Dosing via i.p. injection results in higher systemic tissue concentrations of Cr(VI) compared to oral and inhalation exposure because this route bypasses Cr(VI) reduction mechanisms that would otherwise dampen systemic Cr(VI) distribution and absorption (see Section 3.1 of the toxicological review and Appendix C.1). Systemic effects are more likely following i.p. injection compared to oral exposure. However, some mechanistic studies aim to examine the effects of Cr(VI) on target tissues, irrespective of route, and i.p. injections may be the only feasible method to expose some systemic target organs to carefully controlled and consistent concentrations of Cr(VI).

Although in vitro studies of human cells were prioritized over other mammalian cells, Pool-Zobel et al. (1994) compared responses from both human and rat cells. This study performed the comet assay for measuring DNA strand breaks on human and rat gastric mucosal cells from macroscopically healthy tissues of patients collected during biopsy or from Sprague-Dawley rats treated with 0.087−0.349 µmoles/mL Cr(VI) in vitro. The results showed genotoxicity occurring at non-cytotoxic doses, with responses in the cells from SD rats paralleling those from human cells, providing some evidence of species concordance for genotoxicity induced by Cr(VI).

Signature mutations

Other investigations of specific Cr(VI)-induced mutations that may be relevant to GI carcinogenesis have been reported. An analysis of the specific types of point mutations induced by a chemical can determine whether, compared to spontaneous mutations, certain mutations are more associated with exposures, i.e., signature mutations. Chemical-specific mutational signatures can potentially establish an association between chemical exposure and mutation, as well as lending mechanistic insight into the types of DNA damage most associated with the specific mutation. In addition to analyzing mutation frequency, two studies examined specific types of point mutations in the mouse small intestine after 28 or 90 days of exposure. G:C to T:A transversions, mutations that frequently result from the DNA damage associated with oxidative stress, were observed to occur at a slightly higher frequency (11%) in the lung of the Cr(VI)-treated transgenic mice (6.75 mg/kg, intratracheal instillation) (Cheng et al. (2000; 1998)), consistent with

in vitro findings by this group (Liu et al., 1999). The G:C to T:A transversions correlated with glutathione levels, presumably because the antioxidant is reducing higher levels of intracellular Cr(VI) and thus increasing reactive oxygen species generation.

In another study in transgenic mice, an increase in G:C to T:A transversions was not observed in mutations recovered from the duodenum in animals exposed to Cr(VI) in drinking water (Aoki et al., 2019). This study did, however, detect a higher rate of A:T to T:A transversions in the Cr(VI)-exposed animals at 28 days that was not detectable at 90 days; the significance of this mutation in relation to Cr(VI) is not known, but it indicates a potential signature mutation that could be investigated further. The Cheng et al. (2000; 1998) study reported a higher frequency of all mutation types in Cr(VI)-exposed animal lung tissue compared to controls, whereas the Aoki et al. (2019) study did not detect an increase in mutations over background in the duodenum. Although the study did not conduct additional testing to determine whether this difference is attributable to a lack of oxidative DNA damage (and subsequent G:C to T:A transversions) in the animals in the Aoki et al. (2019) study, it is possible that mutations related to oxidative damage are more likely to be induced in a single high intratracheal instillation exposure (6.75 mg/kg Cr(VI)) in Cheng et al. (2000; 1998), compared to a longer, lower dose exposure period (up to 0.7 mg/kg-d for 28 days or 0.45 mg/kg-d for 90 days, drinking water) used by Aoki et al. (2019). Some consistency in results is noted by the finding that both studies reported that a high proportion of spontaneous mutations were G:C to A:T transitions. Overall, there is not enough evidence to conclude that there may be a signature mutation associated with Cr(VI) exposure.

In vitro studies

In vitro investigations of the mechanisms of genotoxicity induced by Cr(VI) can provide support to observations in vivo. In general, if a study was conducted only in human primary cells or cell lines derived from a specific tissue (e.g., lung, GI tissues, liver), the genotoxicity evidence is summarized in those sections and not repeated here.

Table C-53. In vitro genotoxicity studies in human cells

System	Exposure[a]	Results	Comments	Reference
Gene and chromosome mutation				
WIL2-NS human B lymphoblastoid cells	0, 0.01, 0.10, 1.00, 10, 100, and 1000 µM $K_2Cr_2O_7$, 48 h	↑ micronuclei, all concentrations ($p < 0.001$) ↑ necrotic cells ≥100 µM ↓ nuclear division index	Folate deficiency increased DNA damage	Alimba et al. (2016)
Primary human lymphocytes from four donors	0, 0.001, 0.01, 0.1, and 0.25 µg/mL $K_2Cr_2O_7$, 48 h	↑ chromosomal aberrations, all concentrations ($p < 0.05$) ↑ micronuclei, all concentrations ($p < 0.05$)	Significant increases in chromosomal mutations occurring at noncytotoxic concentrations	Botta et al. (1996)

System	Exposure[a]	Results	Comments	Reference
	(0, 0.35, 3.54, 35.4, and 88.4 ng/mL Cr(VI))	↓ mitotic index with dose; cytotoxic dose (50% decrease) estimated to be 0.15 µg/mL		
TK6 human lymphoblastoid cells	5 µM $K_2Cr_2O_7$, 5 h	"Hotspot" mutations at the hprt gene (6-thioguanine resistant): C:G→A:T transversion, bp 243 (4.5%) A:T→T:A transversion, bp 247 (2%) G:C→A:T transition, bp 289 (2.5%) C:G→T:A transition, bp 312 (4%)	Hprt bp 243 is hotspot for H_2O_2 (G:C→C:G transversion) and BaP Hprt bp 247 is hotspot for X-rays (A:T bp deletion) Overall, little overlap between Cr(VI) mutation spectra and that of oxidative DNA damaging agents	Chen et al. (1994a, b)
HeLa cells	1, 10, and 100 µM $Na_2Cr_2O_7$; 1, 2.5, 8, 24, or 48 h	Mutation spectra: Single-base substitutions at G/C predominant More transversions and fewer transitions compared to spontaneous	Intracellular Cr(III) inhibits DNA synthesis and replication fidelity by inhibiting DNA synthesome polymerases α, δ, and ε	Dai et al. (2009)
Human dermal fibroblasts	1–6 or 200 µM Na_2CrO_4, 6 h	↑ DNA DSBs (neutral comet assay; γH2AX foci) only in PCNA-positive cells that were ATM+/+ Low cytotoxicity and ROS generation detected previously	Cr(VI) exposure generates S-phase dependent DNA DSBs that activate ATM kinase	Ha et al. (2004)
HeLa and human lung bronchial epithelial cells	0.25 µM Na_2CrO_4, 30 d, or 10 µM, 16 or 48 h	↑ chromosomal aberrations with acute or chronic exposures	Chromosomal instability caused in part by suppressed activation of BubR1 and expression of Emi1, causing activation of APC/C, following nocodazole-induced mitotic arrest activation	Hu et al. (2011)
DNA damage				
TK6 human lymphoblastoid cells	0.2–1 mM $CrCl_3$ and Na_2CrO_4	↑ DNA strand breaks (comet assay); associated with oxidized base damage as measured by FPG and EndoIII addition	Cr(VI) delayed IR-induced DNA damage repair	El-Yamani et al. (2011)
Human fibroblast strains CRL 1187, XP12BE (CRL1223) and	0, 2, 5, 50 µM K_2CrO_4, 4 h	↑ DNA single-strand breaks induced in cells both deficient and proficient in excision repair	Other repair mechanisms involved in repair of DNA SSBs	Fornace (1982)

System	Exposure[a]	Results	Comments	Reference
XP25RO (CRL 1261)				
H460 human lung epithelial cells, IMR90 normal human lung fibroblasts, and normal mouse embryonic fibroblasts	0, 5, 10, 15, and 20 µM K_2CrO_4	DNA damage response to Cr(VI)-induced DNA double-strand breaks (γH2AX foci) dependent on ATR kinase and not ATM in ascorbate-restored cells DNA DSBs only formed in euchromatin	Involvement of ATR and DSBs forming in actively transcribed regions increases the probability that Cr(VI) can generate carcinogenic mutations	Deloughery et al. (2015)
Human U2OS osteosarcoma cells, Werner syndrome skin fibroblasts (AG03141), WI-38 fetal lung fibroblasts, telomerase-immortalized cell lines (hTERT GM01604, (hTERT AMIE15010, AG03141, hTERT BJ skin fibroblasts)	0–4 µM Cr(VI), 6–48 h	↑ γH2AX foci in S-phase ↑ WRN colocalization at γH2AX foci ↑ telomere defects exacerbated by lack of telomerase Lack of WRN slowed Cr(VI)-induced DNA DSB repair	Cr(VI) induces DNA DSBs and stalled replication forks; WRN helicase plays a role in the cellular recovery from Cr(VI)-induced replicative stress	Liu et al. (2010a, 2009)
Wild-type and pol zeta mutated D2781N and L2618M human B-cell leukemia cell line	$Na_2Cr_2O_7$ and $KBrO_3$	Increased sensitivity to DNA damage (micronuclei, SCE) in cells with weaker variants of DNA polymerase zeta	Increased susceptibility to Cr(VI)-induced mutations in variants of DNA replication enzymes	Suzuki et al. (2018)
Human TK6 lymphoblastoid, HeLa cervical carcinoma epithelial, and 293T kidney epithelial cells	1–2000 µg/L K_2CrO_4, 10 min–14 d	Cytotoxicity ≥ 373 µg K_2CrO_4/L (=100 µg Cr/L) with survival rate of 50%, 17%, and 10% for HeLa cells, 293T and TK6 cells, respectively Trace amounts (≥9.8 µg/L) of Cr(VI) initiate DNA damage response and genotoxicity that increases with time and dose	Primary Cr(VI)-induced DNA damage response pathways are error-free HR and error-prone TLS pathways	Tian et al. (2016)
Human SV40 transformed fibroblasts, Werner syndrome fibroblasts, primary human lung IMR90	0–30 µM K_2CrO_4, 3 h	↑ nuclear relocalization of WRN in response to Cr(VI) ↓ cell survival, ↑ DNA DSBs and ↓ RAD51 foci in cells lacking WRN ↓ DNA DSBs in cells lacking mismatch repair	Error-prone mismatch repair of Cr-DNA adducts generates DNA DSBs and repair of persistent DNA DSBs is dependent on WRN helicase	Zecevic et al. (2009)

System	Exposure[a]	Results	Comments	Reference
fibroblasts, and human colon HCT116 MLH1-/- and MLH1+ cells				
GM03714A, GM0131B, and GM0922B human lymphoblastic cell lines	K_2CrO_4 and $^{51}CrO_4^{2-}$ 0, 20, 50, 100, 150, and 200 µM, 3, 6, or 12 h	Differences in cytotoxicity and DNA damage in response to Cr(VI) due to differences in rate of uptake of Cr(VI) among 3 individual cell lines		Zhang et al. (2002)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.3.2.3. *Alters DNA repair or causes genomic instability (KC#3)*

Mechanistic studies relevant to detecting Cr(VI)-induced suppression of DNA repair processes (except for those caused by Cr(VI)-induced epigenetic modifications) or genomic instability resulting from Cr(VI) exposure have been summarized in Table C-54.

Table C-54. Mechanistic studies relevant to altered DNA repair or genomic instability induced by Cr(VI) exposure

Study overview	Exposure[a]	Results	Comments	Reference
Effects on DNA repair				
Exposed: chromate workers (n = 87) *Referents:* employees with no direct contact with chromium products (e.g., managers, officers, support crew) (n = 30) *Exclusions*: cancer, cardiovascular disease, kidney disease, pulmonary disease	Workers exposed to chromate by inhalation for ~5.0 yr (IQR: 3.0–10.0 yr) Postshift fasting blood samples collected; measurement with ICP-MS. Mean (SD) blood Cr in exposed group: 14.5 (33) ng/mL	ELISA of DNA repair-related genes POLBeta, ASCC3, BRCC3, and XRCC2 XRCC2 and BRCC3 protein levels were statistically associated with miR-3940-5p levels	Main limitations are related to lack of description (e.g., for participant selection)	Li et al. (2014b)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: females working in the chromium industry; subgroups based on years of contact with chromium (1–2; 3–5; 7–10; 15+) (n = 66) *Referents:* females with no contact with the chromium industry (n = 15)	Exposure based on years working in the chromium industry (1–2; 3–5; 7–10; 15+) yr	↓ DNA repair synthesis in lymphocytes in exposed group; nonlinear relationship with duration of contact with chromium	Limited sample size within each exposed group when analyzed by duration (1–2 yr: n = 13; 3–5 yr: n = 15; 7–10 yr: n = 21; 15+ yr: n = 17)	Rudnykh and Zasukhina (1985)
hTERT immortalized clonal cell line derived from human bronchial fibroblasts (WTHBF-6)	0.1–0.3 µg/cm^2 zinc chromate, 24, 72, and 120 h	After 120 h, but not 24 h, Cr(VI) induced dose-dependent decreases in nuclear Rad51, inhibition of the nuclear import of Rad51C and BRCA2, inhibition of Rad51 nucleofilaments, and complete blocking of homologous recombination repair (HR)	Prolonged exposure to Cr(VI) suppresses HR, increasing reliance on error-prone DNA DSB repair pathways and the potential for mutation	Browning et al. (2017; 2016)
WTHBF-6 human bronchial fibroblasts	0.1, 0.15, and 0.2 µg/cm^2 zinc chromate (0.12, 0.18, and 0.24 ppm), 24, 48, 72, 96, and 120 h	Time-dependent increases in DNA damage and DNA DSB signaling, decreases in Rad51 foci formation Cr(VI)-induced suppression of E2F1 transcription factor for Rad51 is involved		Qin et al. (2014), Speer et al. (2021)
Aneuploidy and genomic instability				
Primary human fibroblasts	0, 2, 20, and 40 µg/L (0.01, 0.102, and 0.205 µM) K_2CrO_4, 24 h	Using 24 color M-FISH: ↑ chromosomal aberrations (structural and numerical), dose-dependent Simple and complex aneuploidy was observed at all doses, dose-dependent	Slowly resolved with time up to 30 d postexposure	Figgitt et al. (2010)
BJ normal human foreskin fibroblasts, hTERT + and −	0.04, 0.4, and 4 mM Cr (VI) ($K_2Cr_2O_7$), 24 h	In hTERT-deficient cells, 30 d postexposure: Persistent induction of dicentrics, nucleoplasmic bridges, micronuclei and aneuploidy ↓ clonogenic survival ↑ β-gal staining and apoptosis	Cr(VI) induced persistent genomic instability Telomerase-positive cells were not affected except for persistent tetraploidy	Glaviano et al. (2006)
Human MRC-5 cells	0, 0.25, 0.5, 1, 2, and 4 µM $K_2Cr_2O_7$, 30 h	↑ kinetochore-positive micronuclei	Authors determined aneuploidy caused by malsegregation at	Güerci et al. (2000), Seoane et al. (2002; 2001, 1999)

Study overview	Exposure[a]	Results	Comments	Reference
			anaphase and not by nondisjunction	
WTHBF-6 human bronchial fibroblasts	0.5 and 1 µg/cm^2 lead chromate	24 h exposure: no effect 120 h exposure: ↑ aneuploidy; associated with centrosome amplification	Lead oxide had no effect	Holmes et al. (2006)
WTHBF-6 human bronchial fibroblasts	0.1, 0.15, and 0.2 µg/cm^2 zinc chromate (0.12, 0.18, and 0.24 ppm), 24, 72, and 120 h	↑ centrosome amplification ↑ aneuploidy Premature centriole disengagement in S and G2, and premature centrosome separation in interphase		Martino et al. (2015)
Primary human skin fibroblasts	0.01–100 µM Na_2CrO_4 and 0.001–10 µM $CaCrO_4$	↑ aberrant mitotic spindles and cell division patterns, dose-dependent		Nijs and Kirsch-Volders (1986)
Primary human peripheral blood lymphocytes	0.00476 µM and 0.00952 µM $K_2Cr_2O_7$	↑ aneuploidy, dose-dependent ↑ SCEs, dose-dependent No change in cell cycle proliferative index	Aneuploidy and DNA repair initiated at very low subtoxic concentrations	Rao et al. (1999)
BEAS-2B human bronchial epithelial cells	1 µM $K_2Cr_2O_7$	↑ aneuploidy Subclones induced tumors when injected into nude mice No microsatellite instability in aneuploid cells; DNA MMR and MLH1 expression was unaffected		Rodrigues et al. (2009)
WTHBF-6 human bronchial fibroblasts	0.5 and 1 µg/cm^2 lead chromate; 72, 96, and 120 h	↑ spindle assembly checkpoint bypass (centromere spreading, premature centromere division and anaphase, and ↓ MAD2 levels)	No effect with lead glutamate	Wise et al. (2006)
Human primary and immortalized urothelial cells expressing hTERT (hTU1 cells)	1–5 µM $NaCrO_4$	↑ aneuploidy and chromosomal damage in chronic (not acute) incubations in primary and hTERT-immortalized human urothelial cells, dose- and time-dependent	Solid-stain chromosomal analysis could be prone to false positive	Wise et al. (2016)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.3.2.4. *Induces epigenetic alterations (KC#4)*

Seven studies in humans occupationally exposed to Cr(VI) were identified that evaluated epigenetic alterations in relation to Cr(VI) exposure and mechanistic or apical outcomes, including

changes in microRNA levels, global methylation changes, and the methylation of specific genes. The study findings are summarized in Table C-55.

Table C-55. Studies of epigenetic alterations in humans, experimental animals, and human cells in vitro exposed to Cr(VI)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: lung tumor samples from chromate workers with lung cancer during surgery or autopsy (n = 36) *Referents:* lung tumor samples from lung cancer patients without chromate exposure (n = 25)	Exposure intensity ascertained based on work period in chromate industry. Mean (range) of exposure to chromate = 22.61 (12–38) yr	↑ methylation of CpG sites at APC, MGMT, and hMLH1 genes in chromate lung cancer cases compared to lung cancer referents	Limited description of selection; no consideration of confounders; no confirmation of lack of exposure in referent group.	Ali et al. (2011)
Exposed: factory workers with occupational exposure to chromate (n = 87) *Referents:* administrative workers from the same factory, without chromate exposure (n = 30) *Exclusions:* skin infection; cancer; cardiovascular disease; kidney disease; pulmonary disease; history of allergy, asthma, or allergic rhinitis	Air samples collected at 10 locations for 8 h during regular working hours (flow rate: 1L/min); measurement with atomic absorption spectrometry. Median (IQR) air chromium in exposed group = 15.5 (19.0) µg/m^3; referent group = 0.2 (0.4) µg/m^3 Peripheral venous blood collected after work shift; chromium measured by ICP-MS. Mean (IQR) blood chromium in exposed group = 6.4 (7.2) µg/L; referent group = 3.9(1.5) µg/L	↑ methylation of CpG sites at DNA repair genes (MGMT, HOGG1, XRCC1, ERCC3, and RAD51) in exposed groups	Main limitations are related to lack of description (e.g., for participant selection). Simultaneous in vitro work demonstrated hypermethylation in human bronchial epithelial 16HBE cells treated with Cr(VI).	Hu et al. (2018)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: lung cancer cases with chromate exposure (at surgery or autopsy) (n = 23 patients; n = 30 lung cancer tumors) *Referents:* lung cancer cases with no chromate exposure (n = 38)	Chromate exposures for average (SD) 22.9 (6.9) yr	↑ methylation of p16 gene in chromate lung cancer compared to lung cancer referents, but nonsignificant (p = 0.528) ↑ methylation of p16 gene with duration of chromium exposure in chromate lung cancer cases (p = 0.064) Chromate lung cancer with methylation of p16 gene had reduced expression of p16 protein (0.076)	Methylation-specific PCR and immuno-histochemistry of p16 (tumor suppressor gene). Smoking affected methylation of p16 gene in referent lung cancer cases only. No confirmation of lack of chromate exposure in referents. Small sample sizes, especially for some of the subanalyses based on duration of exposure. Analyses based on samples – some people contributed multiple samples to the analysis; these would not be independent. No consideration of confounders.	Kondo et al. (2006)
Cross-sectional study, China. *Exposed*: n = 87 workers at a chromate production facility exposed to chromate *Referent*: n = 30 workers from same facility, but unexposed to any chromium products	Exposure to Cr(VI) inferred based on occupation. Also measured total Cr in blood. Blood chromium levels were significantly higher in exposed compared with control subjects. Mean ± SD levels in blood were 14.5 ± 33 and 4.4 ± 1.9 ng/mL in exposed and referent groups, refer to air monitoring (using cellulose filter) as showing all samples <50 µg/m^3, but data not shown. The exposed group was divided by the median into two subgroups for high and low exposure.	↓ miR-3940-5p expression associated with Cr blood level, after adjusting for work duration, gender, age, smoking, drinking, and BMI ↓ miR-3940-5p & miR-590-5p in exposed group	Main limitations are related to lack of description (e.g., for participant selection).	Li et al. (2014b)
Exposed: chromate workers with lung cancer (n = 26 patients, n = 35 tumors)	Chromate workers exposed to chromate for mean (SD) 22.9 (7.3) yr	↓ expression of hMLH1 and hMSH2 proteins in chromate lung cancer	Several samples taken from the same patients – these are	Takahashi et al. (2005)

Study overview	Exposure[a]	Results	Comments	Reference
Referents: lung cancer cases without chromate exposure (n = 26 patients, n = 26 tumors)		In chromate lung cancer group, ↓ expression of nMLH1 in lung cancers with MSI at 3 or more loci	not statistically independent. No adjustment for covariates, though authors noted no significant differences in age, Brinkman score, cancer stage, etc. in the evaluated characteristics. An additional sub-analysis looked at methylation of MLH1 among chromate lung samples, but it was only conducted among 8 samples. 5 of 8 had methylation at hMLH1 gene, and 4 of those 5 also had repression of hMLH1 protein.	
Cross-sectional study, China. *Exposed:* n = 29 "healthy" chrome platers employed for at least 1 yr at two facilities *Referent*: n = 29 subjects "randomly selected from the healthy workers in the same enterprises and been engaged in public security, support services, or administration work for more than one yr, and had no specific chromate exposure history."	Exposure to Cr(VI) inferred based on occupation. Chrome platers had been employed for at least 1 yr. Also measured Cr in blood; values were significantly higher among exposed compared with unexposed workers, indicating adequate delineation between groups. Mean (range) values were 15.2 (2.1, 42) in exposed vs. 4.6 (0.2, 28) in referent group.	↓ methylation of mitochondrial genes (MT-TF, MT-RNR1) in chromium-exposed workers compared to controls No difference in methylation level of LINE-1 or in mtDNA copy number between groups	Limitations are the limited and poorly described statistical analysis, and limited description (e.g., for participant selection). Small sample size. Inconsistent results might indicate the influence of other occupational hazards on micronuclei concentrations.	Linqing et al. (2016)

Study overview	Exposure[a]	Results	Comments	Reference
Exposed: individuals (n = 115; 29 female, 86 male) with exposure to sodium dichromate for at least 6 mo *Referents:* healthy volunteers (n = 60; 15 female, 45 male) in the same city without chromate exposure history *Exclusions:* medical history of liver or renal disease, hypertension, diabetes, cardiovascular disease, or pregnancy	Air-Cr concentration collected with point dust sampler and measured with electrothermal atomic absorption spectrometry. Personal air samples collected through full shift (8 h) sampling to calculate cumulative dose Postshift blood samples collected; chromium measured with ICP-MS; mean (SD) chromium in blood of exposed workers = 12.45 (20.28) µg/L ↑ accumulation of Cr in peripheral red blood cells	Global DNA hypomethylation in chromate-exposed workers	↑ urinary 8-hydroxy-2-deoxyguanosine, DNA strand breaks. No adjustment for diet or other nonfolate supplements. ↓ serum folate in chromate-exposed workers.	Wang et al. (2012)
Rat, Sprague-Dawley	0, 10.6, 35.4, 106.1 mg/L Cr(VI) 0, 2.49, 7.57, 21.41 mg/kg-d Cr(VI) in drinking water, 4 wk	Mild anemic effects and increased plasma malondialdehyde (MDA) levels occurred in rats exposed to 100 mg/L or 300 mg/L Plasma glutathione peroxidase (GSH-Px) activity decreased in all exposed groups Global DNA methylation, p16 methylation No change in 8-OHdG levels	Mean body weight gain, mean water consumption, clinical chemistry determinations, and oxidative stress levels in plasma.	Wang et al. (2015)
In vitro, 16HBE human bronchial epithelial cells	0, 0.8, 1.6, 3.1, 6.2, 12.5, 25.0, 50.0 and 100.0 µM $Cr_2O_7^{2-}$; 12, 24 or 48 h	↑ toxicity (≥12.5 µM) and DNA damage (comet) (all concentrations), dose-dependent ↓ p16 expression and hypermethylation of p16 CpG1, CpG31, and CpG32 that correlated with toxicity and DNA damage ↑ p53 expression without CpG methylation (≥5 µM)		Hu et al. (2016a)

Study overview	Exposure[a]	Results	Comments	Reference
In vitro, 16HBE human bronchial epithelial cells	0, 2, 5, and 10 µM Na_2CrO_4, 24 h	miR-3940-5p, which normally suppresses XRCC2 and inhibits HR, is downregulated by Cr(VI), enhancing DNA DSB repair	Follow-up study to Li et al. (2014b). Interpreting the effects of one dysregulated miRNA is difficult.	Li et al. (2016)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.3.2.5. *Induces oxidative stress (KC#5)*

Table C-56 summarizes studies of markers of systemic oxidative stress measured in urine and blood in humans occupationally exposed to Cr(VI). Twenty-three studies were identified.

Human studies of systemic oxidative stress

Table C-56. Evidence in human studies prioritized for informing potential Cr(VI)-induced oxidative stress

System	Exposure[a]	Results	Comments	Reference
Exposed: workers exposed to chromium from chemical, building, and metal industries (n = 40) *Referents:* age- and sex-matched individuals, unexposed to Cr, living away from incinerators, industries, energy plants, etc. (n = 40)	*Assessment*: Urinary chromium evaluated from Saturday morning spot samples at end of the work week; assessment with electrothermic atomization-atomic absorption spectrometry. *Levels*: Mean (SD) U-Cr (µg/g creatinine) was 0.62 (0.50) among workers and 0.30 (0.13) among controls. *Duration:* No information provided about duration of Cr exposure.	In red blood cells of exposed individuals: ↓ GSH ↓ GSH/GSSG ratio In plasma: ↓ plasma acid ascorbic levels ↓ total plasma antioxidant capacity ↓ TRAP Null effects on GSSG, DHA, lipoperoxidation (TBA-RM), total thiol levels	Systemic increases in oxidative stress with chromium exposure.	De Mattia et al. (2004)

System	Exposure[a]	Results	Comments	Reference
Exposed 1: Cement workers in building construction (n = 22 males) *Exposed 2:* Tannery workers (n = 20 males) *Referent*: "normal healthy" volunteers (n = 23 males)	*Assessment:* Blood and urine total Cr measured using inductively coupled optical emission spectrometry *Levels:* Highest blood and urine Cr in tannery workers, followed by cement workers, then referents. Group I (control) n = 23 Blood: 3.81 ± 5.57 µg/L Urine: 6.27 ± 5.31 µg/L Group II (cement) n=22 Blood: 15.27 ± 2.61 µg/L Urine: 17.22 ± 3.33 µg/L Group III (tannery) n = 20 Blood: 18.90 ± 1.88 µg/L Urine: 20.84 ± 1.67 µg/L *Duration*: State that "Cement and tannery workers were usually exposed to chromium 8 h daily for a duration ranged from 1 month to 40 years."	↑ plasma malondialdehyde ↓ total thiol ↑ p53 protein	Unclear if exposure was to Cr(VI) specifically, although more likely for cement workers compared with tannery workers (as described in the discussion section); however, separating effects is impossible, given total Cr was measured in blood and urine. Poor working conditions (e.g., lack of PPE) and co-exposures limit ability to attribute effects to chromium. The population also included adolescents (minimum age 14 yr), which may affect comparability to other studies that only included adults.	Elhosary et al. (2014)
Cross-sectional study, Egypt. *Exposed*: n = 41 male electroplating workers exposed to chromium and nickel *Referent*: n = 41 male administrative workers at the same facility	*Assessment*: Exposure to Cr(VI) inferred based on occupation. Also measured Cr (and nickel) in serum. *Levels*: Serum Cr significantly higher in exposed compared with controls. Mean Cr was 3.30 and 0.23 µg/L in exposed and referent, respectively. *Duration*: Exposed workers were required to have worked in electroplating section at least 2 yr, but most worked for considerably longer with mean ± SD = 26.68 ± 11.21 yr.	↑ 8-OHdG adducts in serum	Exposed and unexposed groups are delineated, although limited description of methods (e.g., participant selection) and known coexposure to nickel could limit inference. Results correlated with increased micronuclei in buccal cells.	El Safty et al. (2018)

System	Exposure[a]	Results	Comments	Reference
Exposed: workers from bichromate plant with mixed Cr exposure (n = 10) *Referents:* workers from bichromate plant with no Cr exposure (n = 10), age and alcohol consumption matched to exposed group	*Assessment:* Urine and blood samples collected at the end of the work week; analyzed with electrothermal atomic absorption spectrophotometer. *Levels*: Mean (SD) Cr in whole blood, plasma, and urine of exposed workers: 5.5 (1.2) µg/L, 2.8 (0.4) µg/L, 5.9 (1.1) µg/g creatinine, respectively. Mean (SD) Cr in whole blood, plasma, and urine of referents: 0.7 (0.1) µg/L, 0.7 (0.1) µg/L, 0.7 (0.1) µg/g creatinine, respectively. *Duration:* No information on duration of exposure	No difference in 8-OHdG adducts (lymphocytes and urine) or DNA strand breaks (lymphocytes) between exposed and referents	Did not appear to control for key covariates – presents unadjusted results; very small sample size also limits confidence in results.	Faux et al. (1994)
Exposed: chromium-exposed workers (n = 10) *Referents:* nonexposed workers (n = 10)	*Assessment*: Urine and blood samples taken from workers at the end of a work week. *Levels*: Chromium concentrations in the factory ranged from 0.001 to 0.055 mg Cr(VI)/m^3 (obtained from personal and area samplers). Mean chromium concentrations in urine (5.97 µg/g creatinine), whole blood (5.5 µg/L), plasma (2.8 µg/L), and lymphocytes (1.01 µg/10^{10} cells) of exposed workers were significantly higher than in nonexposed workers. *Duration:* The mean duration of exposure was 15 yr	No difference in 8-OHdG adducts or DNA strand breaks (lymphocytes) between exposed and referents	Also null for DNA strand breaks; authors theorize null findings due to low exposure levels or insensitive measures used (very small sample + low exposure levels – probably very limited power).	Gao et al. (1994)

System	Exposure[a]	Results	Comments	Reference
Exposed 1: Full-time tannery workers (n = 33) *Exposed 2*: Full- or part-time stainless steel welders (n = 16) *Referents:* individuals unexposed to known environmental or occupational carcinogens (n = 30)	*Assessment:* Spot urine and venous blood samples collected from all subjects on the last day of the work week. Analyzed with graphite furnace atomic absorption spectrophotometer. *Levels*: Mean (SD) not reported *Duration*: No information on duration of exposure	↑ lipid peroxidation products (MDA) in urine of welders and tanners ↓ thiol antioxidants (glutathione) in lymphocytes of welders	Cr levels in plasma correlated with urinary MDA in welders, not tanners, who are primarily exposed to Cr(III).	Goulart et al. (2005)
Exposed: Polishers working with chromium-tanned leather (n = 34) *Referents:* Individuals not employed in industry, free of acute or chronic disease (n = 104)	*Assessment:* Chromium measured in air at tannery 1978–1990 *Levels*: Workstation concentrations ranged from mean (SD): 0.023 ± 0.009 mg Cr/m^3 to 0.11 ± 0.07 mg Cr/m^3 *Duration*: Workers exposed to chromium for 3–16 yr	↑ lipid peroxidation (TBARS) & ↓ Se in plasma in exposed group	Exposure assessment methods likely underestimate actual exposure value; TBARS results potentially confounded by other occupational exposures.	Gromadzińska et al. (1996)

System	Exposure[a]	Results	Comments	Reference
Cross-sectional study, China. *Exposed*: n = 87 workers from a single factory in China, who had "occupational exposure to chromate from different work sections" *Referent*: n = 30 working in administrative offices without chromate exposure.	*Assessment*: Exposure to Cr(VI) inferred based on occupation; median duration of employment was 5 yr in both exposed and referent. Also measured total Cr in air samples and in blood. *Levels*: Authors state "The concentration of Cr in the air and blood of subjects in the exposure group were significantly higher than the control group ($p < 0.001$)," which increases confidence in delineation of exposure groups. Geometric mean ± SD of Cr in blood was 8.5 ± 1.3 µg/L in exposed vs. 4.1 ± 1.4 µg/L in referent group, while median (IQR) of air concentrations were 15.5 (19.0) vs. 0.2 (0.4) mg/m^3. *Duration:* Workers had been in the same work section for at least 3 mo and in the factory for at least 1 yr. Median (IQR) yr of working among the Cr group = 5.0 (7.0).	↑ hypermethylation of CpG sites (in RNA isolated from whole blood), serum 8-OHdG, and MN in peripheral blood lymphocytes in exposed workers compared with referent	Main limitations are related to lack of description (e.g., for participant selection).	Hu et al. (2018) Related studies: Li et al. (2014a; 2014b)
Exposed: male chrome-plating workers (n = 25) *Referents:* unexposed males (administrators and others) (n = 28)	*Assessment*: Chromium measured in whole blood, urine, and air; blood and urine measured with graphite furnace atomic absorption. *Levels:* Mean (SD) concentrations for exposed group: air = 65 (23.6) µg/m^3; blood = 5.98 (3.17) µg/L; urine = 5.25 (3.03) µg/g creatinine. *Duration:* Chrome-plating factory workers had been exposed for 1–12 yr [mean (SD): 5.9 (3.5) yr].	↑ Malondialdehyde measured in blood and urine	A strength of this study was that chromium was measured in both air and biological samples. Limited adjustment for confounders.	Huang et al. (1999)

System	Exposure[a]	Results	Comments	Reference
Exposed: chrome-plating workers (n = 50) *Referents*: administrative workers, age and SES matched to exposed (n = 50)	*Assessment:* Chromium in urine samples measured with flameless atomic absorption spectrophotometer with graphite furnace. *Levels:* Mean (SD) in exposed group: 10.42 (8.34 µg/g creatinine). *Duration:* Chrome plating workers had been exposed to chromium for 15–20 yr.	↑ Plasma lipid peroxidation ↓ Erythrocyte antioxidant enzymes	This study is one of the only studies that adjusted for diet in investigating antioxidant enzymes. High variation of urinary chromium among exposed individuals.	Kalahasthi et al. (2006)
Exposed: lead chromate pigment factory workers (n = 22) *Referents:* office workers from chromate factory (n = 16)	*Assessment*: Chromium measured in urine, blood, and air; air sampling for 200 min at flow rate of 2–3 L/min; urine and blood measured with flameless atomic absorption spectrophotometer. *Levels:* Chromium in air ranged from below LOD (0.0005 mg/m^3 among office workers to 0.5150 mg/m^3 in high exposure area of factory (pulverizing process); mean (SD) chromium among exposed group in blood: 6.75 (3.30) µg/L; in urine: 12.97 (16.31) (µg/g creatinine). *Duration*: Mean (SD) duration of work among chromate pigment workers = 9.7 (20.5)* yr.	In blood and sputum: No difference in 8-OHdG adducts (in respiratory epithelial and white blood cells) between exposed and control groups, or with duration of employment among exposed groups	Chromium levels in blood (which are a marker of recent exposure) were similar between exposed and control groups; this suggests that exposure misclassification could be contributing to the null effects reported in the study. The authors also suggest that urinary chromium reflects chromium in reduced form, which might not reflect genotoxicity in blood cells. No adjustment for supplements/vitamins or diet. *SD appears incorrect	Kim et al. (1999)

System	Exposure[a]	Results	Comments	Reference
Exposed: workers from electroplating plants (3 chromium; 1 nickel-chromium; 2 mixed) (n = 50) *Referents:* office workers with no previous exposure to chromium (n = 20)	*Assessment:* Urine samples obtained at end of work shift; analyzed with atomic absorption spectrophotometry. Air chromium measured with personal sampling. *Levels*: Mean (SD) urinary chromium among exposed = 5.72 (7.65) µg/g creatinine. *Duration:* Electroplaters had been employed for mean (SD): 75.6 (73.1) mo.	↑ urinary 8-OHdG adducts among exposed group	High degree of variation in urinary chromium levels among exposed group. Did adjust for some dietary factors (betel nut, alcohol), but this could have been more extensive; no adjustment for supplements/ vitamins. Did not account for coexposures to other metals encountered in the factories, especially the mixed plants	Kuo et al. (2003)
Cross-sectional study, Korea. *Exposed*: n = 51 male chrome plating and buffing workers *Referent*: n = 31 male office workers from "industrial areas" in South Korea.	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Also measured Cr measured in air samples (total and VI), blood, and end-shift urine samples (See Table 1). *Levels:* Concentrations in blood and urine were significantly higher in exposed workers, indicating adequate delineation between groups. For example, the geometric mean blood level of Cr was 0.9 and 0.2 µg/dL in exposed and referent workers, respectively. Differently, while air measures were higher for exposed workers the difference was not statistically significant. *Duration*: Mean duration of occupational exposure was 9.1 yr (range: 1 mo–40 yr).	↑ lipid peroxidation (TBARS) in plasma ↑ frequency of chromatid exchange, chromosome/chromatid breaks and exchanges, and of translocations, correlated with higher blood Cr ↑ frequency of translocations in exposed compared with unexposed	Main limitations are related to lack of description for analysis and results reporting.	Maeng et al. (2004)

System	Exposure[a]	Results	Comments	Reference
Exposed: Electroplaters (n = 90), evenly split among near bath workers, degreasers, and washers *Referent:* Quality control personnel in same facilities (n = 30)	*Assessment*: Air samples (locations not specified) used to measure Cr(VI) using spectrophotometer. *Levels:* Median Cr(VI) exposure level was highest in near bath (0.38 mg/m^3) followed by degreasers (0.20 mg/m^3) and washers (0.05 mg/m^3); levels were below the LOD for referent workers. *Duration:* Median (IQR) working yr among exposed = 4.5 (4.2).	↑ serum malondialdehyde	Cr(VI) was measured in air samples, which lends confidence that exposure was occurring and at significantly higher levels in exposed workers vs. referents.	Mozafari et al. (2016)
Exposed: Electroplaters (n = 105 males) *Referent*: office workers (n = 125 males)	*Assessment:* Air samples from personal breathing zones used to measure Cr(VI) using UV-visible spectrophotometer (also measured total Cr); values combined with duration of employment to estimate cumulative exposure. Total Cr was measured in urine, hair, and fingernails using graphite furnace atomic absorption spectrophotometry. *Levels:* Total and Cr(VI) in air were higher in exposed workers (see Table 2); for example, the geometric mean daily cumulative Cr(VI) was 155.6 (GSD = 3.3) in exposed vs. 4.8 (GSD = 1.9) µg/m^3 in referents. Total chromium in biosamples was also significantly higher. *Duration:* Mean (SD) working yr among exposed group = 9.4 (5.6).	↑ urinary 8-OHdG ↑ urinary malondialdehyde	The sample size is larger compared with other similar studies, and Cr(VI) was measured in air samples, which lends confidence that exposure was occurring and at significantly higher levels in electroplaters vs. referents.	Pan et al. (2017)

System	Exposure[a]	Results	Comments	Reference
Exposed (direct): cement production unit factory workers (n = 60) *Exposed (indirect):* administrative workers in cement production factory (n = 28) *Referents:* healthy individuals from nearby city (n = 30)	*Assessment:* Serum chromium measured with platform partitionate varian graphite furnace. *Levels*: Mean (SE) serum chromium in direct exposed group: 5.2 (0.4) µg/L. *Duration:* mean (SE) yr of employment direct exposed = 4.7 (0.08); indirect exposed = 4.5 (0.17).	↓ TTM & TAC No difference in TBARS or NO (indicators of lipid peroxidation)	No evaluation of air chromium levels; very limited consideration of covariates.	Pournourmohammadi et al. (2008)
Exposed: individuals (n = 115; 29 female, 86 male) with exposure to sodium dichromate for at least 6 mo *Referents:* healthy volunteers (n = 60; 15 female, 45 male) in the same city without chromate exposure history	*Assessment:* Air-Cr concentration collected with point dust sampler and measured with electrothermal atomic absorption spectrometry. Personal air samples collected through full shift (8h) sampling to calculate cumulative dose. Postshift blood samples collected; chromium measured with ICP-MS. *Levels*: Mean (SD) chromium in blood of exposed workers = 12.45 (20.28) µg/L. *Duration:* Mean (SD) yr of employment among exposed group: 12.86 (6.02); range: 1–33.	↑ urinary 8-OHdG, DNA strand breaks and global DNA hypomethylation in chromate exposed workers ↑ accumulation of Cr in peripheral red blood cells & ↓ serum folate in chromate-exposed workers	No adjustment for diet or other nonfolate supplements.	Wang et al. (2012)
Exposed: chromium platers (n = 35) *Referents:* healthy subjects with no history of disease or previous exposure to chromium or other metals (n = 35)	*Assessment:* Personal exposure monitoring for 8-h working shift (1.71/min) on only 10 individuals in the exposed group. Blood and urine samples collected at end of shift and analyzed with atomic absorption spectrophotometry. *Levels:* Individual time-weighted average range: 0.049–1.130 mg/m^3. *Duration*: The mean duration of employment was 6.5 yr.	Significantly lower SOD levels in Cr workers (6.86 ± 0.80 U/mg Hb) compared to controls (7.16 ± 0.53 U/mg Hb) ($p < 0.01$)	Also ↑ sister chromatid exchange and percent high frequency cells in exposed group compared to controls. Personal air sampling only obtained for n = 10 individuals in the exposed group; SCE analysis conducted based on work group rather than measured exposure level. Unable to draw conclusions about effect of genotype due to small sample size.	Wu et al. (2001)

System	Exposure[a]	Results	Comments	Reference
Cross-sectional study, Austria. *Exposed*: n = 22 bright chrome plating workers exposed to chromium and cobalt *Referent*: n = 22 jail wardens	*Assessment:* Exposure to Cr(VI) inferred based on occupation. Welders used mainly TIG process (95%) with smaller proportions of electric arc and very little autogenous welding. Also measured Cr in whole blood; levels were higher in welders compared with controls. *Levels:* Mean + SD levels for exposed workers at the beginning and end of the work week were 1.4 + 0.9 and 2.3 + 1.5 µg/L, respectively, while values for referent were 0.2 + 0.2 µg/L. *Duration:* All workers worked for 8 h per day 3 wk before and during the sample collection	No changes (slight but not statistically significant) in plasma malondialdehyde, oxidized low density lipoprotein, and total antioxidant capacity (TEAC) (biochemical parameters of redox status)	Limitations are due to small sample size and presence of coexposures, which precluded more detailed analysis to separate effects. ↑MN and rates of Nbuds in buccal and nasal mucosal cells.	Wultsch et al. (2014)
Exposed: n = 319 living in villages with historic Cr contamination *Referents:* n = 307 living in villages without historic Cr contamination	*Assessment:* Cr measured in groundwater (7-m or 8-m deep wells), soil (field surface), and air (24 h/d for 5 d in both exposed and unexposed villages). *Levels[median (min, Q1, Q3, max):* Groundwater mg/L exposed: 0.002 (0.002, 0.002, 1.1, 2.5), n = 13; unexposed: 0.002 (0.002, 0.002, 0.002, 0.002), n = 18 Soil mg/kg exposed: 69.5 (48.7, 59.1, 93.9, 417.1), n = 45; unexposed: 29.2 (20.1, 26.4, 30.4, 41.11), n = 30 Air ng/m^3 exposed: 19.3 (10.1, 13.7, 28.4, 82.9), n = 15; unexposed: 13.12 (5.0, 10.9, 16.8, 18.7), n = 15 *Duration*: Mean (SD) yr of residence: 45 (13).	In serum of exposed group: ↑ MDA ($p < 0.001$) ↑ Catalase activity ($p < 0.001$) ↑GSH-Px activity ($p < 0.001$) ↑ 8-OHdG ($p = 0.008$) ↓ SOD activity ($p < 0.001$)	Systemic increases in oxidative stress observed with increasing chromium exposure.	Xu et al. (2018)

System	Exposure[a]	Results	Comments	Reference
Exposed: Electroplaters (n = 117) at one of five different metal factories *Referent*: office workers (n = 45)	*Assessment:* Total Cr in urine measured using graphite atomic absorption spectrophotometry. *Levels:* Urine Cr was higher in exposed compared to referent (mean [SD] of 0.74 [0.53] vs. 0.34 [0.18] µg/g creatinine, respectively). *Duration:* individuals with <9 yr of exposure: mean (SD) = 8 (2); individuals with >10 yr of exposure = 10 (8).	↑ urinary 8-OHdG	Unclear if exposure was to Cr(VI) specifically (possible with electroplaters but seem to have measured total Cr in urine). Also, while difference in mean urine Cr was significant, the levels seem somewhat low. Coexposures with nickel, did not exclude smokers (high prevalence), and significantly higher alcohol consumption among exposed workers may affect results.	Yazar and Yildirim (2018)
Exposed: Electroplaters at 7 workshops in Tehran (n = 30 males) *Referent*: Age- and sex-matched dairy production workers (n = 30 males)	*Assessment:* Blood Cr levels measured using flameless atomic absorption spectrometer. *Levels:* Blood Cr higher in exposed vs. referent (mean [SD] = 5.97 [1.74] vs. 4.22 [0.08] ng/mL), increased from 4.42 µg/L to 10.6 µg/L. *Duration:* Work duration 1–10 yr.	↑ lipid peroxidation ↓ plasma antioxidant capacity ↓ plasma total thiol (SH groups)	Unclear if exposure was to Cr(VI) specifically (possible with electroplaters). Also, while difference in mean blood Cr was significant, the levels were more similar than expected between exposed and referent.	Zendehdel et al. (2014)
Exposed: electroplating workers (n = 157) *Referents:* individuals without exposure to chromium or known physical/chemical genotoxic agents (n = 93)	*Assessment:* Air-Cr and blood Cr determined by graphite furnace atomic absorption spectrophotometer. *Levels*: median (range) Cr in erythrocytes (µg/l) among exposed: 4.41 (0.93–14.98); among controls: 1.54 (0.14–4.58). Median (range) short-term concentrations of Cr in air: 0.060 (0.016–0.531) mg/m^3. *Duration:* Median (min–max) yr of exposure among exposed group: 5.3 (0.5–23).	↑ urinary 8-OHdG adducts among exposed compared to referents ↑ DNA damage (measured by the comet assay) in lymphocytes among exposed compared to referents	Limited adjustment for confounders (including diet). Potential coexposures to other metals in the workplace.	Zhang et al. (2011)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

Human in vitro studies of oxidative stress

Table C-57 summarizes in vitro studies of markers of oxidative stress in response to Cr(VI) exposure. Because all in vivo animal studies of oxidative stress following Cr(VI) exposures focusing on organ- or tissue-specific oxidative stress are already categorized within the health effect section for supporting evidence relevant to the study (i.e., respiratory, GI, hepatic, hematological, male or female reproductive, developmental), they have not been repeated here. In vitro studies of oxidative stress induced by Cr(VI) were included if they were conducted in human primary cells or immortalized human cell lines and not already summarized in another health effect section.

Table C-57. In vitro studies of Cr(VI)-induced oxidative stress

System	Exposure[a]	Results	Reference
Human chronic myelogenous leukemic (CML) K562 cells, promyelocytic leukemic HL-60 cells, and normal human peripheral blood mononuclear (HPBM) cells	12.5 and 25 µM $Na_2Cr_2O_7$, 24 or 48 h	↓ cytochrome c (↑ SOD) ↑ hydroxyl radical ↑ intracellular 2,7-DCFD fluorescence ↑ DNA fragmentation No apoptosis (TUNEL) in HPBM; ↑ apoptosis in K562 at low dose but necrosis at high dose Human cultured leukemic cells more sensitive than primary cells	Bagchi et al. (2001; 2000b)
Primary human lymphocytes	0, 50, 100, 200, 600, and 1000 µM $K_2Cr_2O_7$, 1 h	↑ DNA strand breaks (comet) (≥400 µM; $p < 0.001$) DNA damage ↑ with Endo III and ↓ with catalase ($p < 0.001$), indicating oxidative lesions Slight reduction in cell viability (trypan blue exclusion) (viability at top dose was 84.7%)	Blasiak and Kowalik (2000)
Human umbilical vein endothelial cells (HUVECs)	1–20 mM $K_2Cr_2O_7$	↑ stress response/ inflammatory pathways (JNK, p38 MAPK, NLRP3, ICAM-1, VCAM-1, TNF-α, IL-1β) ↑ intracellular ROS ↑ apoptosis induced by mitochondrial (intrinsic) pathway	Cao et al. (2019)
Whole human blood	0.01–40.0 µg $K_2Cr_2O_7$/mL	↑ glutathione peroxidase ↓ SOD, GSH ↓ ferric-reducing ability of plasma (FRAP)	Dlugosz et al. (2012)
Primary human lymphocytes and erythrocytes	$K_2Cr_2O_7$	↓ GSH, ↑ GSSG and ROS	Husain and Mahmood (2017)
Primary human lymphocytes	1–100 µM $Na_2Cr_2O_7$, 1 h	↑ standard and FPG-modified comet assay DNA strand breaks (≥100 nM) ↑ 8-OHdG (>10 µM) Significant interindividual variation in comet and FPG-comet DNA damage correlated with OGG1 polymorphisms	Lee et al. (2005, 2004)

System	Exposure[a]	Results	Reference
Primary human fibroblasts	0.5–500 µM Cr(VI)	↓ O_2 consumption, dose-dependent (20–500 µM) ↑ standard and FPG-modified comet assay DNA strand breaks (0.5–3 µM) Attributed to affected mitochondrial function and glucose catabolism	Liu et al. (2010b)
Human leukemic T-lymphocyte MOLT4 cells	0–200 µM K_2CrO_4, 2 h	↓ multiple antioxidants, dose-dependent ($p < 0.01$ at 10 µM) ↑ DNA-protein crosslinks (25 µM) ↑ ROS (DCFH-DA) ↑ DNA-protein crosslinks and protein carbonyls (2 h) and MDA (4 h), dose-dependent ESR showed reaction of Cr(VI) with NADPH, glutathione reductase or H_2O_2-generated Cr(V) and OH radicals Pretreatment with antioxidants reduced protein carbonyl, MDA and DPC formation but not with catalase inhibitor or riboflavin pretreatments	Mattagajasingh et al. (2008; 1997, 1996, 1995)
Human diploid fibroblasts	0, 0.2, 0.5, 1, 2, 3, 5 µM $K_2Cr_2O_7$	↑ DNA strand breaks ≥0.5 µM Inhibition of excision repair did not prevent repair of breaks Scavenging superoxide (SOD) or H_2O_2 (catalase) but not hydroxyl radicals (KI) reduced DNA damage; reduced glutathione potentiated damage	Snyder (1988)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate).

C.3.2.6. *Induces chronic inflammation (KC#6)*

Mechanistic studies relevant to immunomodulation (including immune stimulation) are summarized in Appendix C.2.5.

C.3.2.7. *Immunosuppression (KC#7)*

Mechanistic studies relevant to immunomodulation (including immune suppression) are summarized in Appendix C.2.5. The evaluation of evidence for effects of Cr(VI) on the immune system, presented in Section 3.2.6 of the toxicological review, suggests that Cr(VI) could have immunomodulatory effects that can suppress (as well as stimulate) the immune system. This immunosuppressive effect was primarily determined from a limited number of host resistance assays, and the significance for Cr(VI)-induced carcinogenesis is not currently known.

C.3.2.8. *Modulation of receptor-mediated effects (KC#8)*

No evidence exists that Cr(VI) itself has receptor binding activity, although indirectly it can initiate cell signaling cascades involving receptor-mediated pathways (summarized in Appendix C.3.3) and can affect the expression of sex hormone cell receptors (summarized in Appendix C.2.6 and C.2.7).

C.3.2.9. *Causes immortalization (KC#9)*

Enabling replicative immortality is a hallmark of cancer and may be informed by studies that indicate inhibition of senescence induced by Cr(VI) exposure. Mechanistic studies reporting endpoints relevant to senescence are summarized in Table C-58.

Table C-58. Mechanistic studies informing Cr(VI)-induced cellular immortalization

System	Exposure[a]	Results	Comments	Reference
Exposed: male welders (n = 75) and sandblasters (n = 5) from shipyard industry *Referents:* subjects from exposed group with chromium blood levels >2 µg/L who underwent intervention to reduce exposure for 5 mo (n = 9)	Shipyard industry welders with mean (range) yr working in industry: 18.5 (2–35). Chromium measured in blood and urine with atomic absorption spectrometer; mean (range) Cr levels in first sampling period: blood = 0.91 (0.1–6.1) µg/L; urine = 1.33 (0.1–50.2) µg/L	Cr levels in blood and urine associated with ApoJ/CLU glycoprotein levels in serum	Authors conclude the upregulation of Apolipoprotein J/Clusterin glycoprotein that promotes cellular senescence by Cr(VI) is induced by oxidative stress. Findings differ from earlier study by this group (Katsiki et al., 2004). Small sample size for the intervention arm of the study.	Alexopoulos et al. (2008)
Exposed: male workers (n = 55 welders; n = 10 sandblasters; n = 15 other) (total n = 80) *Referents:* nonexposed males of the same age range (n = 30)	Blood and urine samples collected; analyzed with graphite furnace atomic absorption spectroscopy Higher Cr(VI) in blood (11×) and urine (57×) in welders compared to controls	↓ serum ApoJ/CLU in exposed; dose-dependent decrease based on level of exposure and duration of exposure	Reduced biomarker of cell survival and senescence Apolipoprotein J/Clusterin Findings differ from later study by this group (Alexopoulos et al., 2008) Did not appear to adjust for covariates. Did not provide sample size for subgroup analyses by duration of exposure – difficult to assess confidence in these results.	Katsiki et al. (2004)
L-02 human fetal hepatocytes	0, 5, 10, 15 µM Cr(VI)	↑ Clusterin (CLU), dose-dependent	Overexpression of CLU can counteract Cr(VI)-induced MRCC I inhibition, enhancing survival.	Xiao et al. (2019)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate); chromium trioxide units conversion: Cr(VI) = 0.52 × CrO_3.

C.3.2.10. *Alters cell proliferation, cell death, or nutrient supply (KC#10)*

Table C-59 summarizes human, animal, and in vitro studies of markers of cell proliferation, cell death, or changes in cellular nutrient supply in response to Cr(VI) exposure. Human occupational and in vivo animal studies and in vitro studies using human primary or immortalized cell lines relevant to cell proliferation and death following Cr(VI) exposures using organ-specific

test systems or markers from these systems have already been categorized within the corresponding health effect sections for supporting evidence. Human or animal in vivo studies were included here if they measured any systemic markers of cell proliferation or death or were not previously summarized elsewhere. Similarly, in vitro studies were included if they were conducted in human primary cells or immortalized human cell lines that have not already been summarized in another health effect section. An exception has been made for studies of Cr(VI)-induced changes in cellular energetics. These tables include all identified mammalian in vivo and human in vitro studies that pertain to cellular nutrient supply, regardless of whether they were also reported elsewhere.

Table C-59. Mechanistic studies relevant to Cr(VI)-induced cell death, cell proliferation, and changes in cellular energetics

System	Exposure	Results	Comments	Reference
Cell cycle progression				
Human lung fibroblasts (HLFs)	1 µM Na2Cr2O4, 24 h	↑ G1/S and G2/M arrest G1/S checkpoint bypass involves Akt1 ↑ cell survival and ↑ mutation frequency (but ↓ DNA DSBs and CAs) with inhibition of protein tyrosine phosphatase (PTP), mediated by polo-like kinase 1 (Plk1) No change in apoptosis	Plk1 mediates cell cycle checkpoint bypass and mitotic progression leading to increased survival of cells with Cr(VI)-induced DNA damage	Kost et al. (2012); Chun et al. (2010); Bae et al. (2009a); Lal et al. (2009)
Cell death				
Exposed: Chrome-plating workers (n = 19) *Referents 1*: hospital workers (n = 18) *Referents 2:* university personnel (n = 20)	Total Cr measured in urine, erythrocytes, and lymphocytes using graphite furnace atomic absorption Total Cr was higher in exposed workers compared with hospital workers (see Table 3; for example, postshift mean urine levels were 7.31 [SD = 4.33] in exposed vs. 0.12 [SD = 0.07] µg/g crt in referent).	In peripheral blood lymphocytes: No change in apoptosis (nuclear fluorescence measured by FACS flow cytometry) ↑ DNA damage (measured by the comet assay)	Did not exclude smokers (high prevalence) although did present results stratified by smoking (small numbers). Unclear if exposure was to Cr(VI) specifically (possible with chromeplating workers, but measured total Cr in urine). State that previous air monitoring for total chromium showed levels of 0.4 to 5.6 µg/m^3, which is fairly low.	Gambelunghe et al. (2003)
HLF fetal human lung fibroblasts L-41 human epithelial-like cells	1, 2, 5, 10, 15, 20, 25, and 30 µM $K_2Cr_2O_7$, 2, 24 or 48 h	↑ cytotoxicity (MTT assay), dose- and duration-dependent (significant ≥20 µM); ≤5 µM cytotoxicity recovered after 24 h Toxicity at 20 µM due to apoptosis (morphology, caspase-3, DNA fragmentation) ↑ ROS (DCFH-DA) at 2 h ↑ antioxidant enzymes (glutathione peroxidase, glutathione reductase, catalase) 1–5 µM	Oxidative stress and antioxidant enzymes induced at mildly toxic µM concentrations.	Asatiani et al. (2011; 2010; 2004)

System	Exposure	Results	Comments	Reference
Human chronic myelogenous leukemic (CML) K562 cells, promyelocytic leukemic HL-60 cells, and normal human peripheral blood mononuclear (HPBM) cells	12.5 and 25 µM $Na_2Cr_2O_7$, 24 or 48 h	↓ cytochrome c (↑ SOD) ↑ hydroxyl radical ↑ intracellular 2,7-DCFD fluorescence ↑ DNA fragmentation No apoptosis (TUNEL) in HPBM; ↑ apoptosis in K562 at low dose but necrosis at high dose	Human cultured leukemic cells more sensitive than primary cells.	Bagchi et al. (2001; 2000b)
Human umbilical vein endothelial cells (HUVECs)	1–20 mM $K_2Cr_2O_7$	↑ stress response/ inflammatory pathways (JNK, p38 MAPK, NLRP3, ICAM-1, VCAM-1, TNF-a, IL-1b) ↑ intracellular ROS ↑ apoptosis	Apoptosis induced by mitochondrial (intrinsic) pathway.	Cao et al. (2019)
HLF human lung fibroblasts (LL-24 cell line)	3, 6, and 9 µM Na_2CrO_4, 24 h	↑ cytotoxicity, duration- and dose-dependent (stat. sig. ≥6 µM) ↑ apoptosis ↑ p53 (4- to 6-fold) ↑ Cr-DNA adducts	Pretreatment with 1 mM ascorbate or 20 µM tocopherol had no ameliorative effects.	Carlisle et al. (2000a)
HeLa cells	1, 10, and 100 µM $Na_2Cr_2O_7$; 1, 2.5, 8, 24, or 48 h	Intracellular Cr(III) inhibits DNA synthesis and replication fidelity by inhibiting DNA synthesome polymerases α, δ, and ε		Dai et al. (2009)
Human lymphoma U937 cells lacking functional p53 gene	20 µM Cr(VI), 24 h	↑ mitochondria-dependent apoptotic pathway changes (intracellular Ca^{2+}, DNA fragmentation, caspase-3, low mitochondrial membrane potential (MMP), and nuclear morphology) ↑ hydroxyl and superoxide anion radicals (measured by ESR-spin trapping) Apoptosis inhibited by NAC DNA fragmentation suppressed by inhibiting intracellular Ca^{2+} and calpain No increases in Fas or JNK	Authors conclude $Ca(^{2+})$-calpain- and mitochondria-caspase-dependent pathways play significant roles in the Cr(VI)-induced apoptosis via the G2/M cell cycle checkpoint.	Hayashi et al. (2004)
Normal human foreskin (BJ) fibroblasts immortalized by human telomerase (BJ-hTERT)	0–6, 9, or 12 µM Na_2CrO_4, 24 h	↑ cell cycle arrest ↓ clonogenic survival, dose-dependent ↑ % apoptotic cells with dose		Pritchard et al. (2001)

System	Exposure	Results	Comments	Reference
Primary human lymphocytes	Cr(VI) complexes sodium bis(2-ethyl-2-hydroxybutyrato)oxochromate(V), Na[Cr(V)O(ehba)(2)] and sodium bis(2-hydroxy-2-methylbutyrato)oxochromate(V), Na[Cr(V)O(hmba)(2)]	↑ apoptosis and ROS and ↓ cell viability with Cr(V) and Cr(VI) Cr(V)-induced apoptosis partially reversed with antioxidants Cr(V) and Cr(VI) activate Src-family protein tyrosine kinases leading to caspase-3 activation	Cr(VI)-induced apoptosis partially induced by ROS generated by Cr(V) intermediates via SFKs.	Vasant et al. (2003; 2001)
Cellular energetics				
BEAS-2B human bronchial epithelial cells	1 µM Cr(VI), 48 h	↑ glycolysis ↓ respiration ↓ protein levels of β-F1-ATPase ↑ GAPDH	Cr(VI) caused shift to fermentative metabolism.	Cerveira et al. (2014)
BEAS-2B human bronchial epithelial cells	5–20 µM $Na_2Cr_2O_7$	↑ NOTCH1 (Notch1) ↑ CDKN1A (P21) ↓ FBP1	FBP1, involved in gluconeogenesis, is lost in Cr(VI)-transformed cells. Reintroduction of FBP1 caused ↑ROS and ↑apoptosis.	Dai et al. (2017a)
L-02 human fetal hepatocytes	4–32 µM	↓ mitochondrial respiratory chain complex (MRCC) I and II activity (25 µM)	Cr(VI)-induced MRCC I inhibition activates caspase-3; process dependent on ROS.	Xiao et al. (2012a; 2012b)
L-02 human fetal hepatocytes	0, 2, 8, 32 µM Cr(VI), 24 h	↑ voltage-dependent anion channel 1 (VDAC1) expression, ROS, and apoptosis with ↓ ATP (32 µM) Effects reversed with NAC pretreatment or blocking VDAC1	Cr(VI)-induced apoptosis and decreased ATP mediated by ROS and VDAC1.	Yuan et al. (2012)

[a]Potassium dichromate units conversion: Cr(VI) = 0.353 × $K_2Cr_2O_7$; potassium chromate units conversion: Cr(VI) = 0.268 × K_2CrO_4; sodium dichromate dihydrate units conversion: Cr(VI) = 0.349 × $Na_2Cr_2O_72H_2O$ (usually denoted as $Na_2Cr_2O_7$ because study authors frequently list the salt as the chemical compound even if concentration or dose is based on the dihydrate).

C.3.3. Gene Expression Studies Relevant to Gastrointestinal Cancer Cell Signaling Pathways

Mechanistic evidence investigating the cell signaling pathways involved in carcinogenesis following exposure to Cr(VI) is summarized in Table C-61. Studies identified in preliminary title and abstract screening as "mechanistic" were further screened and tagged as "cell signaling" if they reported relevant gene expression data. Studies were prioritized if they were (a) oral, inhalation, or intratracheal instillation exposures in vivo, or (b) in vitro exposures in human cells. Two studies

in humans, two in vivo studies in rats, and 84 in vitro studies in human cells were identified. This does not include studies reporting toxicogenomic data, which are summarized in Appendix C.3.4.

The human studies, presented in Table C-60, measured increases in p53 expression in the peripheral blood of chromium-exposed workers compared to unexposed workers. Although these studies were not formally evaluated for risk of bias and sensitivity, the potential for coexposures among these workers (Elhosary et al., 2014) or lack of Cr measures in exposed workers (Hanaoka et al., 1997) precludes certainty regarding the potential association between increased p53 expression and Cr(VI) exposure specifically.

Table C-60. Gene expression studies in humans exposed to Cr(VI)

System	Exposure	Results	Reference
Exposed 1: Cement workers in building construction (n = 22 males) *Exposed 2:* Tannery workers (n = 20 males) *Referent*: "normal healthy" volunteers (n = 23 males)	Blood and urine total Cr measured using inductively coupled optical emission spectrometry Highest blood and urine Cr in tannery workers, followed by cement workers, then referents. Total chromium levels (µg/L) mean ± SD: Referent (n = 23): Cr content in blood: 3.81 ± 5.57 Cr content in urine: 6.27 ± 5.31 Cement (n = 22): Cr content in blood: 15.27 ± 2.61 Cr content in urine: 17.22 ± 3.33 Tannery (n = 20): Cr content in blood: 18.90 ± 1.88 Cr content in urine: 20.84 ± 1.67 State that "Cement and tannery workers were usually exposed to chromium 8 h daily for a duration ranged from 1 month to 40 years." Unclear if exposure was to Cr(VI) specifically, although more likely for cement workers compared with tannery workers (as described in the discussion section); however, separating effects is impossible, given total Cr was measured in blood and urine. Poor working conditions (e.g., lack of PPE) and coexposures limit ability to attribute effects to chromium. The population also included adolescents (minimum age 14 yr), which could affect comparability.	↑ p53 protein expression (detected by immuno-cytochemistry) in peripheral blood of tannery and cement workers	Elhosary et al. (2014)
Exposed: chromate plant workers (n = 31 males) *Referents:* volunteers without occupational chemical exposures (n = 10)	Duration of exposure in workers = 0–23 yr No assessment of Cr levels in workers or referents	↑ serum p53 protein expression (detected by ELISA) in serum of chromium workers	Hanaoka et al. (1997)

All other studies were reviewed for effects relevant to the KEGG (Kyoto Encyclopedia of Genes and Genomes, https://www.genome.jp/kegg/pathway.html) "Pathways in cancer" maps for

humans (https://www.genome.jp/pathway/hsa05200). Table C-61 summarizes the reference gene IDs and direction of change for each. KEGG pathways are publicly available, manually drawn, and curated pathway maps, based on evidence from recognized evidence-based relationships among genes involved in cancer-related processes. Data from the two rat oral studies or from the 90 in vitro studies in human cells specific to Cr(VI) were then overlayed onto the cancer pathway KEGG maps for rats and humans, respectively, creating two maps (Figures C-25 and C-26). A third map (Figure C-27) was created using gene expression changes reported by ToxCast/Tox21 high throughput screening (HTS) assays in human cells exposed to Cr(VI) in vitro. Genes are color coded: red = activation or increased expression, turquoise = inactivation or decreased expression, violet = discordant changes showing both activation and inactivation among different studies, and yellow = proteins that were modified or have changed localization. Green indicates a gene whose expression (or activity of its products) was not tested or not found to have changed.

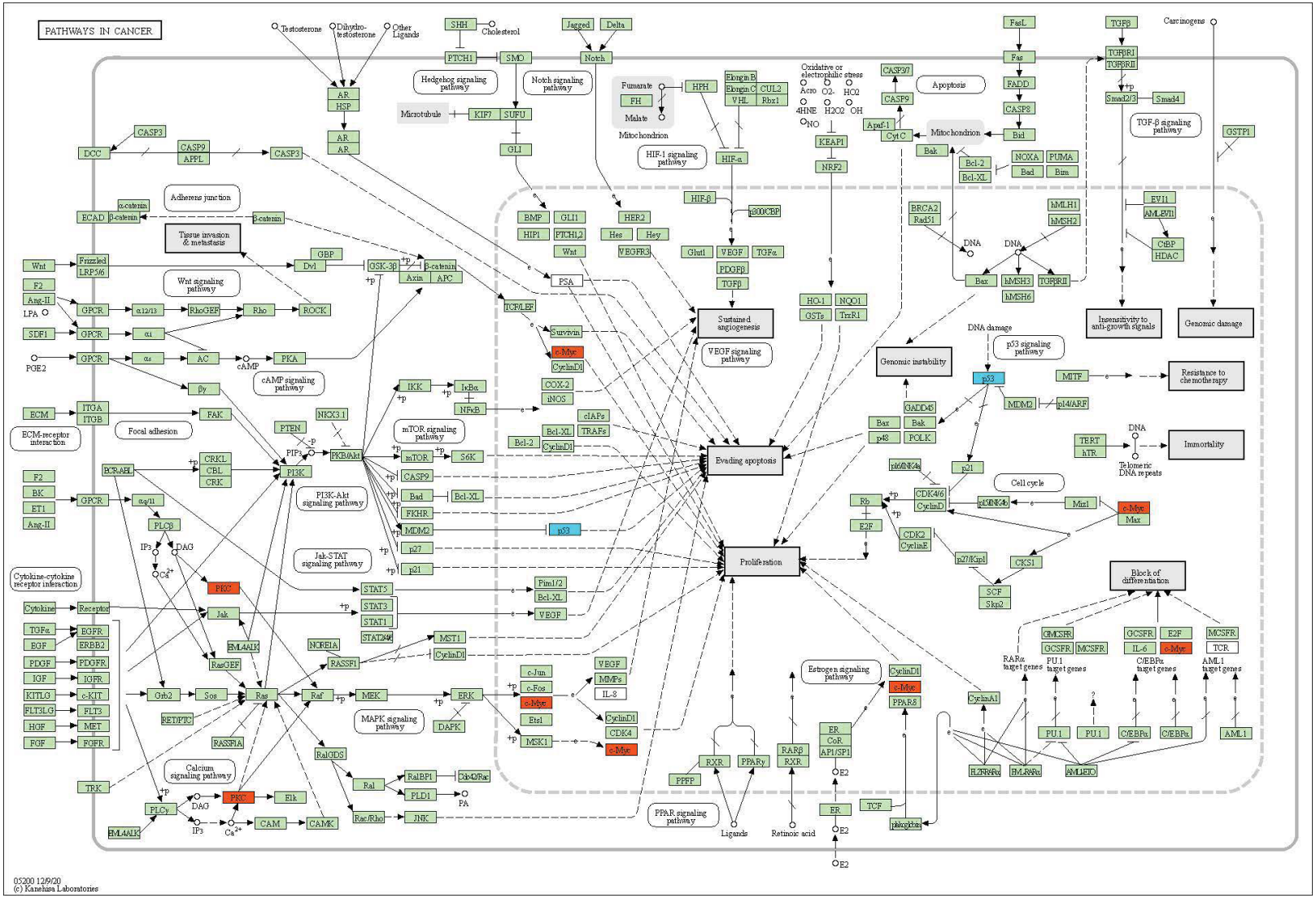

Figure C-25. KEGG pathways of gene expression changes in rats exposed to Cr(VI) via ingestion. Red = activated or increased expression; turquoise = inactivated or decreased expression; green = no data or no change detected.

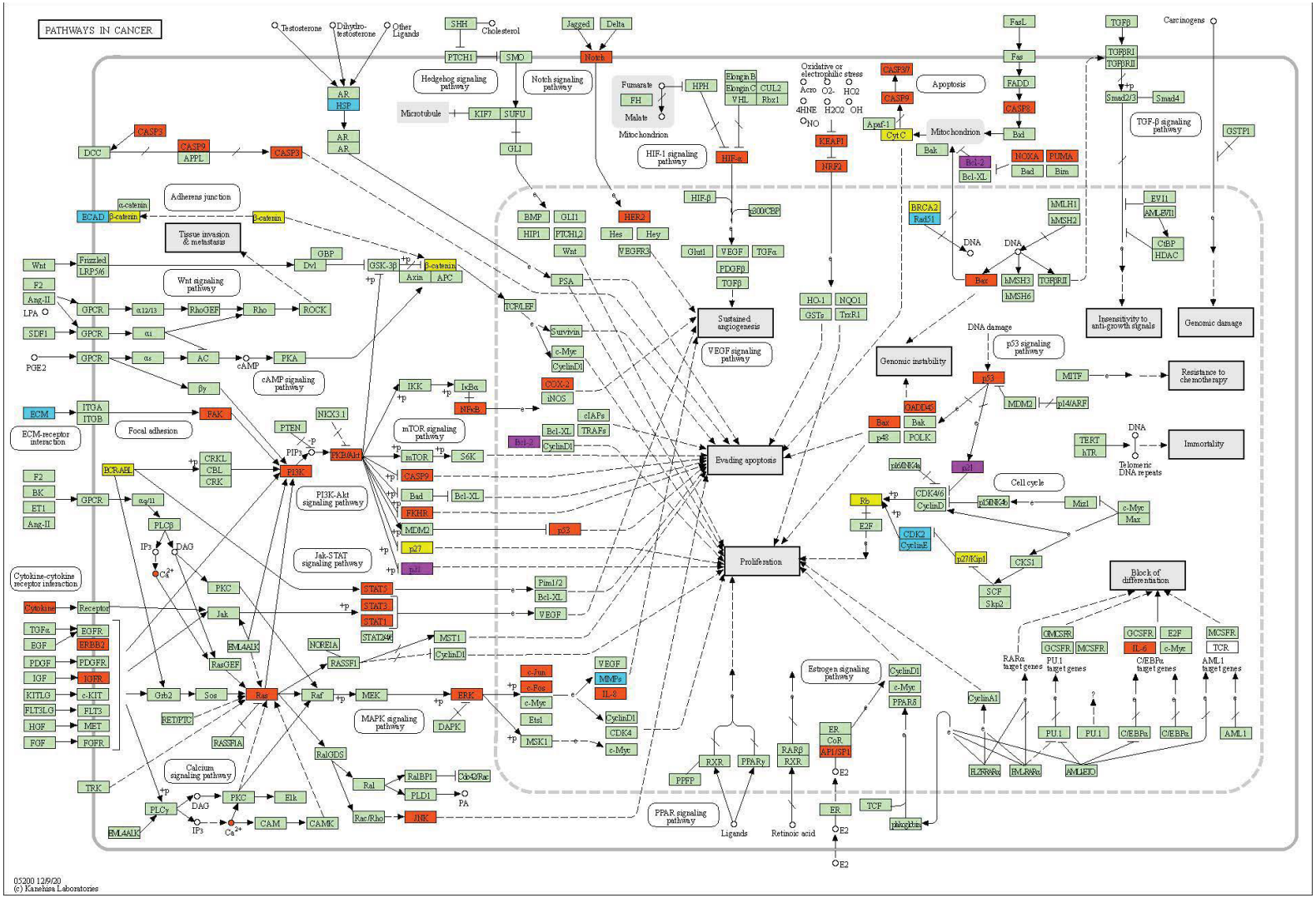

Figure C-26. KEGG pathways of gene expression changes in human cells exposed to Cr(VI) in vitro. Red = activated or increased expression; turquoise = inactivated or decreased expression; violet = discordant results from different studies; yellow = proteins that were modified or have changed localization; green = no data or no change detected.

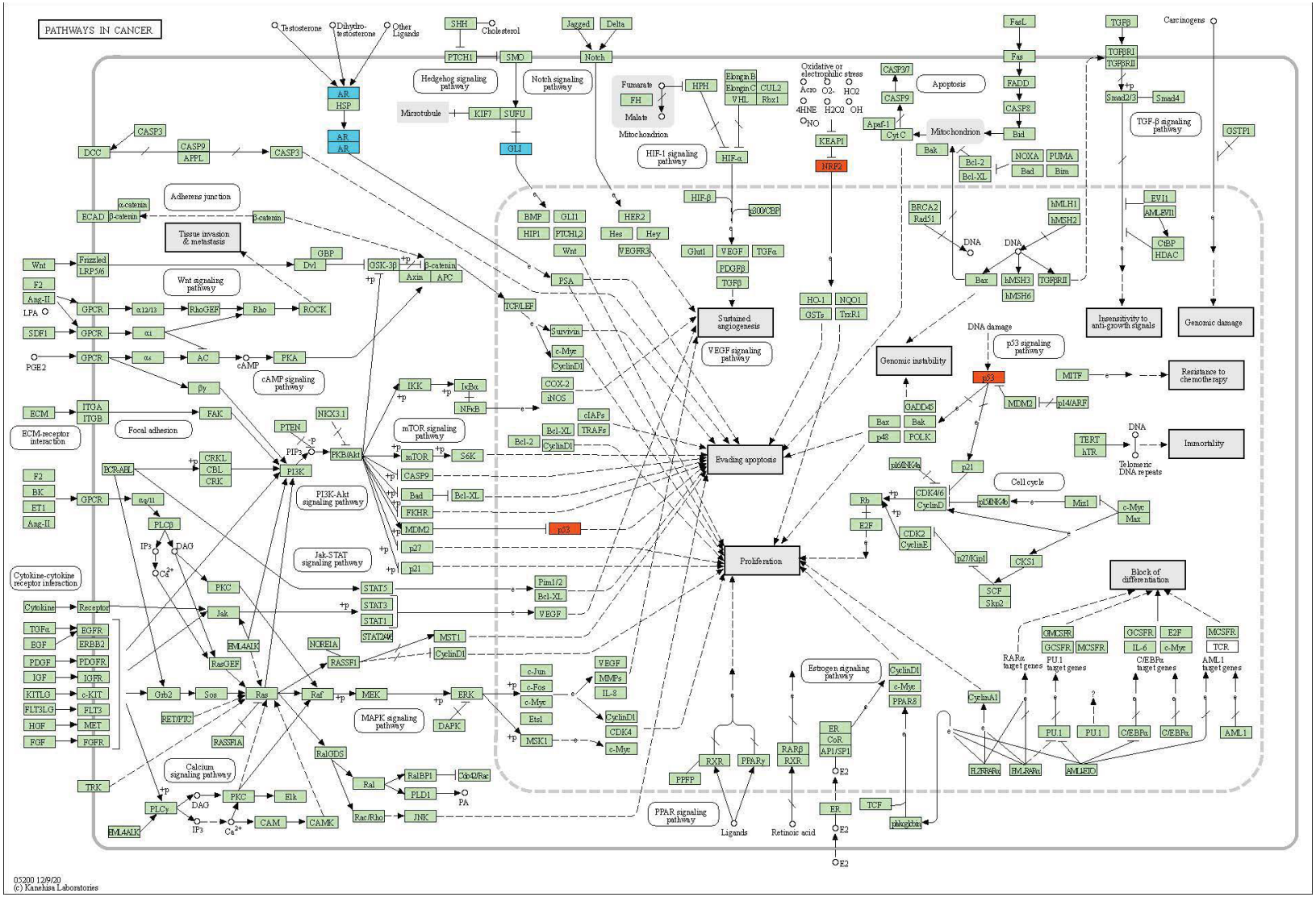

Figure C-27. KEGG pathways of gene expression changes in cells exposed to Cr(VI) reported by ToxCast/Tox21 HTS assays. Red = activated or increased expression; turquoise = inactivated or decreased expression; green = no data or no change detected.

C.3.3.1. *Cell signaling pathways*

Tissue-specific in vivo animal evidence

The oncogene c-Myc was found to show a dose-dependent increase (protein and mRNA) in the stomach and colon of male Wistar rats after 60 days of exposure to Cr(VI) in drinking water, supporting increased cell proliferation in these tissues (Tsao et al., 2011). The same study also observed decreased stomach and colon expression of the tumor-suppressor p53, MAPK inhibitor RKIP, and Rho-GDIα, which is involved in the Rho-regulated pathways for metastasis/cytoskeleton reorganization. Down-regulation of RKIP led to the activation of MEK/ERK signaling pathway in the rat stomach and colon. Activation of the ERK/MAPK signaling pathway promotes cell proliferation, tumor cell invasion, and angiogenesis and inhibits apoptosis (Guo et al., 2020). Tsao et al. (2011) also reported increased galectin-1. Galectins are associated with gastric cancer cell motility in response to integrin signaling, and galectin-1 is overexpressed in gastric tumor cells and digestive cancers (Wu et al., 2018; Kim et al., 2010). In a separate study, Ki-67—a nuclear protein associated with cellular proliferation, malignant metastasis, and tumor growth (Li et al., 2015)—showed non-dose-dependent increases in transcript expression in the duodena of mice after oral exposure through drinking water at 11.6 and 31 mg/kg Cr(VI)-day (Rager et al., 2017; Kopec et al., 2012a).

In vitro human evidence

In vitro studies in various human cell types demonstrated the role of several processes relevant to the cancer development that include (1) activation of MAPK signal pathway extracellular signal-regulated kinase (ERK), Jun kinase (JNK/SAPK), and p38 MAPK involved in cell proliferation; (2) changes involving DNA damage checkpoint/DNA repair components (e.g., ATM, ATR, XRCC1, RAD17, RAD51, TP53 and DNA-PK); (3) changes in the expression of genes involved in the reactive oxygen species homeostasis (e.g., NFE2L2, NOX, SOD1, SOD2, CAT, GSR); (4) changes in apoptosis-regulating genes (BCL2, MCL1, BBC3, BAX, CASP3, CASP9); and (5) changes suggesting tissue remodeling and epithelial-mesenchymal transition (SNAI2, ZEB1, PLAUR, CDH1, KLF8) and pathways with pleiotropic roles in cancer (NOTCH, HIF-1α, PI3K/Akt).

The effects of chromium exposure were shown to be dependent on cell context and exposure level/time. For instance, exposure to Cr(VI) resulted in considerably different changes in nuclear binding of transcription factors AP-1, NF-κB, SP1, and YB-1 in human MDA-MB-435 breast cancer cells in comparison with rat H4IIE hepatoma cells (Kaltreider et al., 1999). Exposure level/time dependence was shown on transcriptional activity of NF-κB: At low exposure levels of 20 μM for 2 hours, Cr(VI) exposure inhibited both basal and TNF-α-stimulated NF-κB-driven transcriptional activity in human A549 lung carcinoma cells. This inhibition occurred through the interaction of NF-κB with transcriptional coactivators (Shumilla et al., 1999). In contrast,

exposures of HepG2 cells to potassium dichromate at 10 μM for 48 hours significantly increased transcription from the NF-κB response element (Tully et al., 2000).

Discordant changes in the expression or activity of certain genes were observed between experiments in cells exposed to cytotoxic levels of Cr(VI) and cells transformed by Cr(VI). This can be exemplified by the expression of BCL2 gene, a founding member of the BCL2 gene family of apoptosis regulators. In immortalized human hepatocytes exposed to cytotoxic levels of Cr(VI), decreased expression of the anti-apoptotic BCL2 gene led to increased apoptosis (Zhong et al., 2017b), while in Cr(VI)-transformed BEAS-2B cells, the BCL2 gene was upregulated, contributing to an apoptosis-resistant phenotype that is consistent with the malignant properties of transformed cells (Medan et al., 2012). These results exemplify the complexity of molecular changes induced by exposure of cells to Cr(VI) and their dependence on exposure level and cellular context.

Table C-61. Gene expression corresponding to positive results of Cr(VI) assays performed in vivo (rats) or in vitro (human cells or TOX21 HTS assays).
Direction of change (measuring mRNA or protein): ↑ (upregulated or activated); ↓ (downregulated or inhibited); Δ (protein posttranslational modification or change of intracellular localization).

Study	Gene symbol	KEGG ID
Rat in vivo studies (Rattus norvegicus)		
Bagchi et al. (1997a)	Prkca↑	24680
Tsao et al. (2011)	Tp53↓ Arhgdia↓ Pebp1↓ Myc↑ Lgals1↑	24842 360678 29542 24577 56646
Human in vitro studies (Homo sapiens)		
Abreu et al. (2018)	HSPA1A (Hsp72)↓ Hsp90α ↓	
Adam et al. (2017)	NLRP3↑ IL1B (IL-1b)↑	
Akbar et al. (2011)	IL-2 down↓	3558
Antonios et al. (2009)	CD86↑	
Asatiani et al. (2004)	CAT (Catalase)↑ SOD1 (Cu,Zn-SOD)↑	
Bae et al. (2009b)	FGR Δ ABL1 (ABL) Δ	 25
Barchowsky (2006)	Lck↑ Fyn↑	
Browning and Wise (2017)	Rad51c Δ BRCA2 Δ	 675

Study	Gene symbol	KEGG ID
Cammarota et al. (2006)	MMP2↓ TIMP1 (TIMP)↑	4313
Carlisle et al. (2000a; 2000b)	P53↑	7157
Castorina et al. (2008)	ERBB2↑ (24h+) ERBB3↑ (24h+)	2064
Ceryak et al. (2004)	TP53↑ CDKN1A (P21)↑ MAPK3, MAPK1 (ERK1/2)↑	7157 1026 5594, 5595
Chuang et al. (2000)	JNK↑ MAPK11-14 (P38)↑ MAPK3, MAPK1 (ERK1/2)↑	5599 5594, 5595
Chuang and Yang (2001)	MAPK3, MAPK1 (ERK1/2)↑ JUN↑	5594, 5595 3725
Chun et al. (2010)	Plk1↑	
Clementino et al. (2019)	SIRT3↑ Pink1↑ PRKN (Parkin)↑	
Curtis et al. (2007)	IL1a↑	3552
Dai et al. (2017a)	NOTCH1 (Notch1)↑ CDKN1A (P21)↑ FBP1↓	4851 1026
Deloughery et al. (2015)	ATR↑	
Ding et al. (2013)	CDH1↓ VIM ↑ FN1↓ CTNNB1 (β-catenin -Δ) SNAI2 (Slug)↑ Zeb1↑ KLF8↑	999 2335 1499
Dubrovskaya and Wetterhahn (1998)	HO↑	
Gambelunghe et al. (2006)	TP53↑ CASP3↑ CASP8↑ CASP9↑	7157 836 841 842
Ganapathy et al. (2017)	BCl2↑ KRAS (Ras)↑	596 3845
Hayashi et al. (2004)	CAPN1 (calpain)↑	
He et al. (2013)	IGF1R (IGF-1R)↑ IRS1↑ HIF1A↑ RELA (NFkB)↑	3480 3091 5970

Study	Gene symbol	KEGG ID
	CXCL8 (IL-8)↑	3576
Hill et al. (2008a)	TP53↑ CDKN1A (P21)↑ ATM↑ PRKDC (DNA-PK)↑ ATR↑ AKT1 (AKT)↑ MAPK11-14 (P38 MAPK)↑	7157 1026 207
Hill et al. (2008b)	TP53↑ CDKN1A (P21)↓ PUMA↑ BAX ↑ PRKDC (DNA-PK)↑	7157 1026 27113 581
Hodges et al. (2004)	JUN↑ JNK↑	3725 5599
Hu et al. (2018)	MGMT↓ XRCC1↓ OGG! (HOGG1)↓ RAD51↓	 5888
Kaczmarek et al. (2007)	HIF1A↑	3091
Kaltreider et al. (1999)	FOS, JUN (AP1)↑ NFkB↑ SP1↑ YBX1 (YB1)↑	2353, 3725 5970 6667
Kim et al. (2003)	RELA (NFkB)↑	5970
Kost et al. (2012)	PTP↓	
Lal et al. (2009)	CDKN1B (P27) Δ RB1 Δ	1027 5925
Li et al. (2016)	XRCC2↑	
Liu et al. (2009)	WRN Δ	
Lozsekova et al. (2002)	VCL (Vinculin)↓ TLN1 (Talin)↓ CDH1 (E-cadherin)↓ DSP (Desmoplaktin)↓	 999
Lu et al. (2018b)	STK11 (LKB1)↓	
Majumder et al. (2003)	SLC30A1 (Zn-T1)↓	
Medan et al. (2012)	BCL2↑	596
Myers et al. (2011)	TXN (TRx) Δ TXNRD1 (TrxR)↓	 7296
Nemec and Barchowsky (2009)	STAT1↑ VEGFA↓	6772

Study	Gene symbol	KEGG ID
	SP1↑	6667
Nemec et al. (2010)	Fyn↑ STAT1↑ IRF1↑	6772
O'Hara et al. (2003)	MAPK8 (JNK)↑ Fyn↑ Lck↑	5599
O'Hara et al. (2004)	Bmx↑ PTK2 (Fak)↑ PTK2B (Pyk2)↑ Fyn↑ STAT5A, STAT5B (Stat5)↑ Ap1↑	5747 6776, 6777 2353, 3725
O'Hara et al. (2005)	STAT3↑ Lck↑	6774
O'Hara et al. (2007)	Lck↑ STAT3↑ IL-6↑	 6774 3569
Pritchard et al. (2000)	ICAM1↑	
Reynolds and Zhitkovich (2007)	TP53↑	7157
Rizzi et al. (2014)	MAPK3, MAPK1 (ERK1/2)↑	5594, 5595
Russo et al. (2005)	BBC3 (PUMA) ↑ PMAIP1 (NOXA)↑ BAX Δ CYCS Δ CASP3 ↑	27113 5366 581 54205 836
Shumilla et al. (1999)	RELA (NFkB)↓	5970
Shumilla and Barchowsky (1999)	PLAU (uPA)↓ PLAUR (uPAR)↑	
Park et al. (2015)	TP53↑ CDKN1A (P21)↑	7157 1026
Park et al. (2016)	ERFFI1↓	
Tessier and Pascal (2006)	MAPK11-14 (P38)↑ MAPK8 (SAPK/JNK)↑ MAPK3, MAPK1 (ERK1/2)↑	 5599 5594, 5595
Tully et al. (2000)	TP53↑ FOS↑ RELA (NFkB)↑ AHR↑ (inferred) GADD45↑ HSPA1A (HSP70)↑	7157 2353 5970 1647

Study	Gene symbol	KEGG ID
Vasant et al. (2003)	Lck ($p56^{lck}$)↑ FYN ($p59^{fyn}$)↑ Ly($p56/53^{ly}$)↑ CASP3↑	 836
Vilcheck et al. (2006)	FANCD2↑	
Wakeman et al. (2005)	MAPK11-14 (P38)↑	
Wakeman and Xu (2006)	ATM↑ SMC1A (SMC1)↑ ATR↑ RAD17↑	
Wang et al. (2019)	RELA (NFkB, p65) ↑ IL-6↑ HIF1A (HIF-1a)↑	5970 3569 3091
Xia et al. (2011)	BTD↓	
Xiao et al. (2012b)	MRCCI↓ HSP1A1 (HSP70)↓ HSP90AB1 (HSP90)↓	 3326
Xiao et al. (2012a)	MRCC1, 2↓ BUB1B (BuBR1)↓ CDC25A (CDC25)↓	
Yang et al. (2017)	MAP1LC3A (LC3II)↑ Atg12-Atg5↑ Atg4↑ Atg10↑ HMGA1↑ HMGA2↑ SQSTM1 (p62)↓	
Yi et al. (2016)	STIM1↑ MAPK3, MAPK1 (ERK1/2)↑ RELA (NFkB)↑ Ca2+↑	 5594, 5595 5970 C00076
Yi et al. (2017)	VDAC1↑	
Zeng et al. (2013)	SOD1 (SOD)↓ GSR (GR)↓ CAT↓ NO↓	
Zhang et al. (2016)	TP53↑ BCL2↓ MCL1 (Mcl-1)↓ CDK2↓ CCNE1 (Cyclin E)↓	7157 596 1017 898
Zhang et al. (2017)	PI3K/Akt↓	

Study	Gene symbol	KEGG ID
	ER stress Mito dysfunction	
Zhong et al. (2017b)	ETFDH↓ SOD↓ CASP3↑ CASP9↑ BCL2↓ Ca^{2+}↑ CYCS Δ	 836 842 596 C00076 54205
Zhong et al. (2017a)	SOD1↑ SOD2↑ KEAP1↑ NFE2L2 (NRF2) ↑ PPARGC1A (PGC-1a)↑ NRF1↑ TFAM↑ SIRT1↑ FOXO1↑ AKT1↑ CREB1↑	 9817 4780 2308 207
Zuo et al. (2012)	RELA (NFkB)↑ JUN↑ AP1↑ PTGS2 (COX2)↑	5970 3725 5743
Tox21 Assays, Assay ID: DTXSID6032061 (sodium dichromate dihydrate)		
TOX21_TR_LUC_GH3_Antagonist	THRB↓	
TOX21_SSH_3T3_GLI3_Antagonist	GLI3↓	2737
TOX21_p53_BLA_p2_ch2 TOX21_p53_BLA_p2_ratio TOX21_p53_BLA_p3_ch2 TOX21_p53_BLA_p3_ratio TOX21_p53_BLA_p5_ch2 TOX21_p53_BLA_p5_ratio	TP53↑	7157
TOX21_GR_BLA_Antagonist_ch2 TOX21_GR_BLA_Antagonist_ratio	NR3C1↓	
TOX21_CAR_Antagonist	NR1I3↓	
TOX21_Aromatase_Inhibition	CYP19A1↓	
TOX21_RORg_LUC_CHO_Antagonist**	RORC↓	
TOX21_PR_BLA_Antagonist_ratio**	PGR↓	
TOX21_H2AX_HTRF_CHO_Agonist_ratio**	H2AFX↑	
TOX21_ERR_Antagonist**	ESRRA↓	
TOX21_ERb_BLA_Antagonist_ratio**	ESR2↓	

Study	Gene symbol	KEGG ID
TOX21_ARE_BLA_agonist_ratio**	NFE2L2↑	4780
TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_R1881**	AR↓	367

C.3.4. Toxicogenomic Studies

Several studies of Cr(VI) exposure measuring toxicogenomic or cell signaling changes were identified in the evidence base. Given the complexity of these studies and comprehensive applicability of the evidence reported, an extra level of review and analysis was applied to these studies.

C.3.4.1. *Prioritization of studies for consideration*

Full-text screening of 39 mechanistic studies identified as reporting toxicogenomic data was performed; these studies are summarized in Table C-62. Studies were prioritized on the basis of relevance for providing mechanistic insight for Cr(VI)-mediated carcinogenesis in the lung or GI tract. Of these 39 studies, 13 studies were identified that fit these criteria. A further targeted evaluation of these 13 studies was conducted to determine relevance; 8 were prioritized for evaluation in HAWC (the preliminary evaluations of the 5 studies that were not evaluated in HAWC can be found in Appendix C.3.4.3). Of these eight studies selected for evaluation in HAWC, five used the same microarray dataset, so only one evaluation was necessary for these five (details below); an independent analysis using this dataset was also conducted by EPA. In addition to this evaluation (Kopec et al., 2012b), one study in humans occupationally exposed to Cr(VI) (Hu et al., 2017), one additional in vivo animal study (Chappell et al., 2019), and one in vitro study (Huang et al., 2017) were evaluated for risk of bias and sensitivity in HAWC.

Two of the included studies, Kopec et al. (2012b; 2012a), generated microarray datasets from tissues collected in female B6C3F1 mice and F344 rat duodenal and jejunal epithelia following 7 and 90 days of exposure to 0.3–520 mg/L (as sodium dichromate dihydrate, SDD) in drinking water, bioassays originally reported by Thompson et al. (2012c; 2011b). Five additional studies reported analyses using the same datasets: four from the same research group (Rager et al., 2017; Thompson et al., 2016; Suh et al., 2014; Thompson et al., 2012b) and one analysis conducted independently by EPA (Mezencev and Auerbach, 2021). Five of these studies were included in the synthesis of toxicogenomic data analysis; one, Suh et al. (2014), was not included because the scope was restricted to genes involved in iron homeostasis. One study evaluation, pertaining to (1) the quality of the animal study that generated the microarray data, and (2) the quality and usability of the generated microarray, was deemed sufficient to determine confidence in this original dataset, and this could apply to all studies using this dataset. The essential details of this evaluation can be found in the HAWC database under Kopec et al. (2012b).

The analysis by EPA, described in Mezencev and Auerbach (2021), provides mechanistic insight interpretable toward human relevance of the NTP 2-year rodent bioassays and suggests the

existence of potentially vulnerable subgroups. As a part of the independent analysis of this dataset by Mezencev and Auerbach (2021), an evaluation of the microarray data was conducted; these details are described in the following section.

Table C-62. Summary of considered toxicogenomic studies for Cr(VI) overall confidence classification

Author (year)	Species (strain)	Exposure design	Exposure route	Inclusion	Microarray
Hu et al. (2017)	Human study of chromate production workers in China	Cohort	Occupational	Yes, evaluation in HAWC	M
Kopec et al. (2012b)[a]	Rat (F344/N), mouse (B6C3F1)	Subchronic	Drinking water	Yes, evaluation in HAWC	H
Chappell et al. (2019)	Mouse (B6C3F1)	Subchronic	Drinking water	Yes, evaluation in HAWC	M
Huang et al. (2017)	Human (BEAS-2B human lung epithelial cell line)	--	In vitro	Yes, evaluation in HAWC	H[b]
Kopec et al. (2012a)	Rat (F344/N), mouse (B6C3F1)	Subchronic	Drinking water	Yes, but not evaluated, same dataset as Kopec et al. (2012b)	
Thompson et al. (2012b)	Rat (F344/N), mouse (B6C3F1)	Subchronic	Drinking water	Yes, but not evaluated, same dataset as Kopec et al. (2012b)	
Thompson et al. (2016)	Rat (F344/N), mouse (B6C3F1)	Subchronic	Drinking water	Yes, but not evaluated, same dataset as Kopec et al. (2012b)	
Rager et al. (2017)	Mouse (B6C3F1)	Subchronic	Drinking water	Yes, but not evaluated, same dataset as Kopec et al. (2012b)	
Mezencev and Auerbach (2021)	Mouse (B6C3F1)	Subchronic	Drinking water	Yes, but not evaluated, same dataset as Kopec et al. (2012b)	
Sánchez-Martín et al. (2015)	Mouse (C57BL/6J)	Subchronic	Drinking water	No, targeted evaluation below	
Izzotti et al. (2002)	Rat (Sprague-Dawley)	Short-term	Intratracheal instillation	Yes, targeted evaluation below	
Lu et al. (2018a)	Human (BEAS-2B)	--	In vitro	Yes, targeted evaluation below	
Clancy et al. (2012)	Human (BEAS-2B)	--	In vitro	Yes, targeted evaluation below	
Chen et al. (2002)	Human (BEAS-2B)	--	In vitro	Yes, targeted evaluation below	

Author (year)	Species (strain)	Exposure design	Exposure route	Inclusion	Microarray
Suh et al. (2014)	Rat (F344/N), female; mouse (B6C3F1), female	Subchronic	Drinking water	No, limited scope	
D'Agostini et al. (2002)	Rat (Sprague-Dawley)	Short-term	Intratracheal instillation	No, study limited in scope to a subset of genes; same data as Izzotti et al. (2002)	
Izzotti et al. (2004)	Rat (Sprague-Dawley)	Short-term	Intratracheal instillation	No, same data as Izzotti et al. (2002)	
Madejczyk et al. (2015)	Rat	Acute	Injection-i.p.	No, limited scope	
Kumar et al. (2013)	Mouse (Swiss albino)	Acute	Injection-i.p.	No, limited scope	
Hamilton et al. (1998)	Chick embryo	Acute	Injection-i.p.	No, limited scope, and model system less relevant to intestinal or respiratory carcinogenesis	
Pritchard et al. (2005)	Human (fibroblasts with ectopic expression of h-TERT)	--	In vitro	No, limited scope	
Andrew et al. (2003)	Human (BEAS-2B)	--	In vitro	No, limited scope	
Joseph et al. (2008)	Human (skin fibroblasts)	--	In vitro	No, model system less relevant to intestinal or respiratory carcinogenesis	
Sun et al. (2011)	Human (BEAS-2B)	--	In vitro	No, limited scope	
Gavin et al. (2007)	Human (peripheral blood mononuclear cells)	--	In vitro	No, limited scope	
Lei et al. (2008)	Rat (lung epithelial cells)	--	In vitro	No, limited scope	
Guo et al. (2013a)	Human (skin fibroblasts)	--	In vitro	No, model system less relevant to intestinal or respiratory carcinogenesis	
Vaquero et al. (2013)	Human (Alexander hepatoma cells)	--	In vitro	No, limited scope	
Guo et al. (2013b)	Acellular protein binding	--	In vitro	No, limited scope	
Ovesen et al. (2014)	Mouse (Hepa-1c1c7)	--	In vitro	No, limited scope	
Lou et al. (2015)	Human (B lymphoblastoid cells)	--	In vitro	No, limited scope	
Johnson et al. (2016)	Yeast (*Saccharomyces cerevisiae*)	--	In vitro	No, limited scope, and model system less relevant to intestinal or respiratory carcinogenesis	

Author (year)	Species (strain)	Exposure design	Exposure route	Inclusion	Microarray
Luczak et al. (2016)	Human (H460 lung carcinoma cell line)	--	In vitro	No, limited scope	
Bruno et al. (2016)	Human (BEAS-2B)	--	In vitro	No, limited scope	
Hu et al. (2016b)	Human (16HBE bronchial epithelial cell line)	--	In vitro	No, limited scope	
Park et al. (2017)	Human (BEAS-2B)	--	In vitro	No, limited scope	
Chen et al. (2019)	Human (16HBE)	--	In vitro	No, limited scope	
Hu et al. (2019)	Human (16HBE)	--	In vitro	No, limited scope	
Wu et al. (2012)	Human (BEAS-2B)	--	In vitro	No, limited scope	

High (H), medium (M), low (L), or uninformative (U).

[a]This study used animals from Thompson et al. (2011b) and Thompson et al. (2012c). Additional included analyses using the same dataset: Kopec et al. (2012a), Thompson et al. (2012b), Thompson et al. (2016), and Rager et al. (2017). Suh et al. (2014) used same dataset but the analysis was limited in scope.

[b]Study was *high* confidence for all reported endpoints except for qPCR, which was determined to be *uninformative*.

C.3.4.2. *Analysis of data reported by Kopec et al. (2012b; 2012a)*

Several identified studies used the microarray dataset generated by Kopec et al. (2012b; 2012a) from tissues collected in female B6C3F1 mice and F344 rat duodenal and jejunal epithelia following 7 and 90 days of exposure to 0.3–520 mg/L (as sodium dichromate dihydrate, SDD) in drinking water, bioassays originally reported by Thompson et al. (2012c; 2011b). The exposure levels and tissues were selected based on previously reported significant occurrence of tumors of the small intestines in mice following chronic exposure to Cr(VI) in drinking water (NTP, 2008).

Description of the studies and dataset

Mice B6C3F1 were continuously exposed to drinking water containing SDD at target concentrations 0 (control), 0.3, 4, 14, 60, 170, and 520 mg/L SDD until study termination at days 8 or 91, when the animals were euthanized and specimens of intestinal tissues (duodenum, jejunum) and oral mucosa (palate) were collected for gene expression analysis (Kopec et al., 2012a; Thompson et al., 2011b). Tissue collection, isolation of RNA, design and implementation of microarray experiment, and the processing of microarray data have been described in detail (Kopec et al., 2012a). The dataset "Transcriptomic data to assess hexavalent chromium mode of action in mice and rats" is deposited in the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/) as a SuperSeries GSE87262. This dataset consists of 394 microarrays from the platforms Agilent-014868 Whole Mouse Genome Microarray 4x44K and Agilent-014879 Whole Rat Genome Microarray 4x44K. The mouse subset of the data was deposited under the accession number GSE87259 and includes 214 microarrays. The data are available in the

functional genomics data repository GEO supporting MIAME-compliant data submissions in the form of raw data (.gpr files) and normalized data (normalized following a referenced semiparametric approach).

Evaluation of microarray experiment and generated microarray data

A summary of the microarray study design performed by Kopec et al. (2012b; 2012a) can be found in Figure C-28. An evaluation of the microarray data reporting quality was conducted using the Minimum Information About a Microarray Experiment (MIAME) (Brazma et al., 2001) (Table C-63). An evaluation focusing on study design and implementation and on the quality and usability of preprocessed expression data for their reanalysis was also conducted using criteria developed by Bourdon-Lacombe et al. (2015) (Table C-64). Additional criteria for DNA microarrays presented by this group were not applied, as this evaluation is not focusing on the reported results of the microarray study.

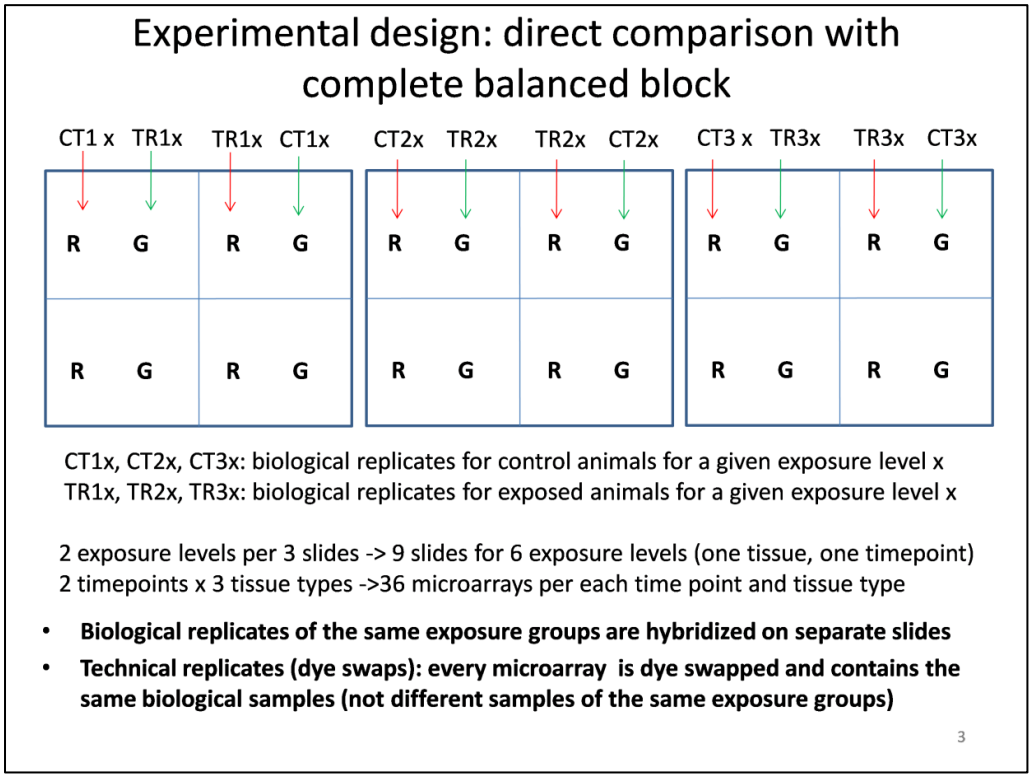

Figure C-28. Design of microarray experiments conducted by Kopec et al. (2012b; 2012a). Multiplexing of the treatment-control pairs were performed on the same chips, indicating a limited influence of interchip differences in the comparative expression analysis.

Table C-63. Evaluation of the information available with microarray data using MIAME sections

MIAME section	Evaluation of the available information
Part 1: Experimental design	Information provided in sufficient detail. Dose-response type of experiment [0.1, 1.4, 5, 20, 50, 180 mg/L Cr(VI)) in drinking water continuously] with two timepoints (8 and 91 d). Other experimental variables: 3 tissue types (duodenum, jejunum, palate epithelium). Three biological replicates per exposure level/tissue/timepoint.
Part2: Array design	Information available due to the commercial nature of microarray platform. Commercial microarray Agilent-014868 Whole Mouse Genome Microarray 4x44K (www.agilent.com). Designed to represent all known genes in the mouse genome and their resulting transcripts, the microarray comprises 41,534 60-mer oligonucleotide probes representing over 41,000 mouse genes and transcripts.
Part 3: Samples	Information provided in sufficient detail. Organism: Mus musculus strain B6C3F1; sex = female; 6–7 wk old at exposure. Sample: RNA (isolation and evaluation of purity and integrity reported). Labeling: Following manufacturer's protocol.
Part 4: Hybridizations	Information provided in sufficient detail. Hybridization was performed following manufacturer's protocol (Agilent Manual: G4140-90050 v. 5.0.1). Information on the dye swap and hybridization design reported adequately (see Figure C-28).
Part 5: Measurements	Reported sufficiently. Original scans: not available (these are usually not provided). Raw data provided. Normalized data provided as a gene expression matrix. Normalization approach (a semi parametric) was reported and properly referenced.
Part 6: Normalization controls	Included in microarray design.

Table C-64. Evaluation of the DNA microarray experiments in Kopec et al. (2012b; 2012a) using criteria outlined by Bourdon-Lacombe et al. (2015)

Criterion	Status for Kopec et al. (2012b; 2012a)
Mandatory or important criteria important in evaluating the overall quality of toxicogenomics experiments	
Control animals were handled alongside treated animals using identical procedures (e.g., controls in oral gavage experiments received vehicle only) and at similar times.	True. No additional variable (including time) was identified between exposure groups and corresponding controls. (Equivalent to confounding/variable control and exposure domains in the study evaluation in HAWC.)
A minimum of three biological replicates (animals) were used per group.	True for all exposures/tissues/timepoints with single exception for mice-duodenum-90-d-1.4 mg/L Cr(VI) exposure and control groups (2 replicates available only). This deficiency affects only 1 of 18 tissue-exposure groups from 90-d mouse study. The impact is limited.
If temporality is considered, time-matched controls were used.	True. Two timepoints have separate time-matched controls. In fact, each exposure group even has separate unexposed controls.

Criterion	Status for Kopec et al. (2012b; 2012a)
The appropriate animal model and tissue was used, and a rationale is given for the doses selected.	True. The study used the same mouse strain and exposure levels as previous NTP bioassay (NTP, 2008, 2007f) and focused on the tissues (duodenum, jejunum) in which the NTP study detected pathological changes of interest. (The same as the exposure design domain in the study evaluation in HAWC).
If dose–response is considered for risk modeling (including estimation of the BMD), a minimum of three doses plus control was used; ideally, at least one of these doses should be near the NOAEL.	True. Six doses plus control were employed. LOAEL for duodenal epithelial hyperplasia in female mice was at 5 mg/L Cr(VI) exposure in 2-yr NTP bioassay (38% cumulative incidence). The evaluated study included much lower exposures [1.4 mg/L and 0.1 mg/L Cr(VI), and shorter time].
Tests to assess various toxicities (e.g., histopathology, biomarkers of disease) were done using the same biological samples.	Partially true. Animals from the same study and exposed under the same conditions were used for histopathology evaluation and other phenotypic assays of target tissues.
Criteria that are required or should be considered in DNA microarray methodologies	
RNA A260/A280 ratios are reported and are above 1.8 to indicate sample purity or are consistent across samples.	**Partially true.** Determination of the purity of RNA by A260/A280 has been indicated in the text, but the values have not been reported. This reviewer's experience is that these values are frequently determined and used to assess the quality of RNA preparations, but they are usually not reported, because of irrelevance of their actual values with respect to publication (if >1.8, the RNA is used for downstream experiments; If not, RNA is isolated again). **This reviewer considers the fact that the ratio has been determined and used to assess the purity of RNA as sufficient even if its value is not reported.**
The integrity of RNA was assessed [common strategies include an RNA integrity number (RIN), an RNA quality indicator (RQI) or 28s:18s ratio] to ensure minimal RNA degradation or consistency across samples.	**True.** Determination of the RNA integrity was performed using denatured gel electrophoresis. This is an older and more laborious, but less expensive method than using a lab-on-a chip (e.g., Agilent Bioanalyzer), which provides a specific RIN score. **This reviewer considers the fact that the integrity of RNA was verified by denatured electrophoresis as sufficient.**
When multiple microarrays are necessary and the experiment was run over different days, the samples were randomized across the slides/days to avoid confounding effects (often referred to as a block design). Note: not always specified in the methods.	Of three biological replicates for given exposure level, one exposure and one control specimen were always hybridized on the same microarray slide. Three replicates were spread across three different slides. This design ensures that even if each of these 3 slides is processed on a different day, the confounding due to batch effect can be eliminated if the data are analyzed with consideration for pairing of specimens on the same slides. The information on timing of microarray processing was not provided; nevertheless, the batch effect can be identified through data analysis (if present) and under some circumstances it can be also corrected.
Generally, gene annotation and data quality are more robust when commercially produced microarray platforms are used.	**True.** Commercial microarray platform has been used.

Criterion	Status for Kopec et al. (2012b; 2012a)
Species appropriate microarrays were used (i.e., mouse arrays for mouse samples).	**True.** Mouse microarray Agilent-014868 Whole Mouse Genome Microarray 4x44K has been used.
Labeling and hybridization were done according to manufacturer protocol. Any deviations are reported.	**True.** Manufacturer's protocol has been reportedly followed (Agilent Manual: G4140-90050 v. 5.0.1), and no deviation was indicated.
When cohybridizations of treated and control samples are done (use of different fluorophores for control and treated samples), dye-swapping experiments were done, or that dye bias was assessed statistically is indicated.	**True.** Dye-swapping was performed (see Figure C-28; green and red colors represent Cy3 and Cy5 dyes).
Scanner specific quality control software was used to test microarray quality.	**True.** GenePix Pro 6.0 software was used for data collected by GenePix 4000B scanner. All data has reportedly passed quality control. The results of quality control assessment were not presented (which is not unusual in the field).
Data quality was assessed (through MA plots, heat maps, boxplots, scatterplots, signal to noise ratio, etc.).	**Partially true.** Heatmaps for duodenal and jejunal data for 8-d and 90-d timepoints with hierarchical clustering on specimens was provided [Figures 6 (8 d) and 8 (91 d), (Kopec et al., 2012b)]. This is not an unsupervised analysis and only differentially expressed genes were analyzed. This reviewer does not consider this criterion to be "a hard criterion." Data quality plots can be usually re-created when needed and assessed by study evaluator.
In the case that outliers are identified, a minimum of three replicates per group remain and a justification for removal has been provided.	**Partially true.** In one specific tissue/exposure combination, only 2 replicates are available. An explanation for the missing replicates was not provided, but it is not certain that the replicates represented outliers (it could have been a technical failure affecting 2 specific microarrays). Other than that, removal of other microarrays was not identified.
The data were preprocessed (e.g., background subtracted and log transformed) and normalized (i.e., adjusted to remove technical variations between arrays) prior to statistical analysis.	**True.** Preprocessed data were submitted to the GEO repository.
Data files were made available through an open access public database such as Gene Expression Omnibus (GEO), Chemical Effects in Biological Systems (CEBS) or ArrayExpress).	**True.** See GEO https://www.ncbi.nlm.nih.gov/geo/); SuperSeries GSE87262.

Distribution of normalized expression intensities (from GEO)

The dataset for the mouse small intestine reported by Kopec et al. (2012b; 2012a) was further analyzed. Distributions of normalized expression intensities were retrieved using the GEO2R tool (Figures C-29 through C-32). The distributions demonstrate that the values submitted by the study authors are median-centered and therefore cross-comparable.

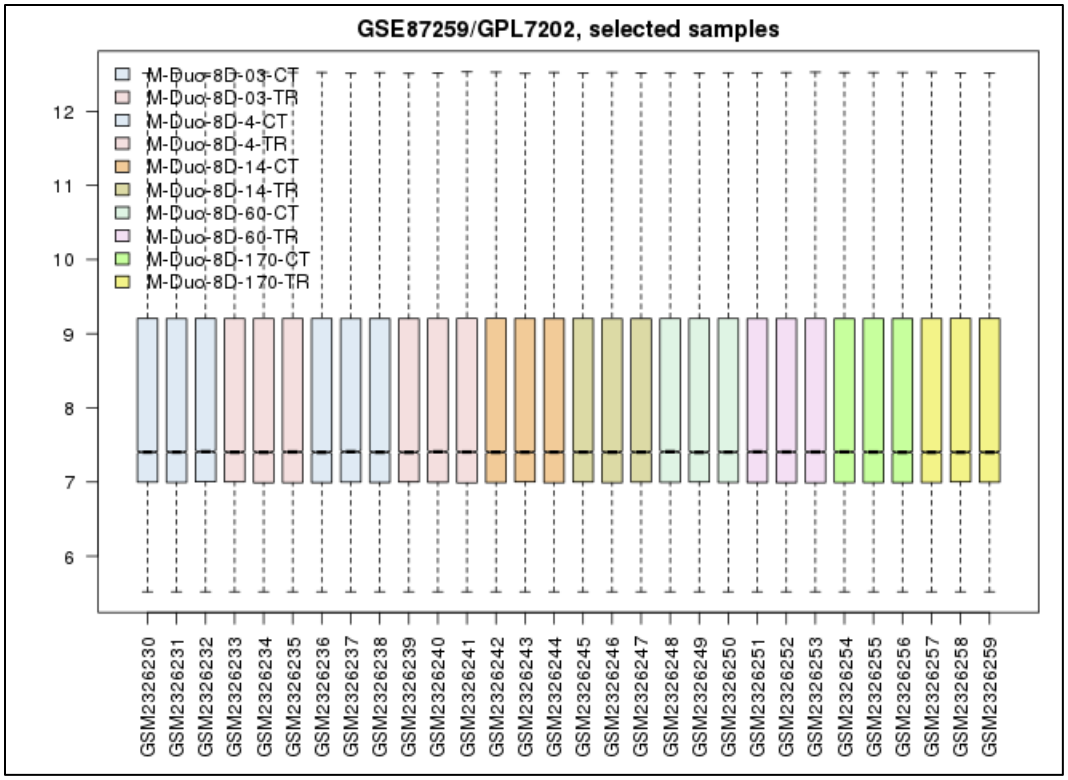

Figure C-29. Signal intensity boxplots for 8-day exposure mouse data (duodenum, top dose excluded). Due to the limitation in number of boxplots, this image does not include 520 mg/L SDD [180 mg/L Cr(VI)] exposure and control group. Note: 1 mg/L SDD = 0.349 mg/L Cr(VI).

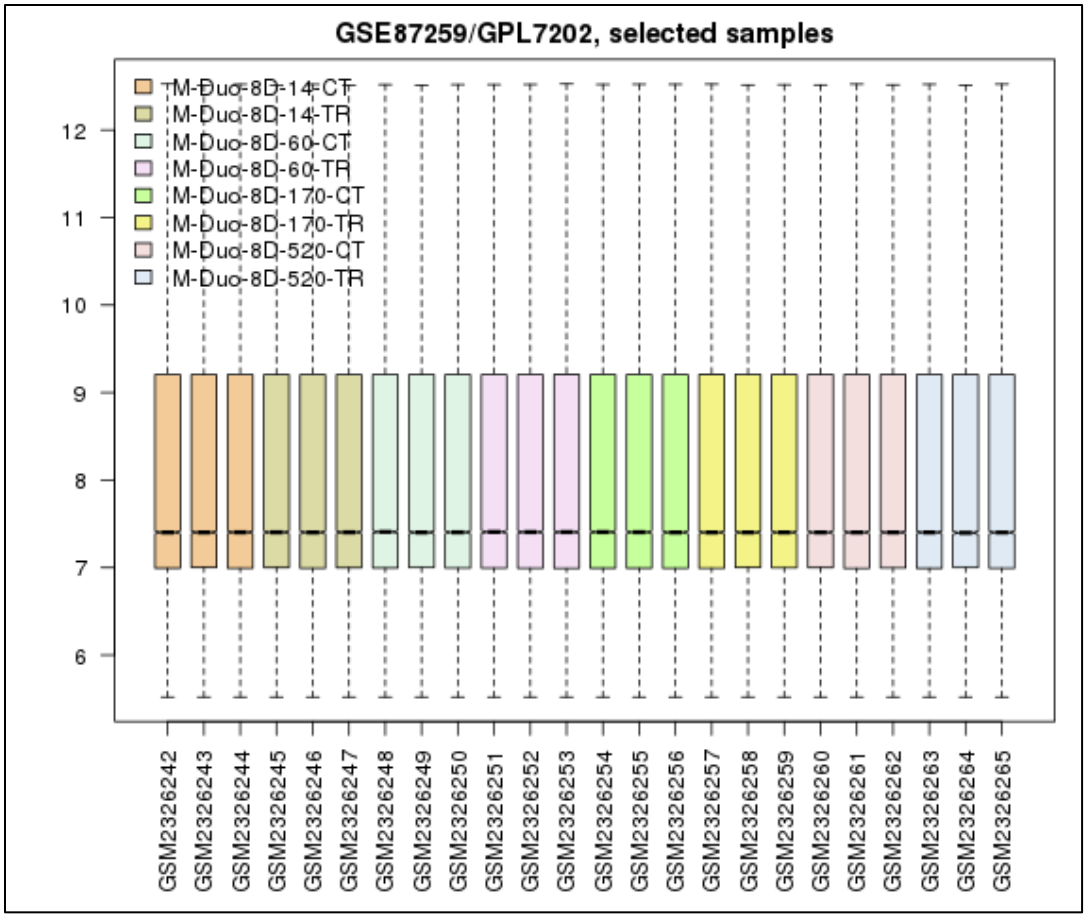

Figure C-30. Signal intensity boxplots for 8-day exposure mouse data (duodenum, top 4 dose groups). The image includes top 4 exposure groups and corresponding controls. Note: 1 mg/L SDD = 0.349 mg/L Cr(VI).

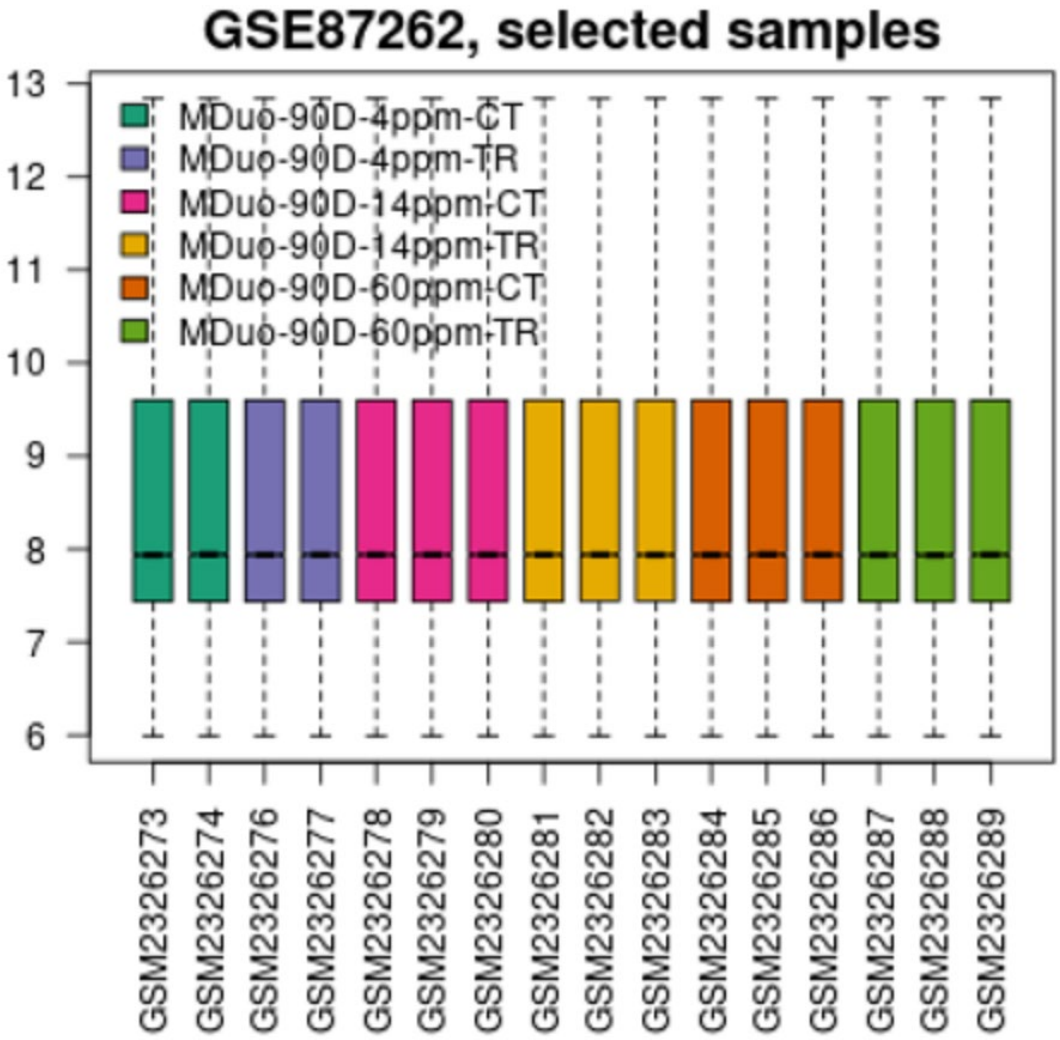

Figure C-31. Signal intensity boxplots for 90-day exposure mouse data (duodenum). The image includes all exposure groups and corresponding controls for 4 – 60 mg/L SDD. Note: 1 mg/L SDD = 0.349 mg/L Cr(VI).

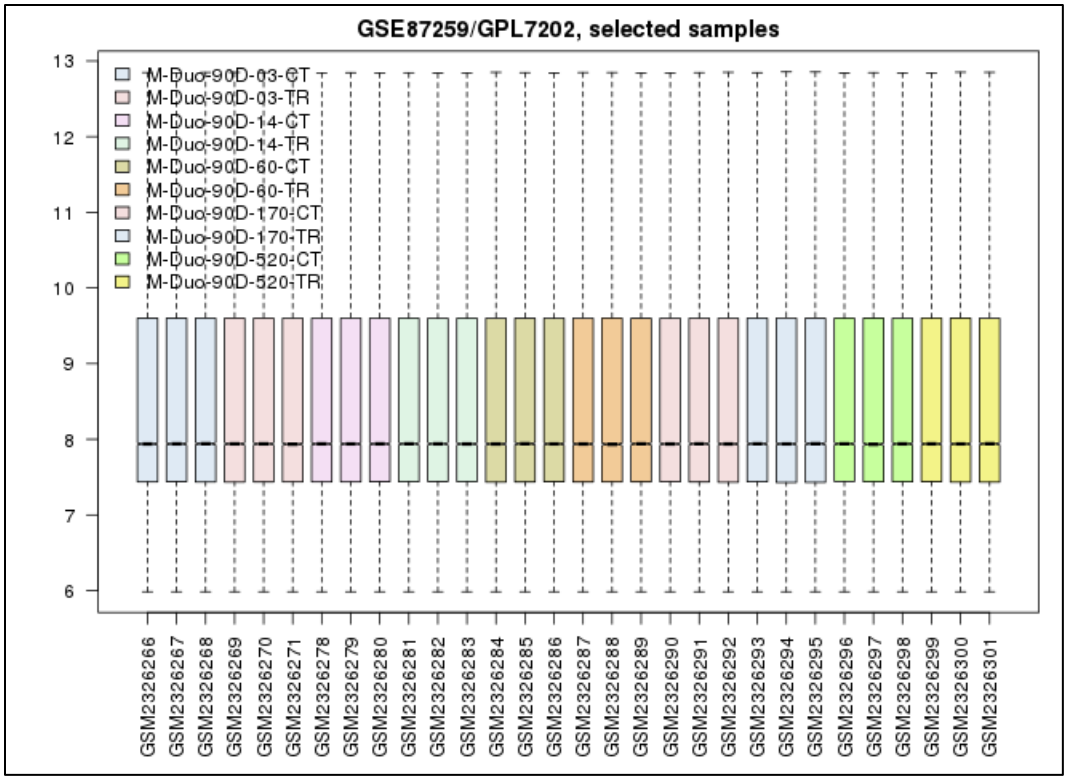

Figure C-32. Signal intensity boxplots for 90-day exposure mouse data (duodenum). The image includes all exposure groups and corresponding controls except for 4 mg/L SDD exposed and control groups. Note: 1 mg/L SDD = 0.349 mg/L Cr(VI).

Principal component analysis

Principal component analysis was performed to visualize multidimensional gene expression data and identify relationships among specimens. This analysis was executed using BMDExpress 2.20.0148 BETA (Sciome, 2018) separately for 8-day and 91-day mouse duodenum gene expression data. The data were normalized and log2-transformed. This method reduces high-dimensionality of microarray data (41,268 signal values per microarray) onto 2-dimensional space with orthogonal variables PC1 and PC2 that capture the maximum amount of variance. The 8-day exposure duodenal data show separation for three highest exposure levels along PC2 (Figure C-33). The 90-day data show separation only for two highest exposure groups (combined) and 4.61 mg/kg-day group from all other groups (Figure C-34). The results suggest separation of microarray data by exposure, which is more pronounced in the 8-day than in the 90-day dataset and for higher but not for lower exposure levels.

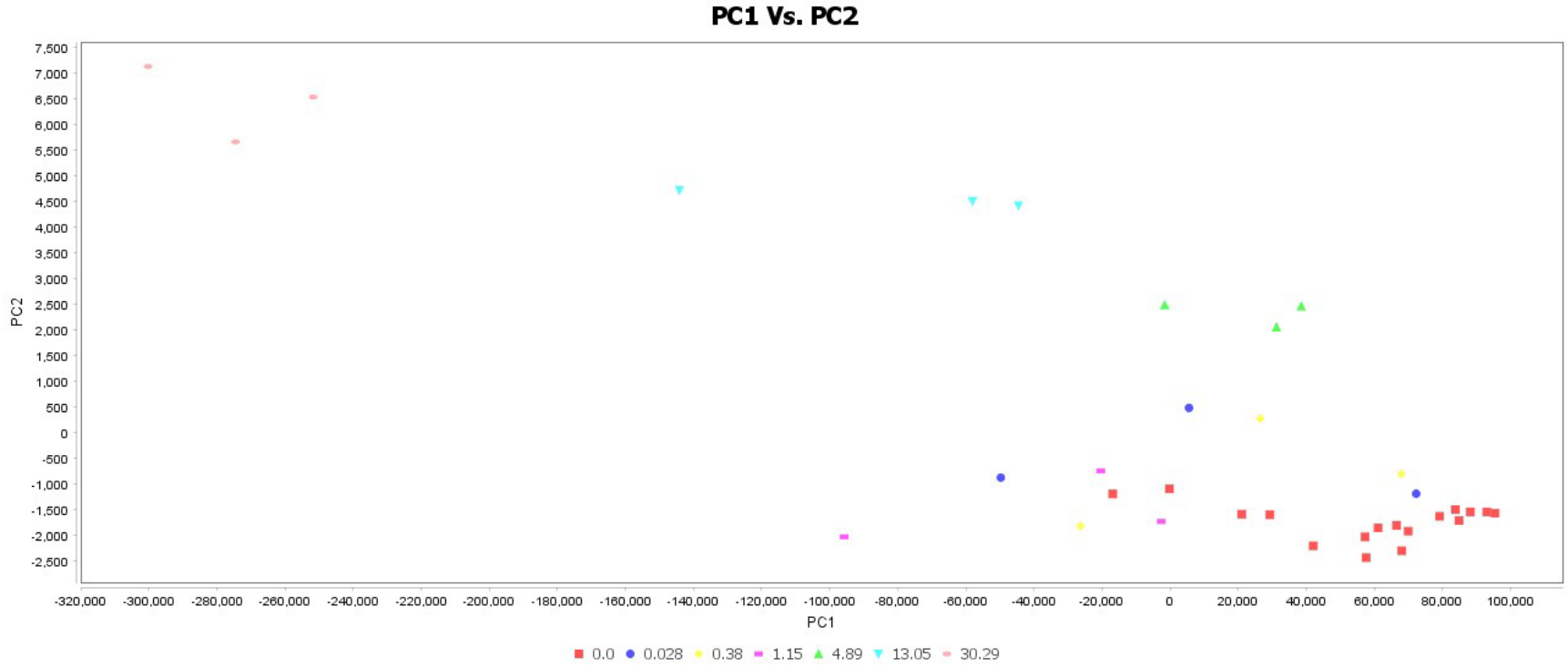

Figure C-33. Principal component analysis of 8-day exposure data for mice and duodenal tissues. Exposure levels [mg/kg-day Cr(VI)] are color-coded.

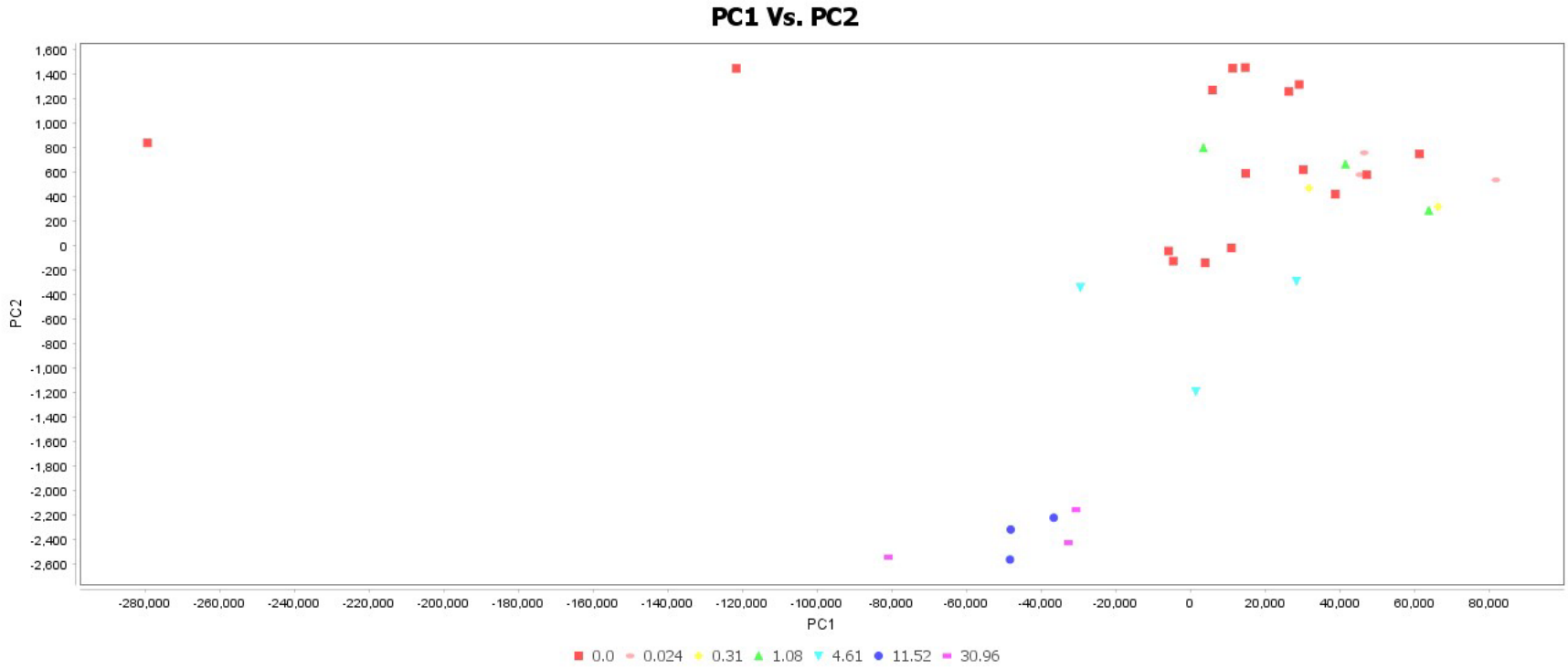

Figure C-34. Principal component analysis of 90-day exposure data for mice and duodenal tissues. Exposure levels [mg/kg-day Cr(VI)] are color-coded.

Hierarchical clustering

Hierarchical clustering was performed with the GENE-E tool (Broad Institute) for all mouse-related data with GEO accession number GSE87259 (Figure C-35). Data used were all signal intensities normalized by the study authors; distance metrics were 1- Pearson correlation coefficient; the linkage method was average. Separation between 8-day and 90-day data was forced through their separate analysis by hierarchical clustering.

The result of this unsupervised clustering displays clear separation of overall gene expression of palate specimens from duodenum and jejunum for both 8-day and 91-day exposures, which is consistent with expected biological differences. Duodenum specimens for 8-day exposure to 520 mg/L clearly separate from all other duodenum and jejunum specimens. Duodenum specimens [8 day/20−60 mg/L Cr(VI)] and jejunum specimens [8 day/20−180 mg/L Cr(VI)] cluster together but separately from those exposed to 0.1−5 mg/L Cr(VI) for 8 days. Low exposures [0.3 mg/L and 1.4 mg/L Cr(VI)] tend to cluster together with vehicle controls. In 90-day data, duodenum and jejunum specimens from mice exposed to the highest concentrations of Cr(VI) (60 mg/L and 180 mg/L) form a well-defined cluster with separation between duodenum and jejunum specimens.

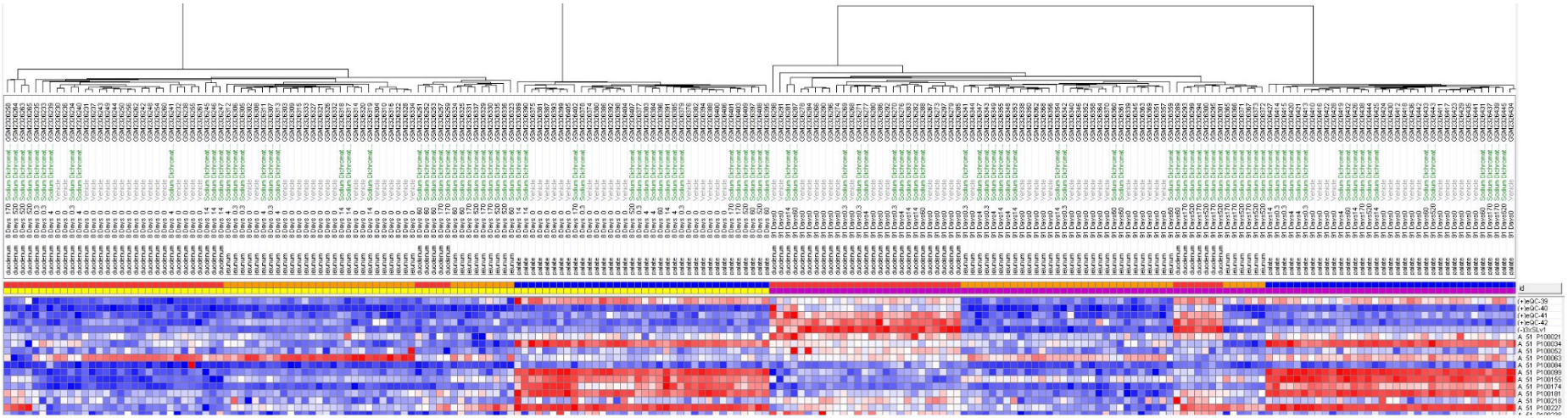

Figure C-35. Hierarchical clustering of microarrays from duodenum, jejunum, and palate tissues from mice exposed to SDD for 7 days and 90 days. This visualization cannot provide adequate resolution and serves only for illustrative purposes. Text color coding: Green-exposed, gray-controls. Colored squares: red – duodenum, beige – jejunum, blue – palate; yellow – 8 days, violet – 91 days. Expression color coding: blue-low, red-high. For a higher resolution image, see (**U.S. EPA, 2022a**).

The study that generated microarray dataset GSE87259 does not substantiate major concerns with respect to the risk of bias. The only potential issue, which has been identified, is apparently incomplete outcome data due to the discrepancy between the number of mice reportedly allocated to the gene expression study and the number of mice needed to produce the dataset GSE87259. This discrepancy is of possibly little significance, because the number of allocated mice has been reported in an article that was not actually reporting microarray data generation, processing, or interpretation (Thompson et al., 2011b). The study authors could have refined the design of the microarray study and eventually processed less mouse tissue for gene expression analysis than originally planned. Issues specific to reporting and design of the microarray experiment were of little significance with respect to the quality and usability of data for toxicogenomic analysis. The results of the principal component analysis of normalized data supplied by study authors demonstrated that the microarrays are cross-comparable among different dose levels for a given tissue type and exposure time, which supports their use for transcriptomics BMD determination and for analysis of gene expression differences between exposed and control animals within the same tissue type.

In addition, the expression data were found to be similar for jejunum and duodenum based on the results of unsupervised hierarchical clustering. This clustering presents relationships among specimens by a tree whose branch lengths reflect the degree of similarity in the overall gene expression between specimens. Moreover, the jejunum and duodenum were found to differ considerably from palate tissue with respect to overall gene expression. This finding is consistent with expectations based on biological differences and supports the quality of microarray data through biological plausibility. Furthermore, duodenum specimens [8-day, 20−60 mg/L Cr(VI)] and jejunum specimens [8-day, 20−180 mg/L Cr(VI)] were shown to cluster together but separately from the same specimens isolated from mice exposed to 0.1−5 mg/L Cr(VI). This finding supports the existence of dose dependence of overall expression data and implies the existence of differences between low and high exposure groups. Interestingly, the low exposures 0.1 mg/L and 1.4 mg/L Cr(VI) tend to cluster together with vehicle controls. Thus, the result of hierarchical clustering shows consistency with biological expectations (support for quality of microarray data) and identifies meaningful natural classes among specimens.

Another issue not addressed by this evaluation is related to the use of single-channel data from two-color microarrays used in accordance with a two-color protocol and with cohybridization of Cy-3 and Cy-5 labeled specimens. During a discussion with collaborators, a concern was raised that Cy-3 only data were used, but Cy-5 data were excluded from further analysis. The study authors argued in their report that Cy-5 data can be unreliable due to sensitivity of this dye to ambient ozone. This issue has been recognized by the scientific community and the means for its remediation are available from the microarray supplier (Agilent). Most likely, these means have not been used by the study authors and they have decided to disregard affected Cy-5 data after the experiment was completed. Therefore, it is unlikely that this approach does not represent a

selective reporting that increases the risk of bias. Although some concerns could remain with respect to the data processing, separate channel analysis for two-channel microarrays has been explored and recommended by other investigators (Smyth and Altman, 2013).

This evaluation did not address the raw gene expression data and their preprocessing due to time and resource limitations. Nevertheless, a collaborator was able to process raw data using a code supplied by the study author and demonstrate reproducibility of the raw data processing through independent generation of the same normalized data as supplied by study authors to the GEO [personal communication].

C.3.4.3. *Targeted study evaluations*

The following five studies were prioritized for relevance for providing mechanistic evidence informative to Cr(VI)-mediated carcinogenesis in the lung or GI tract, but preliminary targeted evaluations determined that full study evaluations in HAWC were not warranted. Because these have not been included in the HAWC database, the limited preliminary evaluations have been provided below.

Lu et al. (2018a)

A full study evaluation to judge the potential risk of bias is not warranted. The source of BEAS-2B cells was not reported, and the description of transformation of cells is very limited, missing any narrative on how the cell culture changed during the 6-month incubation, whether the cell growth was evaluated in the process, or how often cultures had to be subcultured, which are all good practices to report for development of new cells by long-term exposures. Small, medium, and large colonies were reportedly used for implantation in the animal study, but only a large colony from the soft agar assay has been reportedly isolated and maintained as a cell culture, indicating inconsistency in reporting. The growth of tumors seems to be too high for 6-day time after implantation. The concentrations of Cr(VI) at which transformation of cells was achieved were comparable to those used in similar studies, equivalent to 0.037 mg/L and 0.074 mg/L of sodium dichromate dihydrate [0.013 and 0.026 mg/L Cr(VI)].

Sánchez-Martín et al. (2015)

This study examines changes in (1) histopathology, (2) IHC markers of proliferation (Ki-67) and DNA damage (p-γH2AX), and (3) expression of selected genes by qPCR in the liver and in the proximal (PSI) and distal (DSI) "sections of gastrointestinal tract" of the C57BL/6 J mice exposed to Cr(VI) in drinking water. Mice were exposed to 0, 19, 191, and 1,919 µg/L Cr(VI) for 60 days and subsequently to the same concentration of Cr(VI) in drinking water and 0–125 mg/kg/day B[a]P for 90 days.

This summary addresses the gene expression analysis reported in the study by Sánchez-Martín et al. (2015). Gene expression changes reported in this study are of little informative value due to the reasons indicated below. Even though the study suggests interesting patterns of gene

expression with discordant expression changes across anatomical sites and exposure levels, an evaluation is not justified because of considerable reporting deficiencies and the high risk of bias.

- Changes in gene expression are reported only in the form of a heat map. Information about the color coding of expression changes in the heat map is incomplete. No expression values and no statistical tests for significance of their differences are reported.

- The study is not a whole-genome ("omics") study, and it deals only with expression of selected genes with limited justification for their selection.

- The sample size appears to be 4 animals per exposure level (2 animals of each sex). This design allows identification of only differentially expressed genes that do not show substantial sex differences in response to the Cr(VI) exposure.

- The study uses qPCR for the evaluation of expression of selected genes in the proximal (PSI) and distal (DSI) "sections of the gastrointestinal tract." These sections are not sufficiently characterized, which allows ambiguous interpretation. The "proximal" and "distal" are indicated to reflect position of the section relative to the stomach, but this does not add sufficient information to ascertain whether only the small intestine or also the colon were examined and which specific segments of these anatomical structures were sampled for downstream analysis.

- The study employs GAPDH as an endogenous control for normalization of the gene expression. The choice of GAPDH is not justified and its invariant expression in the liver and intestine across all exposures has not been demonstrated. There is a lack of confidence for appropriateness of the use of GAPDH as an endogenous control in this study.

- Primers used in the qPCR studies are not reported. Although this information is mentioned as being provided in the supplemental data, the information on the sequences and origin of primers (references, software used for their design, experimental validation of primers) is missing.

- The authors indicate the use of the ΔΔCt method for calculation of gene expression from the qPCR data. Since no information is given on the validation of primers and amplification efficacy for the target genes and an endogenous control, the use of ΔΔCt method is not supported and this method might not be appropriate in this study.

Clancy et al. (2012)

The source of BEAS-2B cells is reported; description of transformation of cells is sufficiently reported; growth media and exposure conditions were properly reported; exposure was performed at minimally cytotoxic concentration (0.5 μM) of potassium chromate [0.1 μM Cr(VI)], which does not seem to have been determined in this study but is consistent with other reports. The form of Cr(VI) and its source are reported (potassium chromate, Sigma). The cells have been altered by Cr(VI)-mediated transformation (morphology, growth pattern in soft agar), and so sensitivity is not an issue. Methods for mRNA analysis are succinctly described and refer to manufacturers' protocols. qPCR validation relied on the GAPDH gene as an internal control, which is a frequent practice in the field, but not appropriate without justification (the justification has not been

provided in this report). Differentially expressed genes were selected based on t-test *p*-value of 0.05 and a fold-change cut-off of 1.50. The lack of proper qPCR validation does not invalidate a microarray study using systems biology approaches.

Chen et al. (2002)

Sources of BEAS-2B and MEF cells were provided; media composition was reported; sources of vectors pCR-FLAG-IKK, pCR-FLAG-IKK-KM, pcDNA3-myc-IAP1, and pEGFPluc were indicated. The Cr(VI) compound used for this study, however, was not specified. Exposure levels of Cr(VI) were adequately described. For assays other than cytotoxicity/viability, conditions were adequately selected to avoid convolution of the study outcomes with cell death. Likewise, exposure conditions (concentrations, times) were chosen well with respect to sensitivity of outcome detection, as evidenced by demonstrated differences between Cr(VI)-exposed and solvent control cells.

The microarray study employed (1) an old expression array design, (2) only a fold change-based identification of differentially expressed genes, and (3) an unknown number of biological or technical replicates. RT-PCR was used instead of qPCR for validation of selected genes identified by microarray analysis, and endogenous control 7S RNA was used without justification. RT-PCR primer design software, sequences, annealing sites, and amplicon lengths were reported. Reverse transcription conditions were reported but the reverse transcriptase used in the reaction was not described. RT-PCR conditions were reported.

Methods used in this study complemented each other and, in this way, compensated for the identified deficiencies of individual experiments. For instance, deficiencies of microarray experimental design and analysis were compensated by validation RT-PCR and demonstrated IAP-mediated inhibition of cell death in cells exposed to Cr(VI). The somewhat surprising lack of specification of Cr(VI) compound used in this study can be perceived as a critical deficiency rendering most of the study uninformative (at least experiments that employed Cr(VI)-exposure).

Izzotti et al. (2002)

Izzotti et al. (2002) analyzed gene expression in Sprague-Dawley rats intratracheally exposed to sodium dichromate[5] at the dose of 0.25 mg/kg [0.09 mg/kg Cr(VI)] body weight for 3 days and sodium chloride control, using in-house radioactively labeled cDNA microarrays that probed expression of 216 genes tested in duplicates and 5 house-keeping genes. Gene expression was examined in lungs and livers of SDD-exposed and NaCl-exposed (control) groups. Genes were considered differentially expressed if the fold change exceeded 2. This study identified 56 genes overexpressed in lungs of Cr(VI)-exposed rats, which included glutathione metabolism-related

[5]As with many studies, the compound may be referred to as "sodium dichromate" ($Na_2Cr_2O_7$), when the compound is administered in an aqueous solution and the mass units are based on sodium dichromate dihydrate ($Na_2Cr_2O_7$ $2H_2O$). Unless otherwise noted, the conversion factor for sodium dichromate dihydrate (0.349) was used to convert Cr(VI) units for studies labeled as either sodium dichromate or sodium dichromate dihydrate.

genes, membrane channels/transporters, cell signaling molecules, cell cycle-related molecules, stress response/protein folding-related genes, as well as DNA synthesis/DNA repair and apoptosis-related genes. These expression data are consistent with generation of reactive oxygen species, cell proliferation, and inhibition of apoptosis. Protein misfolding-related genes are likely reflecting oxidative protein damage and increased protein synthesis. The study found no changes in gene expression in livers of Cr(VI)-exposed mice relative to control animals, which indicated no significant systemic effects after intratracheal exposure. Although these study results support findings of other toxicogenomic and non-omic mechanistic studies, the study likely provides an incomplete picture of molecular changes induced by Cr(VI) exposure. This is because (1) it evaluated expression of a limited range of genes using in-house produced microarrays, and (2) the dose used in this study [0.09 mg/kg Cr(VI)] failed to induce lung tumors as in other studies in Sprague-Dawley rats exposed 5 times per week over 30 months (Steinhoff et al., 1986).

C.3.4.4. *Toxicogenomic analyses*

Toxicogenomic analyses of genome-wide changes in gene or protein expression in response to Cr(VI) exposure can help inform carcinogenic signaling pathways relevant to lung and GI cancer. Four studies were fully evaluated in HAWC: one human study (Hu et al., 2017), two in vivo animal studies (Chappell et al., 2019; Kopec et al., 2012b), and one in vitro study using the human BEAS-2B cell line (Huang et al., 2017)), with one evaluation, Kopec et al. (2012b), representing five studies that used the same microarray dataset (see details below). An independent analysis of the published in vivo toxicogenomic data by Kopec et al. (2012b) was conducted by Mezencev and Auerbach (2021) and is described below.

In vivo studies

One *medium* confidence toxicogenomic study was identified in humans. Hu et al. (2017) performed proteomic analysis of sera in male workers recruited from a chromate production facility in China. Primary limitations of this study were the lack of description of participant selection and a relatively small sample size. There were two stages of analysis; first, 25 exposed and 16 unexposed workers underwent "proteomics technology and bioinformatics analysis," and second, 41 exposed and 25 unexposed workers underwent a validation analysis to confirm findings from the first stage. Sixteen significantly enriched pathways were identified related to innate immune system function, extracellular matrix organization, platelet-related processes, and metabolism (Hu et al., 2017). Notably, the increased abundance of SHH, a gene that promotes tumor growth and metastasis if overactivated, in the sera of Cr(VI) exposed workers is consistent with the potential role of SHH in Cr(VI)-mediated carcinogenesis identified by other toxicogenomic studies (Mezencev and Auerbach, 2021; Huang et al., 2017).

Six of the eight in vivo toxicogenomic analyses in animals after oral exposure to Cr(VI) were published by the ToxStrategies firm. A *high* confidence study, Kopec et al. (2012b), conducted an analysis of gene expression in the oral mucosa and duodena in tissues collected from female Fischer

344 rats and female B6C3F1 mice exposed to sodium dichromate dihydrate (SDD) in drinking water as described in the original studies by Thompson et al. (2012c; 2011b). Because the same dataset was used in four other studies published by this group repeated (Rager et al., 2017; Thompson et al., 2016; Kopec et al., 2012a; Thompson et al., 2012b), this study evaluation (in HAWC) specific to the original animal studies and the microarray dataset generation was not repeated.

Kopec et al. (2012a) reported gene expression changes in mouse intestinal epithelia after 8 days or 91 days corresponding to oxidative stress, xenobiotic metabolism signaling, glutathione metabolism, cell cycle progression, lipid metabolism, and immune response pathways. In addition, canonical DNA repair pathways (i.e., NER, MMR, and BRCA1) were enriched for genes differentially expressed in the duodena of mice exposed to SDD for 8 days; however this response was absent in duodena of mice exposed for 90 days and in jejuna of mice exposed for both time periods (Kopec et al., 2012a). A subsequent publication using the same mouse dataset reported gene expression changes indicating reduced apoptosis at day 91 and increased cell growth and proliferation at days 8 and 91 (Rager et al., 2017). Cancer-related signaling identified from the 8-day exposure data largely reflected increased expression of matrix metalloproteases (Mmp2, Mmp7, Mmp9, Mmp10, and Mmp13). Mmp10 and Mmp13 showed dose-dependent upregulation at day 91, which indicated cell migration, tissue remodeling and angiogenesis. In the same study, a parallel analysis of ToxCast/Tox21 and Comparative Toxicogenomics Database (CTD) data for Cr(VI) compounds showed a variety of differences when comparing these in vitro results to the in vivo results for this particular dataset; for example, some pathways associated with DNA damage (e.g., p53) were only activated in vitro (Rager et al., 2017). In a toxicogenomic study in duodena of rats exposed to SDD in drinking water at concentrations up to 180 mg/L, functional analysis revealed enrichment of cell cycle, DNA metabolism, DNA replication, and DNA repair pathways at day 8 but not day 91 (Kopec et al., 2012b). A comparative analysis of the same datasets for rats and mice showed a strong dose-response relationship of the number of differentially expressed genes in the duodenum in both species when total Cr tissue levels exceeded 10mg/kg, with a minimal transcriptomic response in the oral mucosa evidenced by very few gene expression changes showing dose-responsive statistical significance (Thompson et al., 2016).

Additional reports published by this group included a reanalysis of the mouse dataset, limited to 7 of 23 gene categories, which suggested a higher similarity in Cr(VI) induced gene expression changes in the mouse small intestine to expression changes induced by four nonmutagenic carcinogens versus four mutagenic carcinogens (Thompson et al., 2012b). The comparison dataset represented gene expression in rat liver reported by Ellinger-Ziegelbauer et al. (2005). The limited nature of the analysis (cross-species, cross-tissue and cross-platform comparison of gene expression data for the chemical of interest using a single in vivo study annotated for four mutagenic and four nonmutagenic carcinogens) make the results difficult to interpret.

Another *medium* confidence gene expression comparison study by the same group using a new dataset reported significant overlap between DEGs induced by oral exposure Cr(VI) and two

fungicides, captan and folpet, that also cause intestinal tumors in mice (Chappell et al., 2019). Common pathways modulated by Cr(VI) and the higher concentrations of captan or folpet include those involving HIF1, AP1, PPAR, mTOR 4, and Peroxisome (Chappell et al., 2019). Although these authors suggest the commonalities between two nonmutagenic compounds and Cr(VI) imply a nonmutagenic MOA for Cr(VI)-induced mouse intestinal tumors, concordance among gene expression across these three toxicants does not provide solid evidence for ruling out mechanisms that are not shared by all these toxicants. The study was also limited by a single timepoint and reporting inconsistencies for pathways found to be unique for duodena of Cr(VI) exposed mice.

An independent analysis of the 8- and 91-day B6C3F1 mouse data subset published by ToxStrategies, Inc. (Rager et al., 2017; Kopec et al., 2012b; Kopec et al., 2012a; Thompson et al., 2011b) that was deposited in the Gene Expression Omnibus implicated activation of oncogenic signaling (MYC, MYCN, EGFR, ERBB2, TRIM24) and inhibition of tumor suppressors (CDKN2A, STAT1), which support sustained cell proliferation in the duodenum (Mezencev and Auerbach, 2021) (see Appendix C.3.4.2). Similarly, a parallel analysis of enrichment of the cancer "hallmark" and oncogenic signature gene set collections from the Molecular Signatures Database (MSigDB) identified multiple molecular changes in duodena of mice orally exposed to Cr(VI) known to be relevant for carcinogenesis, including c-Myc targets, E2F targets, and alterations in G2M checkpoint and DNA repair pathways. Gene sets enriched in the duodena of mice exposed for 8 days support angiogenesis, impaired apoptosis, and epithelial-mesenchymal transition, which also represent hallmarks of cancer. Enrichment of the cholesterol homeostasis gene set found for 8-day and 90-day exposures at several exposure levels implies activation of cholesterol biosynthesis that is associated with intestinal crypt hyperproliferation and tumorigenesis. Enriched gene sets from the Oncogenic Signature collection imply oncogenic activation of KRAS, SRC, SHH, and PI3K/AKT/mTOR signaling and inactivation of signaling mediated by tumor suppressors PTEN and RB (Mezencev and Auerbach, 2021).

The analyses by Mezencev and Auerbach (2021) (see Appendix C.3.4.2) also indicate oxidative stress in duodena of mice exposed to Cr(VI) for 91 days through inferred activation of the NFE2L2 upstream regulator. This gene encodes a redox-sensitive transcription factor NRF2, which, upon activation, accumulates in the nucleus where it regulates expression of genes involved in the oxidative stress response (He et al., 2020). In addition, a collection of 26 genes known to be responsive to oxidative stress was also significantly enriched in duodena of mice exposed to Cr(VI) for 91 days. This is in contrast with data after an 8-day exposure, which indicate that this collection of genes was enriched in control mice. As a result, in mice exposed to Cr(VI), lower amounts of ROS are inferred in duodena of mice exposed for 8 days, but higher amounts of ROS are inferred in duodena of animals exposed for 91 days.

Taken together, the results support duodenal carcinogenicity of Cr(VI) ingested in drinking water in mice through activation of oncogenic signaling, inactivation of signaling mediated by tumor suppressors, sustained cell proliferation, oxidative stress, impaired apoptosis, and tissue remodeling.

A notable result of the analyses by Mezencev and Auerbach (2021) was the identification of a potential role for the CFTR (cystic fibrosis transmembrane conductance regulator) in carcinogenesis in mouse small intestines. Toxicogenomic analysis of Kopec et al. (2012b; 2012a) datasets by Mezencev and Auerbach (2021) suggested inactivation of CFTR in mice exposed to concentrations of Cr(VI) as low as 0.1 mg/L for 8 days. This inactivation does not appear to be attributable to tissue damage, which was observed in these same animals following subchronic exposure to Cr(VI) concentrations ≥60 mg/L (Thompson et al., 2011b). Therefore, suppression of CFTR activity might represent an early effect of Cr(VI) exposure that contributes to the carcinogenic process. Considering the recently reported tumor-suppressor role of the CFTR gene in mouse and human intestinal cancers (Than et al., 2016), this finding expands the range of plausible mechanisms that could be operative in Cr(VI)-mediated carcinogenesis of intestinal and possibly other tissues, which include mutagenesis, inflammation, or cytotoxicity followed by regenerative proliferation in the carcinogenic MOA of Cr(VI).

Another toxicogenomic study, a limited short-term intratracheal study in rats, was identified. Izzotti et al. (2002) observed gene expression changes in the lung consistent with the generation of reactive oxygen species, cell proliferation, and inhibition of apoptosis. The study found no changes in gene expression in livers of Cr(VI)-exposed mice relative to control animals, which indicated no significant systemic effects after 3 days of intratracheal exposure (Izzotti et al., 2002). The study was determined of limited value, however, due to low exposure levels and to its limited range of genes evaluated by in-house produced microarrays of an old design and therefore was not considered for evaluation in HAWC.

In vitro studies

Four toxicogenomic in vitro studies were also identified as particularly informative for Cr(VI)-induced carcinogenicity and cellular transformation. All four studies were partially evaluated (Appendix C.3.4.3), but only one, Huang et al. (2017), was fully evaluated in HAWC. This study was found to be *high* confidence for all assays reported in the study, including cell transformation, Western blotting, and an siRNA knockdown, but was determined to be *uninformative* for qPCR findings due to reporting issues and lack of optimization for this assay.

Clancy et al. (2012) demonstrated transformation of bronchial epithelial BEAS-2B cells exposed to 0.5 μM Cr(VI) for 4 weeks that coincided with differential expression of genes that showed enrichment in several pathways related to cancer development. These included cell mobility and migration, TGFβ receptor signaling, MAP kinase activity, regulation of apoptosis, response to hypoxia, and pathways involved in pancreatic cancer and small-cell lung cancer (Clancy et al., 2012). Transformation of BEAS-2B cells using a similar study design (0.5 μM Cr(VI) for 4 weeks) was confirmed by a separate group that also demonstrated acquisition of a proliferative, migratory, invasive, and tumorigenic phenotype by Cr(VI)-transformed BEAS-2B cells (Huang et al., 2017). In this study, Cr(VI)-mediated transformation was associated with activation of the hedgehog (Hh) signaling pathway, which interplays with multiple oncogenic pathways, and Gli2-

mediated inhibition of autophagy. Inhibition of autophagy by Hh signaling activation has been found in the lung cancer cell lines, which support biological relevance of this mechanistic finding. Likewise, a study by Lu et al. (2018a) demonstrated the ability of Cr(VI) to transform BEAS-2B cells exposed to 0.125 μM or 0.25 μM of Cr(VI) for 6 months, which displayed tumorigenicity after subcutaneous injection in nude mice. Proteomic analysis revealed downregulation of STK11 encoded by the tumor-suppressor gene LKB1, suggesting possible activation of Wnt/β-catenin and mTOR signaling pathways that are involved in the development of various cancers. A fourth study demonstrated the importance of NF-κB activation for survival and transformation of cells exposed to Cr(VI), with upregulation of transcriptional targets cIAP1 and cIAP2 (Chen et al., 2002).

C.3.5. Susceptible Populations

C.3.5.1. *Genetic polymorphisms*

Summary of evidence in humans

Genetic polymorphisms can alter individual susceptibility to health effects of environmental exposures, including chromium. Thirteen studies in humans were identified that evaluated genetic polymorphisms in relation to chromium exposure and cancer-related outcomes (mechanistic or apical). The study findings are summarized in Table C-65.

Seven studies evaluated genetic polymorphisms in relation to mechanistic outcomes relevant to cancer (e.g., mutations, genome instability). Of these, one focused on micronuclei, with interaction effects reported for some genes related to DNA repair and tumor suppression (XRCC3, BRCA2, NBS1) (Long et al., 2019). Two studies of the same study population reported increased chromosomal aberrations among welders with polymorphisms of one gene that encodes DNA repair enzymes (XRCC1) but not others (XPC, XPD, EPG, XRCC3, hOGG1) (Halasova et al., 2012; Halasova et al., 2008). Similarly, polymorphisms in XRCC1 were also associated with increases in DNA strand breaks among welders (Iarmarcovai et al., 2005) and measures of DNA damage such as olive tail moment, tail length, and tail DNA% among electroplating workers (Zhang et al., 2012). Finally, two studies of electroplating workers from another study population evaluated potential differential effects on sister chromatid exchange due to polymorphisms in genes related to detoxification (GSTM1, GSTT1); interaction effects were detected for GSTT1 (Wu et al., 2001) in one study but not the other (Wu et al., 2000).

Four studies evaluated genetic polymorphisms in the context of cancer. One study identified an increased risk of lung cancer in individuals with certain polymorphisms in XPD (Sarlinova et al., 2015), which is involved in nucleotide excision repair. Three studies approached the question in a different way, probing the frequency of certain gene variants in cancer cases. Polymorphisms in the surfactant protein B gene were found to be more common in small-cell carcinomas from workers exposed to Cr(VI) compared to referents (Ewis et al., 2006). In another study, the odds of hMLH1 polymorphisms was found to be elevated in chromate-related lung cancer cases compared to hospital-matched referents (Halasova et al., 2016). Finally, one study evaluated microsatellite

instability (operationalized as replication error (RER), defined as microsatellite instability at two or more loci) among individuals with lung cancer; study authors report increased frequency of RER among cases with chromate exposure compared to those without chromate exposure as well as an association between duration of chromate exposure and lung cancer cases with RER compared to those without RER (Hirose et al., 2002).

Although it is difficult to draw conclusions based solely on the human evidence, the existing data suggest that genetic polymorphisms may play a role in cancer susceptibility of individuals exposed to Cr(VI), and the impact of polymorphisms relevant to DNA damage and detoxification pathways in particular can provide important insight on the cancer MOA for Cr(VI).

Table C-65. Studies of genetic polymorphisms in humans occupationally exposed to Cr(VI)

Study overview	Exposure	Results	Comments	Reference
Cases: workers in chromate factory who developed lung cancer (n = 31) *Additional case groups*: samples from lung adenocarcinoma (n = 38) and squamous cell carcinoma (n = 46) from individuals never employed in chromate-related industries *Controls 1:* workers in chromate factory who did not develop lung cancer (n = 26) *Controls 2:* randomly selected healthy individuals (n = 89)	Mean (SD) yr of chromate exposure in the workplace: cases = 22.8 (6.56) yr; controls = 20.1 (7.71) yr	↑ SP-B gene variants in chromate case group & in chromate small cell carcinoma compared to referent small cell carcinoma	SNP genotyping of Surfactant protein B gene. No evaluation for potential confounding.	Ewis et al. (2006)
Cross-sectional study, Slovak Republic. *Exposed*: n = 73 male welders *Referent*: n = 71 male controls (administrative officers and hospital employees)	Exposure to Cr(VI) inferred based on occupation. Mean ± SD duration of occupational exposure was 10.2 ± 1.7 yr. Also measured Cr in blood. Exposed workers had average values about twice as high as referent group (stated to be significantly different).	↑ Cas in individuals with Gln/Gln genotype compared to Arg/Gln or Arg/Arg genotypes in XRCC1 Arg299Gln; more pronounced in Cr-exposed workers	Main limitations are related to lack of description (e.g., for participant selection) and lack of evaluation of confounders aside from smoking. SNP genotyping of genes encoding DNA	Halasova et al. (2012)

Study overview	Exposure	Results	Comments	Reference
	Mean ± SE was 0.07 ± 0.04 vs. 0.03 ± 0.007 µmol/L.		repair enzymes (XRCC1, XPC, hOGG1).	
Cross-sectional study, Slovak Republic. *Exposed*: n = 39 male welders *Referent*: n = 31 male controls (source not given)	Exposure to Cr(VI) inferred based on occupation. Mean ± SD duration of occupational exposure was 10.2 ± 1.7 yr. Also measured Cr in blood. Exposed workers had average values about twice as high as referent group. Mean ± SE was 0.07 ± 0.04 vs. 0.03 ± 0.007 µmol/L.	↑ Cas & CTAs in individuals with Gln/Gln genotype compared to Arg/Gln or Arg/Arg genotypes in XRCC1 Arg299Gln	Main limitations are related to sample size, unclear differentiation between exposure groups, and lack of description (e.g., for participant selection). SNP genotyping of genes encoding DNA repair enzymes (XRCC1 and XRCC3).	Halasova et al. (2008)
Cases: chromium-exposed lung cancer patients (n = 45) *Controls:* hospital patients with no previous malignant disease in medical records or family history; matched on age, gender, and ethnicity (n = 61)	Mean(SD) exposure time in cases: 9.3 (1.7) yr	↑ odds of hMLH1 polymorphisms in lung cancer cases	SNP genotyping of DNA repair genes XRCC3, hMLH1, and hMSH2. No detailed information on exposure/occupational history nor were exposure levels quantified; no consideration of confounders.	Halasova et al. (2016)
Exposed: chromate workers with lung cancer (n = 28; n = 38 tumors) *Referents:* lung cancer patients without chromium exposure (n = 26; n = 26 tumors)	Chromate workers exposed to chromium for mean (SD) 22.9 (6.9) yr	↑ frequency of RER in lung cancers with chromate exposure compared to without chromate exposure ↑duration of chromate exposure in chromate lung cancer cases with RER compared to those without RER ↑ MSI with ↑ duration of chromate exposure No difference in frequency of LOH in tumors with or without chromate exposure	Multiple samples taken from some chromate exposed patients—these would not be statistically independent. No consideration of confounders.	Hirose et al. (2002)

Study overview	Exposure	Results	Comments	Reference
Cross-sectional study, France. *Exposed*: n = 60 male welders from 36 workshops in the "building trade" *Referent*: n = 30 office workers recruited from "general or administration services" without history of occupational exposure to welding fume or other physical or chemical agents	Exposure to Cr(VI) inferred based on occupation. State that <5% of welding was done on stainless steel, which raises concern that total Cr measured in blood and urine may be attributed to Cr(III) exposure. Also measured total Cr in blood and urine. Cr levels in blood and urine were higher among both groups of welders compared with controls (means 129 to 145, compared with 92 µg/L), and urinary chromium was higher among welders working without smoke extraction systems.	SNP genotyping of DNA repair genes, XRCC1 and XRCC3 XRCC1 variant allele coding Gln amino acid at position 399 was associated with a higher number of DNA strand breaks	Main limitations are related to lack of description (e.g., for participant selection, analysis), unknown contribution of Cr(VI) to Cr exposure and known co-exposures to other metals. ↑ mean BN % in lymphocytes of welder compared to controls.	Iarmarcovai et al. (2005)
Cross-sectional study, China. *Exposed*: n = 120 chromate exposed workers working at a chromate production facility *Referent*: n = 97 unexposed workers at same facility ("without contact history of harmful substances")	Exposure to Cr(VI) inferred based on occupation. Also measured Cr in whole blood. Cr levels were significantly higher among exposed compared with controls, indicating delineation of exposure. Median (interquartile range) of Cr in whole blood was 2.81 (3.86) and 0.99 (1.21) µg/L in exposed and referent groups, respectively.	Interaction between micronuclei frequency and SNPs in the following genes: XRCC3, BRCA2, NBS1	Main limitations are related to lack of description (e.g., for participant selection and statistical analysis) SNP genotyping of XRCC3, BRCA2, NBS1.	Long et al. (2019)
Exposed: workers in a chromate factory (n = 141) *Referents:* farmers from area approx. 90 miles from chromate factory (n = 54)	Full shift (8 h) personal exposure sample taken; flow 2.1 min^{-1}. Median (IQR) of air Cr(VI) in workers = 17.8 (39.5) µg/m^3; in referents = 0.06 (0.12) µg/m^3 Blood samples collected; analyzed with graphite furnace atomic absorption with Zeeman background correction; Median (IQR) of Cr in workers = 6.0 (7.86); 2.64 (2.11)	↑ accumulation of Cr in RBCs per air Cr(VI) exposure among wild type Band 3 Memphis genotype	SNP genotyping of genes involved in anion transport proteins. No major concerns with study quality, except for minimal information on participant selection.	Qu et al. (2008)
Cases: chromium-exposed lung cancer patients (n = 50) *Controls:* Individuals with no	Mean (SD) exposure time in cases: 9.3 (1.7) yr	↑ risk of lung cancer with the following genotypes: XPD Lys/Gln+XPC Lys/Gln and XPD	SNP genotyping of XPC(rs2228001), XPD (rs13181,) XRCC1(rs25487), and hOGG1 (rs1052123).	Sarlinova et al. (2015)

Study overview	Exposure	Results	Comments	Reference
previous malignant disease in medical records or family history; age, gender, & ethnicity matched to cases (n = 69)		Lys/Gln+XPC Gln/Gln	No quantitative assessment of exposure; no adjustment for missing data.	
Exposed 1: residents of areas contaminated with Cr(VI), asymptomatic with regard to dermal irritation (n = 108) *Exposed 2*: residents of areas contaminated with Cr(VI), reporting dermal irritation (n = 38) *Referents:* asymptomatic residents of area with no history of Cr(VI) contamination (n = 148)	Mean (SD) residing at contaminated site (among exposed group): 24.17 (15.23) yr	↑ OR dermal irritation in GSTM1 null genotype when comparing exposed symptomatic individuals to exposed asymptomatic individuals ↑ OR dermal irritation in GSTT1 null genotype when comparing exposed symptomatic individuals to control asymptomatic individuals	SNP genotyping of genes (GSTT1, GSTM1, NQO1 and hOGG1) involved in Cr(VI) reduction and fate in cell. Only adjusted for smoking, not other confounders.	Sharma et al. (2012)
Exposed: chromium workers (n = 35) *Referents:* age and gender matched controls (n = 35)	Exposure duration ranged from 2 to 14 yr with a mean (SD) of 6.5 (4.2) yr.	↑ sister chromatid exchanges in exposed group; association with work duration; synergy with smoking ↑ high frequency cells in exposed groups; synergy with smoking	SNP genotyping for GSTM1 and T1. Limited sample size. Only adjusted for smoking, not other confounders.	Wu et al. (2000)
Exposed: chromium platers (n = 35) *Referents:* healthy subjects with no history of disease or previous exposure to chromium or other metals (n = 35)	The mean duration of employment was 6.5 yr. Personal exposure monitoring for 8-h working shift (1.71/min); blood and urine samples collected at end of shift and analyzed with atomic absorption spectrophotometry Individual time-weighted average range: 0.049–1.130 mg/m^3	↑ sister chromatid exchange and percent high frequency cells in exposed group compared to controls	SNP genotyping for GSTM1 and T1. Personal air sampling only obtained for n = 10 individuals in the exposed group. Unable to draw conclusions about effect of genotype due to small sample size.	Wu et al. (2001)

Study overview	Exposure	Results	Comments	Reference
Exposed: electroplating workers (n = 157) *Referents:* individuals without exposure to chromium or known physical/chemical genotoxic agents (n = 93)	Air-Cr determined by graphite furnace atomic absorption spectrophotometer	↑ chromium concentrations in erythrocytes among exposed compared to referents ↑ Olive tail moment, tail length, & tail DNA% among exposed compared to referents	Polymorphisms in XRCC1 and Arg399Gln associated with Cr-induced DNA damage SNP genotyping for DNA repair genes: XRCC1 Arg399Gln, XRCC1Arg194Trp,ERCC 1 C8092A, ERCC5 His1104Asp, ERCC6 Gly399Asp, GSTP1Ile105Val, OGG1 Ser326Cys, XPC Lys939Gln, XPDLys751Gln. Limited adjustment for confounders (including diet). Potential coexposures to other metals in the workplace.	Zhang et al. (2012)

[a]Discrepancy between table and text in the original publication. Values from text noted above; values from table reported as 23.8 (7.0) years.

Carriers of the cystic fibrosis mutant allele

Cystic fibrosis is an inherited autosomal recessive disorder caused by inactivating mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which codes for the CFTR anion channel protein. CFTR regulates the secretion of chloride and bicarbonate. Loss of CFTR function causes abnormal mucus production, which affects every organ in the body, particularly the lung and GI tract (De Boeck, 2020). Cystic fibrosis patients have a higher risk of developing colorectal cancer (Miller et al., 2020; Scott et al., 2020). Tumor suppressor status of the CFTR gene has been suggested based on the results of epidemiological, clinical, and experimental studies (reviewed in Zhang et al. (2018)). In a mouse model with an intestinal-specific CFTR gene knock-out, Than et al. (2016) demonstrated that CFTR-deficient mice have a significantly increased risk of development of tumors in the colon and small intestines. In addition, the loss of CFTR activity was shown to enhance intestinal tumorigenesis in ApcMin mice that carry mutated tumor-suppressor gene adenomatous polyposis coli (APC). These findings demonstrate that impairment of CFTR leads to tumorigenesis in the mouse small intestine.

The analyses by Mezencev and Auerbach (2021) (see C.3.13.2) of the toxicogenomic data reported in Kopec et al. (2012b; 2012a) from mice exposed to Cr(VI) have identified a potential role for CFTR in the carcinogenic effects of Cr(VI). These data indicate that CFTR was inactivated in mice exposed to Cr(VI) levels as low as 0.1 mg/L in drinking water for 8 days. This inactivation does not appear to be attributable to tissue damage, which was observed in these animals following

subchronic exposure to Cr(VI) concentrations ≥60 mg/L (Thompson et al., 2011b). Therefore, suppression of CFTR activity might represent an effect of Cr(VI) exposure that contributes to the carcinogenic process.

Tumorigenicity of impaired CFTR activity in animal models supports the relevance of the Cr(VI)-mediated inactivation of CFTR for the development of small intestinal tumors in mice exposed to Cr(VI) in drinking water. These findings indicate the identification of vulnerable groups, such as APC mutation carriers and carriers of the mutated CFTR allele, that can be more sensitive to the Cr(VI)-mediated carcinogenicity. This reasoning likely extends to humans, because (1) CFTR reportedly acts as a tumor-suppressor in human colon (Than et al., 2016) and (2) germline mutations in the APC gene or its regulatory sequences are known to cause familial adenomatous polyposis (FAP) in humans. FAP is associated with high risk of colon cancer and increased risk of cancers at other sites, including the duodenum, thyroid gland, and stomach (Jasperson et al., 2017; Leoz et al., 2015).

In the United States alone, more than 10 million people are carriers of a mutated CFTR allele that confers an approximate 50% reduction in CFTR expression levels. Although these individuals do not develop cystic fibrosis, the deficit in CFTR function has been shown to lead to an increased risk for several conditions associated with the disease, including colorectal cancer (OR = 1.44, 95% CI: 1.01–2.05) (Miller et al., 2020). CFTR suppression induced by low Cr(VI) exposures in drinking water can be expected to occur in all exposed populations, but a more significant effect would be expected in humans already producing low levels of this protein. Moreover, enhancement of tumorigenicity of the APC mutations by CFTR inactivation implies that carriers of these mutations might be more susceptible to the tumorigenicity induced by events that inactivate CFTR, including Cr(VI) exposure. Based on the analogy with the ApcMin mice study, humans affected by germline APC mutations can be reasonably expected to be more vulnerable to carcinogenicity mediated by Cr(VI) or other toxicants that can inactivate CFTR.

C.4. SUPPORTING EVIDENCE FOR EXPOSURE TO THE GENERAL POPULATION

C.4.1. Drinking Water Data from the Third Unregulated Contaminant Monitoring Rule

Cr(VI) was among 30 contaminants selected for monitoring at public water systems (PWS) for the Third Unregulated Contaminant Monitoring Rule (UCMR3) between 2013 and 2015. A PWS is a network of pipes and conveyances constructed to provide water for human consumption (U.S. EPA, 2006a, b). Small systems, serving 10,000 or fewer people, account for more than 97% of the total number of PWSs, while large systems, serving more than 10,000 people, account for the remaining 3% (U.S. EPA, 2006a, b). A majority of the U.S. population is served by large PWSs (nearly 90% (U.S. EPA, 2006a, b)), and all of them (approximately 4,200) were tested under UCMR3. For small water systems, approximately 800 systems were randomly selected and used as a representative sample (U.S. EPA, 2012b). Small water systems were omitted from analyses presented in this section. Although most of the public water systems in the United States have reported Cr(VI) concentrations below 1 µg/L, the highest concentrations have approached the MCL (for total chromium) of 100 µg/L. This is 50 times lower than the lowest concentration used in the NTP (2008) bioassay (5 mg/L = 5,000 µg/L). When converting to dose, the lowest doses in rats and mice were 0.2 mg/kg-day and 0.3 mg/kg-day, respectively. By $BW^{3/4}$ scaling,[6] this would adjust to 0.057 mg/kg-day human equivalent dose for rats and 0.05 mg/kg-day for mice. A standard 70-kg reference human ingesting 2 liters of water/day at 100 µg/L (0.05 mg/L) would ingest a Cr(VI) dose of 0.0029 mg/kg-day. Therefore, the lowest NTP doses are approximately 20 times higher than a potential human drinking water dose at 100 µg/L. This is only an illustrative comparison and does not account for differences in Cr(VI) reduction.

Table C-66. Statistical summary of UCMR3 chromium (VI) concentrations in large public water systems (PWS)

Parameter (units)	Statistic[a]
Total number of facilities reporting	3,927
Number of facilities >MRL	3,573
Number of measurements	45,712
Average PWS mean (µg/L)	0.485
Maximum PWS mean (µg/L)	42.31
Maximum measured value (µg/L)	97.38
25th %tile of PWS means (µg/L)	0.0413
50th %tile of PWS means (µg/L)	0.0963
75th %tile of PWS means (µg/L)	0.229

[6]Assuming rat BW of 0.45 kg, mouse BW of 0.05 kg (based on study-specific data), and human BW of 70 kg.

Parameter (units)	Statistic[a]
95th %tile of PWS means (µg/L)	1.87
Standard deviation of PWS means (µg/L)	1.84

[a]Data below the minimum reporting level (MRL, 0.03 µg/L) are included as ½ the MRL in calculations. Data are from the posted January 2017 release of the EPA Third Unregulated Contaminant Monitoring Rule (UCMR3) (U.S. EPA, 2014c). Only data collected for large PWSs were used for statistical analysis. Statistics performed on the mean PWS values (each PWS had multiple facilities that collected multiple samples).

Table C-67. Summary of UCMR3 chromium (VI) concentration data (in µg/L) grouped by EPA region

Region	Count	Mean	Max	Percentiles			
				25th	50th	75th	95th
1	237	0.131	3.80	0.0359	0.0647	0.128	0.420
2	351	0.281	23.0	0.0432	0.0829	0.239	0.709
3	282	0.165	1.47	0.0502	0.0899	0.189	0.513
4	905	0.124	2.42	0.0364	0.0692	0.133	0.365
5	748	0.206	3.31	0.0265	0.126	0.199	0.751
6	432	0.521	42.3	0.0238	0.0561	0.157	1.77
7	132	0.693	3.16	0.0475	0.277	1.19	2.35
8	162	0.273	1.99	0.0444	0.151	0.381	0.898
9	519	2.050	30.5	0.126	0.586	1.96	8.89
10	159	0.230	1.42	0.0719	0.142	0.274	0.750

Data below the minimum reporting level (MRL, 0.03 µg/L) are included as ½ the MRL in calculations. Data are from the posted January 2017 release of the EPA Third Unregulated Contaminant Monitoring Rule (UCMR3) (U.S. EPA, 2014c). Only data for large PWSs were used for statistical analysis.

Table C-68. Summary of UCMR3 Cr(VI) data for 20 large public water systems with the highest mean concentrations

PWSID	Location	PWSID Name	Mean (µg/L)	Max. (µg/L)	n
OK1020801	OK	Norman	42.3	97.4	80
CA2410005	CA	City of Los Banos	30.5	38.0	8
AZ0407154	AZ	Town of Buckeye Sundance	28.8	33.0	8
AZ0407056	AZ	AZ American Water Co. – Paradise Valley	28.0	30.1	4
AZ0408020	AZ	Kingman Municipal Water	25.6	79.0	24
AZ0407500	AZ	City of Surprise – Mountain Vista	23.9	39.0	16
PR0004074	PR	Guanica Urbano	23.0	26.3	11
CA1010018	CA	City of Kerman	19.4	31.0	16

PWSID	Location	PWSID Name	Mean (µg/L)	Max. (µg/L)	n
AZ0407078	AZ	Valencia Water Co. – Town Division	18.9	22.0	15
CA5010017	CA	City of Patterson	18.2	22.0	12
CA5710006	CA	City of Woodland	17.7	26.0	22
CA5710009	CA	University of California – Davis	17.5	47.0	16
OK2001412	OK	Moore	17.5	54.0	47
OK2000922	OK	Mustang	15.7	29.9	12
CA3310007	CA	City of Coachella	15.6	19.0	16
AZ0407695	AZ	AZ American Water Co. – Agua Fria	15.0	62.0	56
AZ0407094	AZ	Goodyear Water Department	14.4	27.0	20
CA5710001	CA	City of Davis	14.0	41.0	32
CA3310020	CA	Indio Water Authority	13.0	19.0	20
AZ0407025	AZ	City of Phoenix	12.8	54.0	80
				Total n =	515

Data below the minimum reporting level (MRL, 0.03 µg/L) are included as ½ the MRL in calculations. Data are from the posted January 2017 release of the EPA Third Unregulated Contaminant Monitoring Rule (UCMR3) (U.S. EPA, 2014c). Only data collected for large PWSs were used for statistical analysis.

C.4.2. Local Data of Air, Soil, and Dust Cr(VI) Concentrations

Because Cr(VI) is classified as a hazardous air pollutant under the Clean Air Act, data for air, dust, and soil are available from state and local environmental departments. Tables C-69 through C-73 list datasets from publicly available sources that were found by screening national, state, and local environmental department websites. These datasets are not from EPA sources, and values are subject to change. Readers are advised to consult the citations and the state websites for the raw data, and detailed information related to data collection and interpretation. This is not an exhaustive summary of all air, dust, and soil Cr(VI) and total chromium (Cr(VI)+Cr(III)) concentrations in the United States.

Table C-69. Cr(VI) concentrations in ambient PM_{10} (ng/m^3) at monitoring sites in Midlothian, Texas containing three cement manufacturing facilities and a steel mill (ATSDR, 2016)

Location	Mean (confidence interval)
Jaycee Park	0.016 (0.0094–0.024)
Old Fort Worth Road	0.055 (0.029–0.086)
Tayman Drive	0.018 (0.0097–0.035)
Wyatt Road	0.07 (0.037–0.12)

Location	Mean (confidence interval)
JA Vitovsky	0.021 (max)[a]
Midlothian HS	0.039 (max)[a]
Mountain Peak Elementary	0.039 (max)[a]

[a]Maximum value reported only (descriptive statistics not generated by TCEQ because of the small number of observations).

Table C-70. Cr(VI) concentrations in air measured at monitoring sites in Portland Oregon reporting elevated metals concentrations (Oregon DEQ, 2016b)

Location	Date	Mean ± SD[a] (ng/m^3)	Min	Max
Metal finishing site (Southeast Portland)				
Milwaukie Johnson Creek	April–Sept 2016	0.321 ± 0.239	0.047	1.16
SE Harney Dr.	April–Dec 2016	0.121 ± 0.118	0.038	1.01
SE 45th Ave & SE Harney	March 2016–March 2017	0.0707 ± 0.0501	0.035	0.44
Glass producer site (Northeast Portland)				
Daycare Center	March 2016–Feb 2017	0.201 ± 0.332	0.037	3.63
Winterhaven Elementary	March–Sept 2016	0.0759 ± 0.0604	0.037	0.695
Powell & SE 22nd	March 2017	0.147 ± 0.247	0.036	3.1
Haig & SE 20th	March 2017	0.129 ± 0.316	0.038	2.88
Reed College	May–Sept 2016	0.095 ± 0.0374	0.038	0.209
Glass producer site (North Portland)				
Tubman School	March–Aug 2016	0.0625 ± 0.0338	0.037	0.222
Portland North Coast Electric	March–July 2016	0.0993 ± 0.112	0.036	0.655
Portland Water Bureau East	March–Aug 2016	0.118 ± 0.0979	0.038	0.6
Portland Water Bureau West	March–July 2016	0.102 ± 0.0568	0.04	0.271

[a]Average daily value as reported by Oregon Department of Environmental Quality, applying the Kaplan-Meir method for nondetects.

Table C-71. Cr(VI) concentrations (mean ± SD in ng/m^3) in ambient PM_{10} measured in urban and suburban New Jersey (Huang et al., 2014)

Location	Soluble Cr(VI)		Total Cr(VI)	
	Summer	Winter	Summer	Winter
Meadowlands	0.3 ± 0.16	0.11 ± 0.04	1.25 ± 0.58	1.32 ± 0.56
Elizabeth	0.21 ± 0.13	0.19 ± 0.09	1.56 ± 0.48	1.41 ± 0.56
Rahway	0.33 ± 0.36	0.14 ± 0.07	0.99 ± 0.76	1.05 ± 0.36

Location	Soluble Cr(VI)		Total Cr(VI)	
	Summer	Winter	Summer	Winter
Piscataway[a]	0.2 ± 0.18	0.03 ± 0.01	0.86 ± 0.5	0.94 ± 0.49

[a]Suburban (all other locations urban).

Table C-72. Cr(VI) Mean concentration in air districts with chromium plating and anodizing facilities for the year 2005. Data from the California Air Resources Board.

District	Monitoring site	Mean concentration (ng/m^3)
South Coast Air Quality Management District	Azusa-803 Loren Ave.	0.08
	Burbank – W. Palm Ave.	0.113
	North Long Beach	0.10
San Diego County Air Pollution Control District	Chula Vista	0.038
	El Cajon-Redwood Avenue	0.048
Ventura County Air Pollution Control District	Simi Valley-Cochran Street	0.05
Bay Area Air Quality Management District	Fremont-Chapel Way	0.05
	San Francisco-Arkansas Street	0.11
San Joaquin Valley Air Pollution Control District	Fresno-1st Street	0.063
	Stockton-Hazelton Street	0.12
Sacramento Metropolitan Air Quality Management District	Roseville-N Sunrise Blvd	0.058

Adapted from CARB (2006).

Table C-73. Estimated environmental concentrations of chromium in selected locations within the United States

Media and location	Units[a]	Mean	Max.	Reference
Ambient air, Barrio Logan San Diego CA	ng/m^3	0.42	22.0	Residential areas near facilities potentially emitting Cr(VI) from California EPA (CalEPA, 2004, 2003) (May 2001–May 2002)
Ambient air, Portland OR glass and metal sites	ng/m^3	N/A	3.63	Elevated metals site data from Oregon DEQ (Oregon DEQ, 2016b). See Table 5
Ambient PM_{10}, Deer Park and Karnack, Texas	ng/m^3	0.1	0.4[b]	24-h average data from TCEQ (2006–2013) (TCEQ, 2017)
Ambient PM_{10}; soluble+ insoluble Cr(VI), New Jersey	ng/m^3	1.17	1.56	Urban and suburban areas of New Jersey (Huang et al., 2014)
Ambient PM_{10}; soluble Cr(VI), New Jersey	ng/m^3	0.189	0.33	
Surface soil, Portland OR glass and metal sites	mg/kg Cr(VI)	N/A	3.0	Data from Oregon DEQ (Oregon DEQ, 2016a, c)
	mg/kg total chromium	N/A	63	
	mg/kg Cr(III)	19.5	130	

Media and location	Units[a]	Mean	Max.	Reference
Background (bulk soil), Montana	mg/kg Cr(VI)	N/A[c]	1.2	Data from Montana DEQ (Hydrometrics, 2013)
House dust, New Jersey	µg/g	4.6	56.6	Background house dust in NJ (Stern et al., 2010) (µg/m^2 are surface loading units)
	µg/m^2	10	169.3	

[a]Units of Cr(VI) unless otherwise noted.
[b]Maximum highest and second-highest hourly measurements are 1.9 and 0.7 ng/m^3, respectively.
[c]88% of values below the limit of detection (<0.29 mg/kg).

APPENDIX D. DOSE-RESPONSE MODELING

This appendix provides technical detail on dose-response evaluation and determination of points of departure (PODs) for relevant toxicological endpoints. Figure D-1 provides an overview of the process of RfD/RfC derivation. The endpoints were modeled using EPA's Benchmark Dose Software (BMDS, Version 3.2). Sections D.1 (noncancer) and D.2 (cancer) describe the common practices used in evaluating the model fit and selecting the appropriate model for determining the POD, as outlined in the *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012a). Logfiles of BMD model outputs are contained in U.S. EPA (2021a).

Some statistical models (Gamma, dichotomous Hill, Weibull, and log-logistic) were run with constrained slope or power parameters (≥1) (U.S. EPA, 2012a). As noted in the Benchmark Dose Software (BMDS) version 3.2 user guide (U.S. EPA, 2020a), some models with unrestricted coefficients can give complicated shapes, in particular for high-degree polynomial models (which produce unrealistic "wavy" results with negative response rates). Although Bayesian model averaging is an available feature of BMDS 3.2, only frequentist models were run in this assessment.

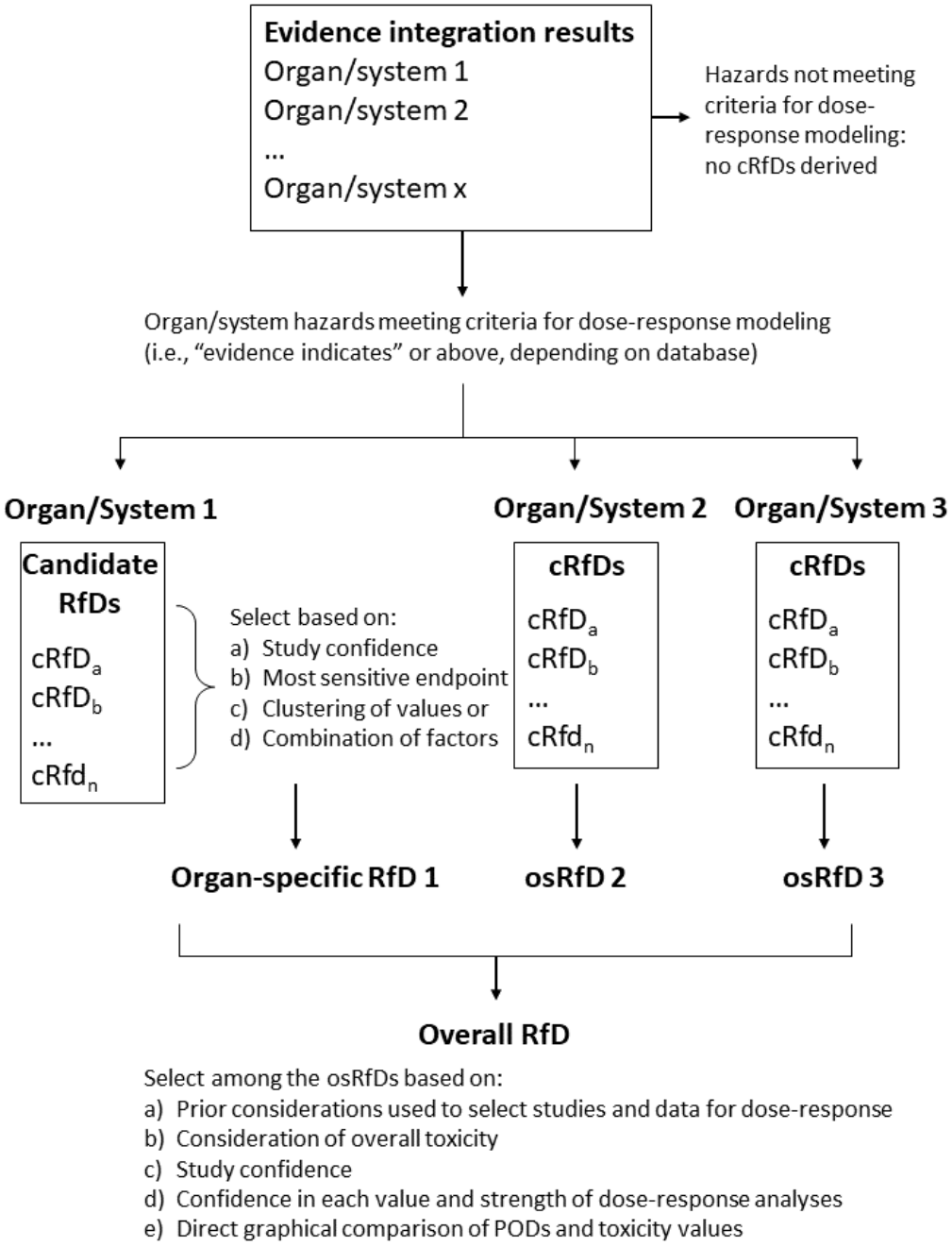

Figure D-1. Overview of the process for deriving candidate, organ-specific, and overall RfDs (process also applicable to RfCs).

D.1. BENCHMARK DOSE MODELING SUMMARY FOR NONCANCER ENDPOINTS

For this assessment, dose-response modeling of endpoints for the oral route of exposure was performed based on the time-weighted average daily dose of Cr(VI), in mg/kg-day. This value could then be converted to an internal rodent dose, depending on the tissue or endpoint. The time-weighted average was calculated based on time-course dose data available through the data collection time for each endpoint. For example, for endpoints measured at 12 months in the NTP (2008) study, the time-weighted average daily dose over 12 months was applied, as opposed to the average daily dose over the full 2-year bioassay.

For dose-response modeling of endpoints for the inhalation route, inhaled concentration was used. Adjustments for respiratory-tract particle dosimetry and 24-hour/day time conversion were performed during the interspecies extrapolation step.

The noncancer endpoints selected for dose-response modeling are presented in Tables D-1 through D-3 (oral) and Table D-4 (inhalation). For each endpoint, the exposure doses and data used for the modeling are presented.

Table D-1. Noncancer endpoints selected for dose-response modeling for Cr(VI) (oral) from NTP (2008)

Species/sex endpoint	Doses and effect data					
Mouse/Male	**Cr(VI) mg/L**	**0**	**5**	**10**	**30**	**90**
	TWA dose mg/kg-d	**0**	**0.450**	**0.914**	**2.40**	**5.70**
Diffuse epithelial hyperplasia (duodenum) at lifetime	Incidence /Total	0/39	11/43	18/45	42/48	32/40
Mouse/Female	**Cr(VI) mg/L**	**0**	**5**	**20**	**60**	**180**
	TWA dose mg/kg-d	**0**	**0.302**	**1.18**	**3.24**	**8.89**
Diffuse epithelial hyperplasia (duodenum) at lifetime	Incidence /Total	0/42	16/42	35/48	31/42	42/48
Chronic inflammation (liver) at lifetime	Incidence/Total	16/49	21/50	22/50	27/50	24/50
Rat/Female	**Cr(VI) mg/L**	**0**	**5**	**20**	**60**	**180**
	TWA dose mg/kg-d	**0**	**0.248**	**0.961**	**2.60**	**7.13**
Fatty change (liver) at lifetime	Incidence /Total	3/50	7/50	10/50	13/50	16/50
Chronic inflammation (liver) at lifetime	Incidence /Total	12/50	21/50	28/50	35/50	39/50

Species/sex endpoint	Doses and effect data					
Rat/Male	**Cr(VI) mg/L**	**0**	**5**	**20**	**60**	**180**
	TWA dose mg/kg-d (lifetime)	**0**	**0.200**	**0.796**	**2.10**	**6.07**
	TWA dose mg/kg-d (12 mo)	**0**	**0.237**	**0.938**	**2.49**	**7.19**
	TWA dose mg/kg-d (3 mo)	**0**	**0.401**	**1.58**	**4.16**	**11.7**
Chronic Inflammation (liver) at lifetime	Incidence/Total	19/50	25/50	21/49	28/50[a]	26/49
ALT (liver) at 12 mo.	IU/L ± SE, n = 10/group	102 ± 6	107 ± 8	135 ± 10	261 ± 23	223 ± 15
ALT (liver) at 3 mo.	IU/L ± SE, n = 10/group	82 ± 4	82 ± 12	135 ± 18	176 ± 13	216 ± 21
Rat/Male	**N**	**10**	**10**	**10**	**8**	**10**
	TWA dose mg/kg-d (12 mo)	**0**	**0.237**	**0.938**	**2.49**	**7.19**
Hematological changes at 12 mo.	RBC (10^6/µL, mean ± SE)	9.27 ± 0.10	9.17 ± 0.07	9.4 ± 0.12	9.61 ± 0.11	9.74 ± 0.08
	MCV (fL, mean ± SE)	52.6 ± 0.2	52.4 ± 0.2	51.9 ± 0.3	51.4 ± 0.3	49.9 ± 0.2
	MCH (pg, mean ± SE)	17 ± 0.1	16.8 ± 0.1	16.6 ± 0.1	16.2 ± 0.1	15.7 ± 0.1
	MCHC (mean ± SE)	32.3 ± 0.2	32.1 ± 0.3	32.0 ± 0.2	31.6 ± 0.2	31.5 ± 0.2
	Hgb (mean ± SE, g/dL)	15.8 ± 0.2	15.4 ± 0.2	15.6 ± 0.2	15.6 ± 0.2	15.3 ± 0.1
Hematological changes at 90d.	N	10	10	10	10	10
	TWA Dose mg/kg-d (90 d)	0	0.401	1.58	4.16	11.7
	Hgb (mean ± SE, g/dL)	15.1 ± 0.1	14.9 ± 0.1	14.9 ± 0.2	14.6 ± 0.2	12.9 ± 0.2
Hematological changes at 22d.	N	10	10	10	10	10
	TWA Dose mg/kg-d (22 d)	0	0.634	2.49	6.67	17.7
	Hgb (mean ± SE, g/dL)	15.5 ± 0.3	15.1 ± 0.2	14.2 ± 0.2	12.0 ± 0.3	10.1 ± 0.2

[a]Revised estimates for time weighted average daily doses calculated from NTP data. These may differ from the average doses presented elsewhere in this toxicological review, which are typically rounded or based on averages of fewer timepoints.

Table D-2. Noncancer endpoints selected for dose-response modeling for Cr(VI) (oral) from NTP (2007f)

Species/Sex endpoint	Doses and effect data						
Rat/Female	**N**	**10**	**10**	**10**	**10**	**10**	**10**
	Cr(VI) mg/L	**0**	**20**	**40**	**90**	**170**	**350**
Liver changes at 90 d	**TWA dose mg/kg-d[a]**	0	1.7	3.5	5.9	11.2	20.9
	ALT (mean ± SE, IU/L)	64 ± 5	437 ± 68	218 ± 27	245 ± 30	246 ± 37	248 ± 22
Rat/Male	**N**	**8**	**10**	**10**	**10**	**10**	**10**
	Cr(VI) mg/L	**0**	**20**	**40**	**90**	**170**	**350**
Liver changes at 90 d	**TWA dose mg/kg-d[a]**	0	1.7	3.5	5.9	11.2	20.9
	ALT (mean ± SE, IU/L)	98 ± 6	274 ± 30	461 ± 102	447 ± 121	740 ± 81	191 ± 17
Rat/Male	**N**	**10**	**10**	**10**	**10**	**10**	**10**
	TWA dose mg/kg-d[a]	**0**	**1.7**	**3.5**	**5.9**	**11.2**	**20.9**
Hematological changes at 90 d	Hgb (mean ± SE, g/dL)	15.3 ± 0.1	15.2 ± 0.1	15.0 ± 0.1	14.4 ± 0.2	13.3 ± 0.2	10.9 ± 0.3
Rat/Male	**N**	**10**	**10**	**10**	**10**	**10**	**10**
	TWA dose mg/kg-d	**0**	**2.92**	**5.55**	**10.3**	**18.3**	**30.6**
Hematological changes at 23 d	Hgb (mean ± SE, g/dL)	15.9 ± 0.1	14.2 ± 0.2	12.0 ± 0.3	10.9 ± 0.3	10.3 ± 0.3	9.2 ± 0.3
Rat/Female	**N**	**10**	**10**	**10**	**10**	**10**	**10**
	TWA dose mg/kg-d[a]	**0**	**1.7**	**3.5**	**5.9**	**11.2**	**20.9**
Hematological changes at 90 d	Hgb (mean ± SE, g/dL)	15.2 ± 0.1	15.4 ± 0.1	14.9 ± 0.1	14.3 ± 0.1	14.1 ± 0.2	12.0 ± 0.2
Rat/Female	**N**	**10**	**9**	**8**	**9**	**10**	**9**
	TWA dose mg/kg-d	**0**	**2.97**	**5.56**	**9.83**	**17.7**	**30.9**
Hematological changes at 23 d	Hgb (mean ± SE, g/dL)	15.9 ± 0.1	14.7 ± 0.3	13.0 ± 0.3	11.8 ± 0.3	10.9 ± 0.2	9.7 ± 0.2

[a]These are the values for both males and females at 14 weeks provided by NTP (2007f). Alternatively, slightly different doses in mg/kg-d may be estimated from the NTP data: 1.74, 3.14, 5.93, 11.2, 20.9 for males, and 1.74, 3.49, 6.28, 11.5, 21.3 for females. For this assessment, the average value was applied to both male and female rats at 14 weeks. For data at 23 days, NTP did not provide time weighted average doses, so they were estimated from raw data. Sex-specific doses at 23 days are listed because they differ greatly at high drinking water concentration.

Table D-3. Noncancer endpoints selected for dose-response modeling for Cr(VI) (oral) from NTP (1997)

Species/Sex endpoint	Doses and effect data				
Mouse/Female	**TWA dose mg/kg-d**	**0**	**11.6**	**24.4**	**50.6**
F1 male pups PND14	Pup weight g ± SE (N litters)	7.95 ± 0.50 (15)	7.69 ± 0.36 (13)	7.51 ± 0.48 (12)	6.93 ± 0.27 (16)
F1 male pups PND21		9.38 ± 0.64 (15)	8.52 ± 0.59 (14)	8.66 ± 0.63 (12)	7.94 ± 0.34 (16)
F1 female pups PND14		7.71 ± 0.38 (15)	7.85 ± 0.36 (15)	8.05 ± 0.53 (13)	7.04 ± 0.33 (18)
F1 female pups PND21		9.03 ± 0.55 (15)	8.77 ± 0.55 (16)	9.01 ± 0.68 (13)	8.17 ± 0.42 (18)

TWA dose is for the female F0 (maternal) generation.

Table D-4. Noncancer endpoints selected for dose-response modeling for Cr(VI) (inhalation)

Species/Sex endpoint	Doses and effect data					
Glaser et al. (1990) (n = 10/group)						
	Concentration (mg/m^3 Cr(VI))	0	0.054	0.109	0.204	0.403
90 d, no recovery						
Lactate dehydrogenase (LDH) in BAL fluid	(U/L) mean ± SD	29 ± 5	34 ± 3	31 ± 4	63 ± 11	83 ± 17
Albumin in BALF	(mg/L) mean ± SD	77 ± 13	115 ± 23	86 ± 13	117 ± 20	184 ± 59
Total protein in BALF	(mg/L) mean ± SD	226 ± 30	396 ± 79	326 ± 35	703 ± 178	975 ± 246
Histiocytosis	Incidence	2/10	9/10	10/10	9/10	10/10

Note: Nominal/target inhalation concentrations were replaced with the reported mean concentrations measured in the studies.

D.1.1. Evaluation of Model Fit and Model Selection

Basic statistical background and guidance on choosing a model structure for the data being analyzed, fitting models, comparing models, and calculating confidence limits to derive a BMDL to use as a POD are outlined in EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012a), Sections 2.3.9 and 2.5. Empirical models that provide the best fit to the dose-response data are typically used in the absence of data to support development of a biologically based model. Although these models are empirical, parameters are typically constrained on some of them for the purposes of strengthening the biological plausibility of the results (i.e., many toxic effects exhibit a monotonic dose-response), and to prevent imprecise BMDs/BMDLs resulting from steeply supralinear models [(U.S. EPA, 2012a) §2.3.3.3]. Consistent with EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012a), initial runs of the log-probit model did not constrain the slope parameter, whereas initial runs of the gamma, dichotomous Hill, Weibull, and log-logistic models constrained their slope or power parameters to be ≥1. As noted in *Benchmark Dose Software (BMDS) Version 3.2 User Guide*

(U.S. EPA, 2020a), some models with unrestricted coefficients can give more complicated shapes, in particular high-degree polynomial models (which produce unrealistic "wavy" results with negative response rates).

For each candidate endpoint/study the following steps were taken:

1) Goodness-of-fit was assessed for all models [(U.S. EPA, 2012a) §2.3.5].

   a. Models having a goodness-of-fit *p*-value of less than 0.1 were rejected.[7]

   b. Models not adequately describing the dose-response relationship (especially in the low-dose region) were rejected on the basis of examining the dose group-scaled residuals[8] and graphs of models and data.

The models that remained (after rejecting those that did not meet the recommended default statistical criteria for adequacy and fail in visual inspection of model fit) were used for determining the BMDL. The default selection criteria are listed below [(U.S. EPA, 2012a) §2.3.9]:

2) If the BMDL estimates from the remaining models were sufficiently close (generally defined as being within threefold, as in the case of this assessment), it was assumed there was no particular influence of the individual models on the estimates. In this case, the model with the lowest AIC was chosen.

3) If the BMDL estimates from the remaining models were not sufficiently close, it was assumed there was some model dependence (i.e., model uncertainty) of the estimate. In this case, if there was no clear remaining biological or statistical basis on which to choose among them, the lowest BMDL was selected as a reasonable conservative estimate (U.S. EPA (2012a) Section 2.3.9).

4) In some cases, modeling attempts did not yield useful results. When this occurred, the NOAEL (or LOAEL) was used as a candidate POD.

Logfiles of BMD model outputs are contained in U.S. EPA (2021a).

D.1.1.1. *Modeling issues related to diffuse epithelial hyperplasia in mice*

Benchmark dose modeling did not result in useful results for diffuse epithelial hyperplasia in female mice from NTP (2008). Using BMDS (v 3.2), three models fit the full dataset adequately (based on goodness-of-fit *p*-value ≥ 0.10): dichotomous Hill, log-logistic, and log-probit. However,

[7]For the $\chi 2$ goodness-of-fit test and a *p*-value of α, the critical value is the $1-\alpha$ percentile of the $\chi 2$ distribution at the appropriate degrees of freedom. Models are rejected if there are large values of $\chi 2$ corresponding to *p*-values less than 0.1, the limiting probability of a Type I error (false positive) selected for this purpose.
[8]Scaled residuals reported by BMDS for dichotomous responses are defined as (Observed − Expected)/SE, where "Expected" is the predicted number of responders and SE equals the estimated standard error of that predicted number. For dichotomous models, the estimated standard error is equal to $\sqrt{[n \times p \times (1-p)]}$, where n is the sample size and *p* is the model-predicted probability of response. Model fit is considered questionable if the scaled residual value for any dose group, particularly the control or low dose group, is greater than 2 or less than −2.

the log-probit model yielded a very low BMDL (150 times lower than the lowest nonzero dose of 0.302 mg/kg-day). Because the model fit was adequate compared to the other two models, it could not be excluded from model selection. The residuals for the log-probit result were sufficiently low, and its AIC was between that of the other two models (see below). Changing model parameter restrictions did not resolve the issue. It was concluded, based on the criteria outlined above in Section D.1.1, that there was too much uncertainty in the BMD estimate to use these model results for determining the POD.

Table D-5. BMD model results for diffuse epithelial hyperplasia in female mice from NTP (2008) (no high doses omitted)

Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	Goodness-of-fit *p*-value	AIC
Log-logistic	10% ER	0.0722	0.0530	0.1145	205.07
Log-probit	10% ER	0.0199	0.00199	0.3043	204.80
Dichotomous Hill	10% ER	0.0561	0.0268	0.4132	204.08

The lowest dose for female mice is 0.302 mg/kg-d.

The primary reason for the high uncertainty on the BMD estimate is that the response rate (38%) at the lowest dose was much higher than the BMR of 10% ER (the control group had 0% response). In addition, the data are supralinear and plateau at the three high doses (as the incidence approaches 100%).

Dropping high doses can address the supralinear shape and high-dose effect, to achieve adequate model fit in the response region of interest. In this case, dropping the highest dose does not resolve the issue because the three high doses exhibit a flat response. However, omitting the two highest doses can achieve an optimal model fit within the set of models run (see below).

Table D-6. Modeling alternatives for diffuse epithelial hyperplasia in mice from NTP (2008)

Species/Sex	Model	Doses dropped	BMR	BMD mg/kg-d	BMDL mg/kg-d
Mice/M	Quantal-linear	1	10% ER	0.148	0.121
Mice/F	Log-logistic	0	10% ER	0.0722	0.0530
	Dichotomous Hill	0	10% ER	0.0561	0.0268
	Log-probit	0	10% ER	0.0199	0.00199
	Quantal-linear	2	10% ER	0.0852	0.0672
	LOAEL	--	--	LOAEL = 0.302	LOAEL/10 = 0.0302

The lowest dose for female mice is 0.302 mg/kg-d.

Other approaches to address the modeling issues for this dataset include increasing the BMR to be closer to the lowest observed response rate (which would decrease the uncertainty on the BMD) or attempting alternative modeling (such as Bayesian model averaging). Other statistical issues can arise when implementing these approaches (e.g., an additional uncertainty adjustment would be needed when increasing the BMR).

As shown in the table above, the LOAEL divided by a $UF_L = 10$ (the LOAEL-to-NOAEL uncertainty factor) produces a reasonable result when compared to the alternative BMDLs. The value (0.0302 mg/kg-day) is within the bounds of the alternatives (significantly higher than log-probit, 13% higher than dichotomous Hill, and 43% lower than log-logistic).

Because the response rate is high at the lowest dose, and there are no data near the true 10% response rate, there is high uncertainty in estimating the lower 95% confidence limit on the BMD_{10}.

Table D-7. RfDs for modeling alternatives of diffuse epithelial hyperplasia in mice from NTP (2008)

Species/Sex	Model	Doses dropped	BMR	BMDL or LOAEL mg/kg-d	Internal dose mg/kg-d	TWA BW kg	$BW^{3/4}$ adjust	POD_{HED} mg/kg-d	Composite UF	RfD mg/kg-d
Mice/M	Quantal-linear	1	10% ER	0.121	0.0182	0.05	2.88×10^{-3}	0.0443	10	4.43×10^{-3}
Mice/F	Log-logistic	0	10% ER	0.0530	0.00792	0.05	1.25×10^{-3}	0.0204	10	2.04×10^{-3}
	Dichotomous Hill	0	10% ER	0.0268	0.00400	0.05	6.32×10^{-4}	0.0106	10	1.06×10^{-3}
	Log-probit	0	10% ER	0.00199	0.000296	0.05	4.68×10^{-5}	7.95×10^{-4}	10	7.95×10^{-5}
	Quantal-linear	2	10% ER	0.0672	0.0101	0.05	$1.60e \times 10^{-3}$	0.0258	10	2.58×10^{-3}
	LOAEL	--	--	0.302	0.0463	0.05	7.32×10^{-3}	0.0911	100	9.11×10^{-4}

Mean and median value of log-logistic, log-probit, and dichotomous Hill results (with 0 dosses dropped) is 1.06×10^{-3} mg/kg-d.

D.1.1.2. *Modeling issues related to chronic liver inflammation in female rats*

An issue similar to that described above for hyperplasia also applied to data for chronic liver inflammation in female rats. Three adequately fitting models produced very different results, with one of them producing a BMDL that was over 75 times lower than the lowest dose.

Table D-8. BMD model results for chronic liver inflammation in female rats from NTP (2008)

Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	Goodness-of-fit *p*-value	AIC
Log-logistic	10% ER	0.232	0.142	0.3871	312.44
Log-probit	10% ER	0.0546	0.00325	0.943	311.63
Dichotomous Hill	10% ER	0.107	0.0424	0.8962	311.73

The lowest dose in female rats was 0.248 mg/kg-d.

As with female mouse hyperplasia, there was too much uncertainty in the BMD estimate to use these model results for determining the POD. As a result, it was determined that this dataset was not amenable to BMD modeling, and the lowest dose was chosen as the LOAEL (greater than 10% extra risk from control occurred at this level).

Table D-9. RfDs for modeling alternatives of chronic liver inflammation in female rats from NTP (2008)

Model	BMR	BMDL or LOAEL mg/kg-d	Internal dose mg/kg-d	TWA BW kg	$BW^{3/4}$ adjust	POD_{HED} mg/kg-d	Composite UF	RfD mg/kg-d
Log-logistic	10% ER	0.142	0.0109	0.260	2.60×10^{-3}	0.0402	10	4.02×10^{-3}
Log-probit	10% ER	0.00325	2.43×10^{-4}	0.260	5.80×10^{-5}	9.97×10^{-4}	10	9.97×10^{-5}
Dichotomous Hill	10% ER	0.0424	3.20×10^{-3}	0.260	7.64×10^{-4}	0.0128	10	1.28×10^{-3}
LOAEL	--	0.248	0.0195	0.260	4.66×10^{-3}	0.0669	100	6.69×10^{-4}

D.1.1.3. *Modeling issues related to liver fatty changes in female rats*

As shown in the table below, all models achieved an adequate fit. Dichotomous Hill and log-probit results were significantly different than the others. The model fits were adequate compared to the other models, and they could not be excluded from model selection. The log-probit BMDL was over 130 times lower than the lowest dose.

Table D-10. BMD model results for fatty change in liver of female rats from NTP (2008)

Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	Goodness-of-fit *p*-value	AIC
Dichotomous Hill	10% ER	0.426	0.0117	0.911	239.410
Log-logistic	10% ER	1.953	1.105	0.394	240.375
Multistage Degrees 1–4 and Gamma, Weibull	10% ER	2.300	1.414	0.335	240.843
Logistic	10% ER	3.480	2.532	0.205	242.244
Log-probit	10% ER	0.342	0.00182	0.995	239.237
Probit	10% ER	3.325	2.387	0.217	242.074

The lowest dose in female rats was 0.248 mg/kg-d.

There was too much uncertainty in the BMD estimate to use these model results for determining the POD. The lowest dose was chosen as the NOAEL (less than 10% extra risk from control occurred at the lowest dose).

D.1.1.4. *Modeling issues related to lower respiratory effects in male rats at 90 days*

The following 90-day datasets in male rats from Glaser et al. (1990) were determined not to be amenable for BMD modeling:

- Histiocytosis: the only adequately-fitting model did not produce a useable result; parameter hit bound
- Total protein, albumen, and LDH in BALF: all models had goodness of fit *p*-value < 0.1

Table D-11. BMD results for histiocytosis in male rats at 90 days from Glaser et al. (1990)

Model	Restriction	Risk type	BMD	BMDL	BMDU	*p*-Value	AIC	BMDS recommend-ation notes
Dichotomous Hill	Restricted	Extra Risk	0.000613	--	0.0387232	0.3535	31.4	BMD computation failed
Log-probit	Unrestricted	Extra Risk	2.61×10^{-5}	--	Infinity	0.3696	31.4	
Log-logistic	Restricted	Extra Risk	8.57×10^{-4}	1.91×10^{-4}	0.0161718	0.4778	29.5	BMD/BMDL ratio > 3 BMD 10× lower than lowest nonzero dose BMDL 10× lower than lowest nonzero dose
Gamma	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.0147435	0.0122	33.0	Goodness of fit *p*-value < 0.1 Goodness of fit *p*-value < 0.1
Multistage Degree 4	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.009323	0.0122	33.0	
Multistage Degree 3	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.009323	0.0122	33.0	
Multistage Degree 2	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.009323	0.0122	33.0	
Multistage Degree 1	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.0089504	0.0122	33.0	
Weibull	Restricted	Extra Risk	4.89×10^{-3}	3.00×10^{-3}	0.0120185	0.0122	33.0	
Logistic	Unrestricted	Extra Risk	9.65×10^{-3}	5.97×10^{-3}	0.015877	0.0011	35.9	
Probit	Unrestricted	Extra Risk	1.21×10^{-2}	8.19×10^{-3}	0.019674	0.0078	37.6	

Table D-12. BMD results for total protein in BALF in male rats at 90 days from Glaser et al. (1990)

Model	Restriction	Risk type	BMRF	BMD	BMDL	BMDU	Test 4 *p*-Value	BMDS recommendation notes
Hill (NCV – normal)	Restricted	Std. Dev.	1	0.1801	--	0.1862	<0.0001	BMD computation failed

Model	Restriction	Risk type	BMRF	BMD	BMDL	BMDU	Test 4 *p*-Value	BMDS recommendation notes
Exponential 2 (NCV – normal)	Restricted	Std. Dev.	1	0.0646	0.0471	0.0894	<0.0001	
Exponential 3 (NCV – normal)	Restricted	Std. Dev.	1	0.0646	0.0471	0.0894	<0.0001	
Exponential 4 (NCV – normal)	Restricted	Std. Dev.	1	0.0181	0.0094	0.0334	<0.0001	
Exponential 5 (NCV – normal)	Restricted	Std. Dev.	1	0.0180	0.0094	0.0365	<0.0001	
Polynomial Degree 4 (NCV – normal)	Restricted	Std. Dev.	1	0.0250	0.0173	0.0389	<0.0001	Goodness of fit *p*-value < 0.1
Polynomial Degree 3 (NCV – normal)	Restricted	Std. Dev.	1	0.0250	0.0173	0.0389	<0.0001	
Polynomial Degree 2 (NCV – normal)	Restricted	Std. Dev.	1	0.0250	0.0173	0.0389	<0.0001	
Power (NCV – normal)	Restricted	Std. Dev.	1	0.0250	0.0173	0.0406	<0.0001	
Linear (NCV – normal)	Unrestricted	Std. Dev.	1	0.0250	0.0173	0.0370	<0.0001	

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Table D-13. BMD results for LDH in BALF in male rats at 90 days from Glaser et al. (1990)

Model	Restriction	Risk type	BMRF	BMD	BMDL	BMDU	Test 4 *p*-Value	AIC	BMDS recommendation notes
Power (NCV – normal)	Restricted	Std. Dev.	1	Failed	--	Infinity	<0.0001	369.1135	BMD computation failed
Exponential 3 (NCV – normal)	Restricted	Std. Dev.	1	0.0554	0.0420	0.0803	<0.0001	373.2741	Goodness of fit *p*-value < 0.1
Exponential 5 (NCV – normal)	Restricted	Std. Dev.	1	0.1789	0.1243	0.1832	0.0724	343.1427	
Hill (NCV – normal)	Restricted	Std. Dev.	1	0.1548	0.1225	0.1580	0.0204	345.2719	
Polynomial Degree 3 (NCV – normal)	Restricted	Std. Dev.	1	0.0464	0.0300	0.0474	<0.0001	374.5440	
Polynomial Degree 2 (NCV – normal)	Restricted	Std. Dev.	1	0.0487	0.0326	0.0497	<0.0001	371.2904	
Linear (NCV – normal)	Unrestricted	Std. Dev.	1	0.0375	0.0282	0.0512	<0.0001	371.7154	

Table D-14. BMD results for albumen in BALF male rats at 90 days from Glaser et al. (1990)

Model	Restriction	Risk Type	BMRF	BMD	BMDL	BMDU	Test 4 *p*-Value	AIC	BMDS recommendation notes
Exponential 2 (NCV - normal)	Restricted	Std. Dev.	1	0.1093	0.0842	0.1484	<0.0001	481.45	
Exponential 3 (NCV – normal)	Restricted	Std. Dev.	1	0.2113	0.0864	0.3101	<0.0001	482.93	
Exponential 4 (NCV – normal)	Restricted	Std. Dev.	1	0.0822	0.0640	0.1101	<0.0001	485.12	
Exponential 5 (NCV – normal)	Restricted	Std. Dev.	1	0.2239	0.1611	0.2647	<0.0001	484.98	
Hill (NCV – normal)	Restricted	Std. Dev.	1	0.2057	0.1468	0.2229	<0.0001	481.81	
Polynomial Degree 4 (NCV – normal)	Restricted	Std. Dev.	1	0.1653	0.0818	0.2777	<0.0001	481.14	Goodness of fit *p*-value < 0.1
Polynomial Degree 3 (NCV – normal)	Restricted	Std. Dev.	1	0.1695	0.0811	0.2698	<0.0001	481.60	
Polynomial Degree 2 (NCV – normal)	Restricted	Std. Dev.	1	0.1593	0.0686	0.2343	<0.0001	483.10	
Power (NCV – normal)	Restricted	Std. Dev.	1	0.0822	0.0578	0.3883	<0.0001	483.12	
Linear (NCV – normal)	Unrestricted	Std. Dev.	1	0.0822	0.0578	0.1254	<0.0001	483.12	

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D.1.2. Calculation of Regional Deposited Dose Ratios (RDDR)

Fractional depositions in the pulmonary region (F_{PU}), the tracheobronchial region (F_{TB}), and the extrathoracic region (F_{ET}) for rats and humans were calculated using the Multi-Path Particle Dosimetry (MPPD) model, a computational model that can be used for estimating airway particle deposition and clearance (ARA (2009)). Logfiles of MPPD outputs are contained in U.S. EPA (2021a). Note: For this assessment, ARA MPPD Version 2.11 was applied. ARA MPPD Version 3.04, and then subsequently EPA MPPD Version 1.01 have since been released. However, they do not have the ability to save or load model runs, or the ability to run batch simulations; therefore, version 2.11 results were maintained due to documentation and QA/QC capabilities. Versions ARA 3.04 and EPA 1.01 were tested using identical inputs as those specified below for Version ARA 2.11, and differences between the older and newer models were negligible.[9]

For the MPPD model runs, the Yeh-Schum 5-lobe model was used for the human and the asymmetric multiple path model was used for the rat. Both models were run under nasal breathing scenarios with the inhalability adjustment selected 'on'.

The human parameters used in the model for calculating F_r (fractional deposition in respiratory tract region r) and in the subsequent calculation of the human equivalent concentration at each rodent concentration were as follows: breathing frequency, 12 per minute (default); tidal volume, 625 mL (default); ventilation rate V_E , 7.5 L/minute (calculated); functional residual capacity, 3,300 mL (default); and upper respiratory tract volume, 50 mL (default). The parameters used for the rat were breathing frequency, 102 per minute (default); tidal volume, 2.1 mL (default); V_E, 0.214 L/minute (calculated); functional residual capacity, 4 mL (default); and upper respiratory tract volume, 0.42 mL (default). All other parameters were also set to the default MPPD software values. The density of sodium dichromate is 2.52 g/cm^3. The aerosol Cr(VI) concentration was converted to aerosol sodium dichromate concentration by molecular weight conversion (see Table D-17). Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) varied slightly with concentration.

RDDR was calculated using the following equation:

$$RDDR_r = \frac{(SA_r)_H}{(SA_r)_A} \times \frac{(V_E)_A}{(V_E)_H} \times \frac{(F_r)_A}{(F_r)_H}$$

For the human, regional-specific surface areas for lung regions (used as normalizing factors) were 200 cm^2 for extrathoracic (ET), 3,200 cm^2 for tracheobronchial (TB), and 54 m^2 for pulmonary (PU) (U.S. EPA, 1994). For the rat, lung surface areas were 15 cm^2 for ET, 22.5 cm^2 for TB, and 0.34 m^2 for PU (U.S. EPA, 1994).

[9]Differences in F_r and $RDDR_r$ between ARA v.2.11 and EPA v.1.01 were less than 10%

Table D-15. Calculation of RDDR for Glaser et al. (1985) and Glaser et al. (1990) using default MMAD parameters

Concentration as reported [mg/m³ Cr(VI)]	Aerosol concentration[a]	MMAD ± GSD (µm)	F_r Rat		F_r Human		RDDR[c]	
			TB	PU	TB	PU	TB	PU
Glaser et al. (1990)								
54	136.0	0.28 ± 1.63	0.0277	0.1355	0.0664	0.1348	1.69	4.56
109	274.6	0.28 ± 1.63	0.0277	0.1355	0.0664	0.1348	1.69	4.56
204	513.9	0.39 ± 1.72	0.0244	0.1117	0.0585	0.1191	1.69	4.25
403	1015	0.39 ± 1.72	0.0244	0.1117	0.0585	0.1191	1.69	4.25
Glaser et al. (1985)[b]								
52	131	0.20 ± 1.5	0.0334	0.1663	0.0781	0.1619	1.74	4.65

[a]Aerosol concentration = Cr(VI) concentration ÷ 0.39696 by molar mass conversion (sodium dichromate MW = 261.97 g/mol and contains 2 moles of Cr; Cr MW = 51.996 g/mol).

[b]Glaser et al. (1985) reported MMAD ± GSD (0.20 ± 1.5 µm) for all exposure groups. Analysis of Glaser et al. (1990) found that aerosol concentration did not impact fractional deposition, and thus only one RDDR calculation was performed for Glaser et al. (1985).

Table D-16. Human equivalent concentrations of Cr(VI) in the 90-day inhalation study in rats by Glaser et al. (1990)

Concentration as reported [mg/m³ Cr(VI)]	Continuous exposure adjustment Factor[a]	RDDR[b]		Human equivalent concentration[c] (mg/m³)	
		TB	Pulmonary	TB	Pulmonary
54	0.917	1.69	4.56	83.5	225.5
109	0.917	1.69	4.56	168.5	455.2
204	0.917	1.69	4.25	316.5	794.8
403	0.917	1.69	4.25	625.3	1570

[a]Continuous exposure adjustment factor = (22/24) × (7/7); animals were exposed to Cr(VI) 22 hours per day and 7 days per week.

[b]Please refer to Table D-17.

[c]Human equivalent concentration = concentration as reported × continuous exposure adjustment factor × RDDR.

As shown in the tables above, the change in RDDR as a function of concentration and the differences in particle size reported by Glaser et al. (1990) are negligible. The values of RDDR were the same for the tracheobronchial region, and within 7% for the pulmonary region. As a result, dose-response modeling does not need to be performed on the human equivalent concentrations and can instead be performed on reported external concentrations. Conversion to a human equivalent concentration can be done after calculating an external point of departure. Furthermore, the RDDR estimated using particle sizes reported by Glaser et al. (1985) differs by

less than 3%. As a result, the same RDDR values would be applied to extrapolations for both studies.

Since RDDR is a strong function of age and physical activity (due to differences in breathing rate, tidal volume, and surface area), MPPD (version 2.11) was run in batch mode for the adult (Ye/Schum 5-lobe, uniform expansion) under varying degrees of physical activity. Values for breathing rate and tidal volume under different physical activities were obtained from U.S. EPA (2011a).

Table D-17. RDDR calculations under different human physiological activity for respiratory effects

Human activity	Breathing rate (min^{-1})	Tidal volume (mL)	V_E L/min (calculated)	F_r Human		RDDR		
				TB	PU	TB	PU	TB+PU
MMAD: Adult Yeh/Schum 5-lobe, uniform expansion Breathing rate/tidal volumes for adult male (U.S. EPA, 2011a)								
Resting 1	12	750	9	0.0657	0.1514	1.4258	3.3799	2.8369
Resting 2	12	500	6	0.0664	0.1096	2.1161	7.0034	5.2491
Resting 3	15	500	7.5	0.062	0.0977	1.8130	6.2851	4.6279
Average RDDR (resting):						1.785	5.556	4.2380
Light work 1	17	1670	28.39	0.0588	0.1472	0.5050	1.1020	0.9478
Light work 2	16	1250	20	0.0599	0.1508	0.7037	1.5270	1.3154
Average RDDR (light work):						0.6044	1.3145	1.1316
Average RDDR (resting & light work):						1.1947	3.4353	2.6848
Heavy work	21	2030	42.63	0.0578	0.1285	0.3422	0.8407	0.6979
Maximal work	40	3050	122	0.0598	0.0806	0.1156	0.4684	0.3236
MMAD default	12	625	7.5	0.0664	0.1348	1.6929	4.5553	3.6733

Human respiratory parameters (tidal volume and breathing rate) obtained from U.S. EPA (2011a).
Aerosol parameters: MMAD (0.28 ± 1.63 µm), concentration 136 mg/m^3, and density 2.52 g/cm^3.
Inhalation parameters: Inhalability adjustment 'on'.
RDDR calculations (see Table D-17: rat F_{TB} 0.0277, rat F_{PU} 0.1355, rat V_E 0.214 L/minute (calculated).
Surface areas (rat): 15 cm^2 for ET, 22.5 cm^2 for TB, and 0.34 m^2 for PU.
Surface areas (adult male human): 200 cm^2 for ET, 3200 cm^2 for TB, and 54 m^2 for PU (U.S. EPA, 1994).
Calculation performed using total fractional deposition in the TB and PU regions and using total surface area (with PU and TB units resolved).
Note: aerosol concentration in mg/m^3 had no impact on predicted fractional lung depositions. Results for F_r of the human TB and PU regions were identical if aerosol concentration was set to 1 or 136 mg/m^3. For consistency, the value 136 mg/m^3 (corresponding to the lowest Cr(VI) concentration in Glaser et al., (1990)) was applied.

For systemic effects (i.e., nonrespiratory-tract organ weights), the total fractional deposition is applied, and RDDR uses species body weight as the normalizing factor:

$$RDDR_{TOT} = \frac{(BW)_H}{(BW)_A} \times \frac{(V_E)_A}{(V_E)_H} \times \frac{(F_{TOT})_A}{(F_{TOT})_H}$$

The current assessment does not apply $RDDR_{TOT}$ to any endpoints.

Table D-18. RDDR calculations under different human ages and physiological activity for systemic effects

Human activity	Breathing rate (min^{-1})	Tidal volume (mL)	V_E L/min (calculated)	F_{TOT} Human	$RDDR_{TOT}$[a]
MMAD: Adult Yeh/Schum 5-lobe, uniform expansion Breathing rate/tidal volumes for adult male (U.S. EPA, 2011a)					
Resting 1	12	750	9	0.2752	2.7579
Resting 2	12	500	6	0.231	4.9285
Resting 3	15	500	7.5	0.2173	4.1914
				Average RDDR (resting):	3.9593
Light work 1	17	1670	28.39	0.2966	0.8112
Light work 2	16	1250	20	0.2871	1.1896
				Average RDDR (light work):	1.0004
				Average RDDR (resting & light work):	2.4798
Heavy work	21	2030	42.63	0.3007	0.5329
Maximal work	40	3050	122	0.3632	0.1542
MMAD default	12	625	7.5	0.2576	3.5357

Human respiratory parameters (tidal volume and breathing rate) obtained from U.S. EPA (2011a).
Aerosol parameters: MMAD (0.28 ± 1.63 µm), concentration 136 mg/m^3, and density 2.52 g/cm^3.
Inhalation parameters: Inhalability adjustment 'on'.
RDDR calculations: rat F_{TOT} 0.228, rat V_E 0.214 L/minute (calculated).
Body weight (rat): 0.5 kg.
Body weight (adult male human): 70 kg.
[a]Calculation performed using total fractional deposition in the ET, TB, and PU regions, and using species body weight as the normalization factor.

D.2. BENCHMARK DOSE MODELING SUMMARY FOR CANCER ENDPOINTS

D.2.1. Cancer Data for Dose Response Modeling

For this assessment, dose-response modeling of endpoints for the oral route was performed on the basis of time-weighted average daily dose of Cr(VI), in mg/kg-day. This value could then be converted to an internal rodent dose, depending on the tissue or endpoint. The time-weighted average was calculated based on time-course dose data available through the data collection time for each endpoint.

The cancer endpoints selected for dose-response modeling are based on the data presented in Table D-19. For reference, historical control data from the National Toxicology Program encompassing the time period of the sodium dichromate dihydrate bioassays are presented in Table D-20. These were not used to make adjustments to the dose-response modeling data.

Datasets modeled were:

- Male mice bearing adenomas *or* carcinomas of the small intestine (duodenum, jejunum, *or* ileum)
- Female mice bearing adenomas *or* carcinomas of the small intestine (duodenum, jejunum, *or* ileum)
- Male rats bearing squamous cell carcinoma *or* papilloma (oral mucosa *or* tongue)
- Female rats bearing squamous cell carcinoma *or* papilloma (oral mucosa *or* tongue)

For each endpoint, the exposure doses and data used for the modeling are presented. The sample sizes were adjusted to be based on the number of animals surviving longer than one year. The incidences were based on the number of tumor-bearing animals. For example, a mouse with two tumors in the duodenum and one tumor in the jejunum is counted only once, and a rat with both a squamous cell carcinoma in the tongue and a squamous cell papilloma in the oral mucosa is counted once.

Table D-19. Data of neoplastic lesions in rats and mice (NTP, 2008)

Tumor type and species/sex		Administered mg/L, mg/kg-d Cr(VI)[a] and incidence/total				
Male B6C3F1 mice		**0 mg/L**	**5**	**10**	**30**	**90**
		0 mg/kg-d	**0.450**	**0.914**	**2.40**	**5.70**
Adenomas (duodenum)		1/50	0/50	1/50	5/50	15/50*
Carcinomas (duodenum)		0/50	0/50	0/50	2/50	3/50
Adenomas or carcinomas (duodenum, jejunum, or ileum)	Incidence/Total	1/50	3/50	2/50	7/50*	20/50*
	Incidence/Total (adj)[b]	1/50	3/49	2/49	7/50*	20/50*
Animals dead prior to day 365		0	1	1	0	0
Female B6C3F1 mice		**0 mg/L**	**5**	**20**	**60**	**180**
		0 mg/kg-d	**0.302**	**1.18**	**3.24**	**8.89**
Adenomas (duodenum)		0/50	0/50	2/50	13/50*	12/50*
Carcinomas (duodenum)		0/50	0/50	0/50	1/50	6/50*
Adenomas or carcinomas (duodenum, jejunum, or ileum)	Incidence/Total	1/50	1/50	4/50	17/50*	22/50*
	Incidence/Total (adj)[b]	1/49	1/50	4/49	17/50*	22/49*
Animals dead prior to day 365		1	0	1	0	1
Male F344 rats		**0 mg/L**	**5**	**20**	**60**	**180**
		0 mg/kg-d	**0.200**	**0.796**	**2.10**	**6.07**
Squamous cell carcinoma (oral mucosa)		0/50	0/50	0/49	0/50	6/49*
Squamous cell papilloma (oral mucosa)		0/50	0/50	0/49	0/50	1/49
Squamous cell carcinoma (tongue)		0/49	1/50	0/47	0/49	0/48
Squamous cell papilloma (tongue)		0/49	0/50	0/47	0/49	1/48
Squamous cell carcinoma or papilloma (oral mucosa or tongue)	Incidence/Total	0/50	1/50	0/49	0/50	7/49*
	Incidence/Total (adj)[b]	0/50	1/47	0/47	0/50	7/49*
Animals dead prior to day 365		0	3	2	0	0
Female F344 rats		**0 mg/L**	**5**	**20**	**60**	**180**
		0 mg/kg-d	**0.248**	**0.961**	**2.60**	**7.13**
Squamous cell carcinoma (oral mucosa)		0/50	0/50	0/50	2/50	11/50*
Squamous cell carcinoma (tongue)		0/45	0/49	0/48	1/48	0/48
Squamous cell papilloma (tongue)		1/45	1/49	0/48	0/48	0/48
Squamous cell carcinoma (oral mucosa or tongue)	Incidence/Total	1/50	1/50	0/50	2/50	11/50*
	Incidence/Total (adj)[b]	1/50	1/50	0/50	2/50	11/50*
Animals dead prior to day 365		0	0	0	0	0

[a]Time-weighted average daily doses calculated from NTP water consumption data.
[b]Tumor incidences adjusted based on the number of animals surviving beyond 365 days. First tumor onset: 451 days for intestinal tumors in mice, and 506 days for oral tumors in rats (both occurring at the highest doses).
*Denotes significant difference from the control group reported by NTP (2008) using the Poly-3 test ($p < 0.05$).

Table D-20. NTP historical control data for animals fed the NTP-2000 diet, from studies of all routes and vehicles of administration (incidence, %, mean % ± standard deviation %)[a]

	Male B6C3F1 mice	Female B6C3F1 mice	Male F344/N rats	Female F344/N rats
Adenomas				
Duodenum	8/1499 (0.53%) 0.55% ± 1.20%	3/1598 (0.19%) 0.19% ± 0.56%	--	--
Jejunum	1/1499 (0.07%) 0.07% ± 0.36%	0/1598 (0.00%) 0.00% ± 0.00%	--	--
Ileum	--	--	--	--
SI unspecified	9/1499 (0.60%) 0.62% ± 1.20%	3/1598 (0.19%) 0.19% ± 0.56%	--	--
Carcinomas				
Duodenum	3/1499 (0.20%) 0.21% ± 0.79%	1/1598 (0.06%) 0.06% ± 0.35%	--	--
Jejunum	25/1499 (1.67%) 1.69% ± 1.83%	4/1598 (0.25%) 0.23% ± 0.57%	1/1449 (0.07%) 0.07% ± 0.37%	0/1350 (0.00%) 0.00% ± 0.00%
Ileum	2/1499 (0.13%) 0.14% ± 0.50%	2/1598 (0.13%) 0.13% ± 0.48%	--	--
SI unspecified	30/1499 (2.00%) 2.03% ± 1.81%	7/1598 (0.44%) 0.42% ± 0.70%	1/1449 (0.07%) 0.07% ± 0.37%	0/1350 (0.00%) 0.00% ± 0.00%
Adenomas or carcinomas				
SI unspecified	38/1499 (2.54%) 2.59% ± 2.26%	10/1598 (0.63%) 0.61% ± 0.90%	1/1449 (0.07%) 0.07% ± 0.37%	0/1350 (0.00%) 0.00% ± 0.00%
	Male B6C3F1 mice	**Female B6C3F1 mice**	**Male F344/N rats**	**Female F344/N rats**
Squamous cell carcinomas				
Oral mucosa	1/1499 (0.07%) 0.07% ± 0.36%	2/1598 (0.13%) 0.13% ± 0.48%	5/1449 (0.35%) 0.32% ± 0.66%	5/1350 (0.37%) 0.38% ± 0.72%
Tongue	1/1499 (0.07%) 0.07% ± 0.36%	4/1598 (0.25%) 0.26% ± 0.63%	0/1449 (0.00%) 0.00% ± 0.00%	2/1350 (0.15%) 0.15% ± 0.52%
Oral cavity[b]	2/1499 (0.13%) 0.14% ± 0.50%	6/1598 (0.38%) 0.39% ± 0.71%	5/1449 (0.35%) 0.32% ± 0.66%	7/1350 (0.52%) 0.54% ± 0.95%
Squamous cell papillomas				
Oral mucosa	1/1499 (0.07%) 0.03% ± 0.18%	0/1598 (0.00%) 0.00% ± 0.00%	1/1449 (0.07%) 0.07% ± 0.37%	2/1350 (0.15%) 0.15% ± 0.52%
Tongue	1/1499 (0.07%) 0.07% ± 0.36%	2/1598 (0.13%) 0.13% ± 0.48%	4/1449 (0.28%) 0.25% ± 0.60%	5/1350 (0.37%) 0.38% ± 0.91%
Oral cavity[b]	2/1499 (0.13%) 0.10% ± 0.40%	2/1598 (0.13%) 0.13% ± 0.48%	5/1449 (0.35%) 0.32% ± 0.66%	7/1350 (0.52%) 0.54% ± 0.95%
Squamous cell carcinomas or papillomas squamous				
Tongue	2/1499 (0.13%) 0.14% ± 0.50%	6/1598 (0.38%) 0.39% ± 0.87%	4/1449 (0.28%) 0.25% ± 0.60%	7/1350 (0.52%) 0.54% ± 1.10%
Oral cavity[b]	4/1499 (0.27%) 0.24% ± 0.59%	8/1598 (0.50%) 0.52% ± 0.91%	10/1449 (0.69%) 0.64% ± 0.78%	14/1350 (1.04%) 1.08% ± 1.58%

[a]March 2007 historical control reports for F344/N rats and B6C3F1 mice (NTP, 2007a, b, c, d). Control data encompass chronic studies that include the NTP sodium dichromate dihydrate study. Denominator is number of animals necropsied.
[b]Oral mucosa, tongue, pharynx, tooth, gingiva. Note: for oral cavity, papillomas include both papillomas squamous and papillomas.

D.2.2. Evaluation of Model Fit and Model Selection

Following EPA's *Benchmark Dose Technical Guidance* (U.S. EPA, 2012a) Sections 2.3.9 and 2.5 and EPA's *Choosing Appropriate Stage of a Multistage Model for Cancer Modeling* (U.S. EPA, 2014a):

1) All orders of the Multistage model up to two less than the number of dose groups were fit (e.g., up to model order k−2 if there are k dose groups).

    a. If all parameter (γ, β1, … , βk-2) estimates were positive, the model with the lowest AIC was chosen as the best-fitting model if at least one of the models provides an adequate fit to the data. Consistent with EPA's guidance when there is an a priori reason to prefer a specific model(s) [(U.S. EPA, 2012a) §2.3.5 and §2.3.9], Multistage models having a goodness-of-fit *p*-value of less than 0.05 were rejected.

    b. Otherwise (i.e., if any parameter is estimated to be zero and is thus at a boundary), the following procedure (2) was followed:

2) Model fits of orders 1 and 2 (linear and quadratic, respectively) were examined for adequate fit. The linear model parameters (γ, β1), and the quadratic model parameters (γ, β1, β2) were examined.

    a. If only one of the models exhibited adequate fit, that model was chosen.

    b. If both models exhibited adequate fit:

        i) The model with the lowest AIC was chosen if all of the parameters (γ , β1,and β2) were positive.

        ii) Otherwise, the model with the lower BMDL (more health protective) was chosen. If the BMD/BMDL ratio is larger than 3, the matter was referred to EPA statisticians and health assessors for a decision.

Logfiles of BMD model outputs are contained in U.S. EPA (2021a).

D.3. ALTERNATIVE APPROACHES FOR CANCER AND NONCANCER DOSE-RESPONSE ASSESSMENT

D.3.1. Noncancer Oral Dose-response Applying Default $BW^{3/4}$ Scaling Approaches

As a comparison against the pharmacokinetic method, RfDs were calculated using default $BW^{3/4}$ scaling. However, this comparison applies $UF_H = 3$ (removing the pharmacokinetic portion of the intraindividual variability). By not accounting for Cr(VI) reduction in either the rodent (gastric pH = 4.5) or the human (gastric pH = 1.3), the default scaling approach focuses on a sensitive population in terms of pharmacokinetics (i.e., a human population where baseline gastric pH = 4.5, and gastric juice reduction capacity is equivalent to that of the rodent). All uncertainty factors are described in Section 4. Study-specific body weights (and not default animal body weights) are used in order to make a direct comparison of default and PBPK methods (which relied on study-specific body weight).

Table D-21. Summary of derivation of points of departure following oral exposure for effects outside of the gastrointestinal tract (default approach)

Species/ Sex	Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	TWA BW (kg)	POD_{HED} mg/kg-d[a]
Diffuse epithelial hyperplasia of the duodenum at 2 years (NTP, 2008)						
Mice/M	Quantal-linear[b]	10	0.148	0.121	0.05	0.0191
Mice/F	LOAEL	--	--	0.302	0.05	0.0478
Changes in the liver enzyme alanine aminotransferase (ALT) (NTP, 2008)						
Rat/M 12 mo.	Exp2[b]	1RD	1.83	1.56	0.395	0.414
Rat/M 3 mo.	NOAEL	--	--	1.58	0.246	0.372
Changes in the liver enzyme alanine aminotransferase (ALT) at 90 d (NTP, 2007f)						
Rat/M	LOAEL	--	--	1.74	0.232	0.404
Rat/F	LOAEL	--	--	1.74	0.160	0.368
Chronic inflammation at 2 years (NTP, 2008)						
Rat/F	LOAEL	--	--	0.248	0.260	0.0592
Mice/F	Log-logistic	10% ER	3.70	1.33	0.05	0.210
Liver fatty change at 2 years (NTP, 2008)						
Rat/F	NOAEL	--	--	0.248	0.260	0.0592
Decreased offspring growth (NTP, 1997)						
Mouse/F	NOAEL	--	--	11.6	0.024	1.53

Species/ Sex	Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	TWA BW (kg)	POD_{HED} mg/kg-d[a]
Decreased hemoglobin (Hb) (NTP, 2008)						
Rat/M (22 d)	Exp-4	1SD	1.07	0.816	0.138	0.166

[a]$BW^{3/4}$ scaling adjustment: mg/kg-day multiplied by $(BW_A/80)^{1/4}$). Animal BW set to study/sex-specific time weighted average values for hybrid PBPK modeling/$BW^{3/4}$ scaling approach to maintain consistency with bioassay PBPK simulation.

[b]Data were amenable to BMD modeling with the highest dose omitted.

Table D-22. Effects and corresponding derivation of candidate values from PODS applying $BW^{¾}$ scaling

Endpoint and reference	POD_{HED} (mg/kg-d)	POD Type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF	Candidate value (mg/kg-d)
Gastrointestinal									
Mouse (M) hyperplasia (NTP, 2008)	0.0191	$BMDL_{10}$	3	3	1	1	1	10	1.91×10^{-3}
Mouse (F) hyperplasia (NTP, 2008)	0.0478	LOAEL	3	3	10	1	1	100	4.78×10^{-4}
Liver									
Rat (M) liver ALT (12 mo) (NTP, 2008)	0.414	$BMDL_{1RD}$	3	3	1	1	1	10	0.0414[a]
Rat (M) liver ALT (3 mo) (NTP, 2008)	0.372	NOAEL	3	3	1	3	1	30	0.0124[a]
Rat (M) liver ALT (90 d) (NTP, 2007f)	0.404	LOAEL	3	3	10	3	1	300	1.35×10^{-3}[a]
Rat (F) liver ALT (90 d) (NTP, 2007f)	0.368	LOAEL	3	3	10	3	1	300	1.23×10^{-3}[a]
Rat (F) liver chronic inflammation (2 yr) (NTP, 2008)	0.0592	LOAEL	3	3	10	1	1	100	5.92×10^{-4}
Mouse (F) liver chronic inflammation (2 yr) (NTP, 2008)	0.210	$BMDL_{10}$	3	3	1	1	1	10	0.0210[a]
Rat (F) liver fatty change (2 yr) (NTP, 2008)	0.0592	NOAEL	3	3	1	1	1	10	5.9×10^{-3}
Developmental									
Mouse (F) decreased offspring growth (NTP, 1997)	1.53	NOAEL	3	3	1	1	1	10	0.153[a]
Hematological									

Endpoint and reference	POD_{HED} (mg/kg-d)	POD Type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF	Candidate value (mg/kg-d)
Rat (M) decreased Hb (22 d) (NTP, 2008)	0.166	$BMDL_{1SD}$	3	3	1	1	1	10	0.0166[a]

[a]Denotes values that are higher than RfDs derived from pharmacokinetic modeling.
RfDs derived from the pharmacokinetic modeling are more health-protective than $BW^{3/4}$ scaling at high doses. This is because at high doses, the model is less sensitive to gastric pH and more sensitive to gastric reducing capacity. The assumed human variability in gastric reducing capacity is very high, causing the lower 1% prediction to ultimately produce a value lower than $BW^{3/4}$ scaling. At low doses, the model is more sensitive to gastric pH. The $BW^{3/4}$ method is essentially assuming that the human gastric pH > 4 (whereas the pharmacokinetic model assumes the human gastric pH = 1.3). As a result, the effectiveness of human gastric reduction when compared to the rodent has a stronger impact on the model at low doses and produces less health-protective RfDs.

D.3.2. Order of Uncertainty Factor Applications

An alternative uncertainty factor approach applies some uncertainty factors that represent uncertainties on the internal rodent dose (specifically UF_L and UF_A) to the rodent internal dose prior to calculation of the human equivalent dose. The remaining uncertainty factors are then applied after HED calculation to estimate the candidate RfDs. This process is outlined in Figure D-2. Because of nonlinearities in the human gastric pharmacokinetics, this ultimately leads to slightly different RfDs. Tables D-23 and D-24 illustrate what some of the PODs and RfDs would be using this approach (with special focus on those leading to the final organ-specific chronic values; not all endpoints were evaluated).

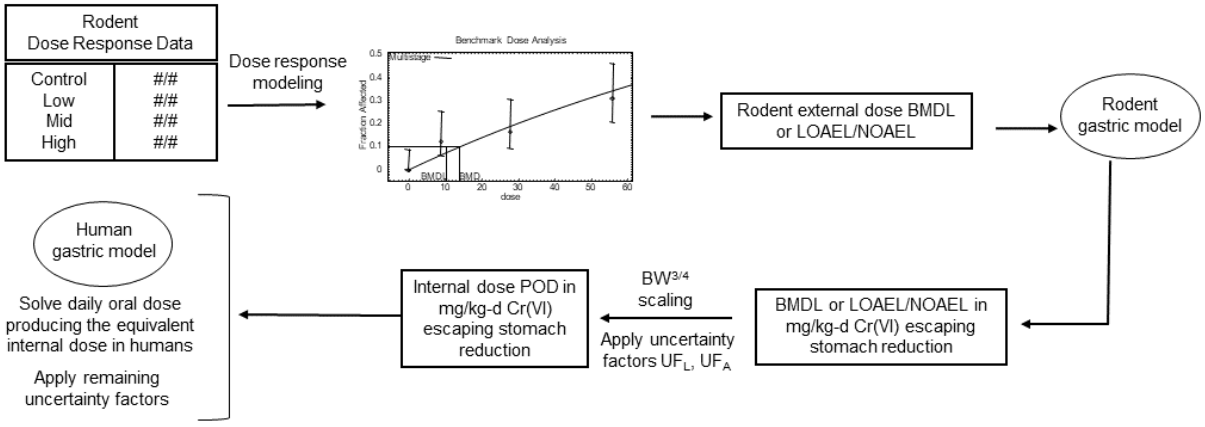

Figure D-2. Alternative process for calculating the human equivalent dose for Cr(VI). Uncertainty factors UF_L and UF_A are applied to the internal rodent dose prior to animal-to-human extrapolation.

Table D-23. Summary of derivation of points of departure following oral exposure using alternative uncertainty factor process

Species/ Sex	Model	BMR	BMD mg/kg-d	BMDL mg/kg-d	Internal dose[a] mg/kg-d	TWA BW (kg)	$BW^{3/4}$ adjust[b]	UF_A, UF_L	Internal dose POD	POD_{HED} (mg/kg-d)[c]
Diffuse epithelial hyperplasia of the duodenum at 2 years (NTP, 2008)										
Mice/M	Quantal linear[d]	10% ER	0.148	0.121	0.0182	0.05	2.88×10^{-3}	3, 1	9.60×10^{-4}	0.0158
Mice/F	LOAEL	--	--	0.302	0.0463	0.05	7.32×10^{-3}	3, 10	2.44×10^{-4}	4.13×10^{-3}
Changes in the liver enzyme alanine aminotransferase (ALT) at 90 d (NTP, 2007f)										
Rat/M	LOAEL	--	--	1.74	0.188	0.232	0.0436	3, 10	1.45×10^{-3}	0.0234
Rat/F	LOAEL	--	--	1.74	0.181	0.160	0.0383	3, 10	1.28×10^{-3}	0.0209
Chronic inflammation at 2 years (NTP, 2008)										
Rat/F	LOAEL	--	--	0.248	0.0195	0.260	4.66×10^{-3}	3, 10	1.55×10^{-4}	2.64×10^{-3}
Mice/F	Log-logistic	10% ER	3.70	1.33	0.225	0.05	0.0356	3, 1	0.0119	0.116
Liver fatty change at 2 years (NTP, 2008)										
Rat/F	NOAEL	--	--	0.248	0.0195	0.260	4.66×10^{-3}	3, 1	1.55×10^{-3}	0.0250
Decreased offspring growth (NTP, 1997)										
Mouse/F	NOAEL	--	--	11.6	3.09	0.024	0.407	3, 1	0.136	0.354

[a]Dose escaping stomach reduction in rodent (mg/kg-d) estimated by PBPK modeling.

[b]$BW^{3/4}$ scaling adjustment: mg/kg-d multiplied by $(BW_A/80)^{1/4}$. Animal BW set to study/sex-specific time weighted average values for hybrid PBPK modeling/$BW^{3/4}$ scaling approach to maintain consistency with bioassay PBPK simulation.

[c]POD_{HED} in mg/kg-d Cr(VI) oral dose ingested by humans (lower 1% value of 20,000 Monte Carlo PBPK simulations needed to achieve the internal dose POD). See Appendix C.1.5 for details.

[d]Data were amenable to BMD modeling with the highest dose omitted.

Table D-24. Effects and corresponding derivation of candidate values using alternative uncertainty factor process

Endpoint and reference	POD_{HED} (mg/kg-d)	POD Type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF[a]	Candidate value (mg/kg-d)
Digestive tract tissues									
Mouse (M) hyperplasia (NTP, 2008)	0.0158	$BMDL_{10}$	[3]	3	[1]	1	1	3[10]	5.27×10^{-3}
Mouse (F) hyperplasia (NTP, 2008)	4.13×10^{-3}	LOAEL	[3]	3	[10]	1	1	3 [100]	1.38×10^{-3}

Endpoint and reference	POD_{HED} (mg/kg-d)	POD Type	UF_A	UF_H	UF_L	UF_S	UF_D	Composite UF[a]	Candidate value (mg/kg-d)
Liver									
Rat (M) liver ALT (90 d) (NTP, 2007f)	0.0234	LOAEL	[3]	3	[10]	3	1	10 [300]	2.34×10^{-3}
Rat (F) liver ALT (90 d) (NTP, 2007f)	0.0209	LOAEL	[3]	3	[10]	3	1	10 [300]	2.09×10^{-3}
Rat (F) liver chronic inflammation (2 yr) (NTP, 2008)	2.64×10^{-3}	LOAEL	[3]	3	[1]	1	1	3 [10]	8.80×10^{-4}
Mouse (F) liver chronic inflammation (2 yr) (NTP, 2008)	0.116	$BMDL_{10}$	[3]	3	[1]	1	1	3 [10]	0.0387
Rat (F) liver fatty change (2 yr) (NTP, 2008)	0.0250	NOAEL	[3]	3	[1]	1	1	3 [10]	8.33×10^{-3}
Developmental									
Mouse (F) Decreased F1 postnatal growth (NTP, 1997)	0.354	NOAEL	[3]	3	[1]	1	1	3 [10]	0.118

[a]UF_A and UF_L have been applied to the internal rodent dose prior to calculation of the POD_{HED}. The composite UF applied to the POD_{HED} reflects those applied after calculation of the POD_{HED} (UF_H, UF_D). The values in [brackets] indicate the product of all the uncertainty factors that have been applied in all steps.

D.3.3. Uncertainty Assessment of Low-dose Extrapolation Method for Oral Cancer Dose-response

Because a mutagenic mode of action for Cr(VI) carcinogenicity (see Section 3.2.3) is "sufficiently supported in (laboratory) animals" and "relevant to humans," EPA used a linear low dose extrapolation from the POD in accordance with *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). However, multiple modes of action for tumor formation in the mouse small intestine could be occurring in parallel, and presenting different approaches may shed light on uncertainties in the assessment (U.S. EPA, 2005). For comparative purposes, a nonlinear estimate is provided using a reference value approach based on one of the other modes of action outlined in Section 3.2.3 (inflammatory hyperplasia being a key event or precursor to tumor development).

The dose-response relationships for diffuse epithelial hyperplasia in the small intestine of male and female mice from the chronic NTP (2008) bioassay were more sensitive than the dose-responses for adenomas and carcinomas in the same tissue (Figure D-3). The nonlinear dose-response approach would assume the noncancer organ-specific reference dose for gastrointestinal toxicity (based on hyperplasia dose-response presented in Section 4.1) is protective of tumors in the small intestine: 9×10^{-4} mg/kg-day.

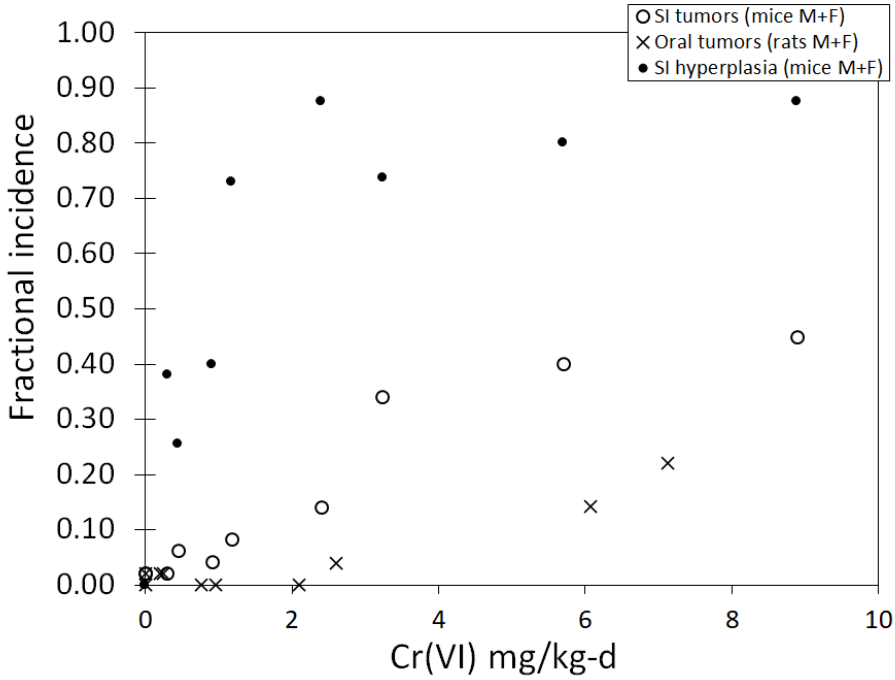

Figure D-3. Dose-response data for tumors and diffuse epithelial hyperplasia of the mouse small intestine (SI) and tumors of the rat oral cavity.

Applying the lifetime OSF for small intestinal tumors of 0.5 risk per mg/kg-day, the oral dose for 1/10,000 risk would be $0.0001/0.5 = 2 \times 10^{-4}$ mg/kg-day. The nonlinear, RfD-based

estimate (9×10^{-4} mg/kg-day) is 4.5× higher. Based on the OSF, there would be a 4.5/10,000 increased cancer risk at the dose estimated using the nonlinear, RfD-based approach.

Tumors of the rat oral cavity did not have a proposed mode of action, and the dose-response for these tumors was less sensitive than that for tumors of the small intestine in mice (see Sections 3.2.3 and 4.1). The adult-based OSF for oral tumors is 0.1 risk per mg/kg-day (see Section 4.3.3), and the ADAF-adjusted lifetime OSF[10] would be 0.17 risk per mg/kg-day. For this tumor type, the oral dose for 1/10,000 risk would be 5.9×10^{-4} mg/kg-day. The RfD-based estimate would be 1.5× higher than this dose. Applying that OSF, there would be approximately a 1.5/10,000 increased cancer risk at the dose estimated using the RfD-based approach.

[10]ADAF calculation: $10 \times 0.1 \times 2/70 + 3 \times 0.1 \times 14/70 + 1 \times 0.1 \times 54/70 = 0.166$ (see Section 4.3.4).

D.4. EXCLUSION OF HUMAN STUDIES FOR EXPOSURE-RESPONSE

Table D-25. Overview of studies excluded for exposure-response analysis of upper respiratory tract (nasal) effects in humans

Study	Population or industry	Reason(s) for exclusion
Armienta-Hernández and Rodríguez-Castillo (1995)	General population & chromate production	Air data and nasal effects data not contained in study, and source of data not cited.
Bloomfield and Blum (1928)	Electroplating	Cannot determine accuracy or precision of air concentration measurements.
Ceballos et al. (2019) (related study: Ceballos et al. (2017))	Paint stripping/aircraft refinishing	Air concentration data not representative of inhaled dose due to full face mask use by exposed workers.
Elhosary et al. (2014)	Cement and tannery facilities	No air concentration data. Cannot determine if exposure was to Cr(VI) or Cr(III).
Fagliano et al. (1997)	Residential (soil)	No air concentration data. Cannot determine if exposure was to Cr(VI) or Cr(III).
Gomes (1972)	Electroplating	Relationship between air concentration and outcome cannot be estimated from presented data.
Horiguchi et al. (1990)	Electroplating	No air measurements.
Kitamura et al. (2003)	Electroplating	Did not include the preferred nasal outcome measurements.
Kleinfeld and Rosso (1965)	Electroplating	Relationship between air concentration and outcome cannot be estimated from presented data. Cannot determine accuracy or precision of air concentration measurements.
Korallus et al. (1982)	Chromate production	No air measurements.
Lee and Goh (1988)	Electroplating	No air measurements.
Lin et al. (1994)	Electroplating	Measurement only for total chromium in air, hexavalent chromium preferred.
Lucas and Kramkowski (1975)	Electroplating	Single exposure group.
Lucas (1976)	Painting/varnishing	Single exposure group, coexposures, did not include the preferred nasal outcome measurements.
Machle and Gregorius (1948)	Chromate production	Relationship between air concentration and outcome unable to be estimated from results as they are presented.
Mancuso (1951)	Chromate production	Measurement only for total chromium in air, hexavalent chromium preferred.

Study	Population or industry	Reason(s) for exclusion
PHS (1953)	Chromate production	Relationship between air concentration and outcome cannot be estimated from presented data.
Royle (1975b)	Electroplating	Relationship between air concentration and outcome cannot be estimated from presented data.
Singhal et al. (2015)	Chromate production and electroplating	No air measurements.
Sorahan et al. (1998) (related: Sorahan et al. (1987))	Ni-Cr platers	Relationship between air concentration and outcome cannot be estimated from presented data.
Vigliani and Zurlo (1955)	Chromate production and electroplating	No description of methods.
Wang et al. (1994)	Ferrochromium production	No air measurements.
Yuan et al. (2016)	Children in school near electroplating plants	Did not include the preferred nasal outcome measurements.

Note: Some studies excluded for consideration of nasal dose-response assessment were still included in the IRIS assessment for other hazards. For some institutional references (e.g., NIOSH reports), the primary investigators or report editors are listed as the authors.

Table D-26. Overview of studies excluded for exposure-response analysis of lung cancer in humans based on screening studies for adequate exposure-response data[a]

Reference	Reason for exclusion
Ahn and Jeong (2014)	Not an occupational study of chromium exposure and cancer; purpose was not to estimate a measure of relative risk.
Alderson et al. (1981)	Exposure assignments were based on tasks/ job title, not chromium measurements. No air sampling was described.
Alexander et al. (1996)	Cumulative exposure estimated using approach with high likelihood of exposure misclassification and lack of confidence in its representation of exposure to individual participants. Median follow-up for most of the cohort was less than 10 yr and median age at end of study was 42 yr, which reduced the ability to ascertain cancer deaths.
Armienta-Hernández and Rodríguez-Castillo (1995)	No air data.
Becker et al. (1985)	Group-level exposure assignments were based on tasks/ job title, not chromium measurements. No air sampling was described.
Beveridge et al. (2010)	Group-level exposure assignments were based on job title, not chromium measurements. No air sampling was described.
Bidstrup (1951)	Chromium exposures were not individually assigned; no measures of association provided. No air sampling was described.
Bidstrup and Case (1956)	Exposure assignments were based on tasks/ job title, not chromium measurements. No air sampling was described.
Blot et al. (2000)	Exposure metrics were not based on air measurements.
Boffetta et al. (2010)	Not an occupational study of chromium exposure and cancer; purpose was not estimating a measure of relative risk.
Brown et al. (2004)	No effect estimates were reported for lung cancer and chromium exposure.
Chatham-Stephens et al. (2013)	Not an epidemiological study. No outcome measurements. Risk assessment was performed.
Cole and Rodu (2005)	Not an epidemiological study (meta-analysis).
Davies et al. (1991)	Group-level exposure assignments were based on job title, not chromium measurements.
Franchini et al. (1983)	No air data.
Frentzel-Beyme (1983)	Group-level exposure assignments were based on job title, not chromium measurements. No air sampling was described.
Girardi et al. (2015)	Exposure metrics were not based on air measurements.
Halasova et al. (2009)	Inadequate exposure information.
Hall et al. (2020)[b]	Group-level exposure assignments were based on tasks/ job title, not chromium measurements. No air sampling was described.
Hayes et al. (1989)	Group-level exposure assignments were based on job title, not chromium measurements. No air sampling was described.
Hill and Ferguson (1979)	Analysis of trends over time; no analyses of associations with exposure metrics based on air measurements.
Johnson et al. (2011)	Ecological study with biomarker data and no air data.
Koh et al. (2013; 2011)	Inadequate exposure information.

Reference	Reason for exclusion
Linos et al. (2011)	Ecological study with no air data.
Milatou-Smith et al. (1997) Sjögren et al. (1987)	Group-level exposure assignments were based on job tasks, not chromium measurements. No air sampling was described.
Moulin et al. (1993b)	Group-level exposure assignments were based on job tasks, not chromium measurements. No air sampling was described.
Moulin et al. (1993a)	No chromium measurements.
Moulin et al. (1990)	No chromium measurements.
NJ DEP (2008)	Relationship between air concentration and outcome cannot be estimated from presented data.
Pesch et al. (2019)	Exposures were based on tasks/ job title and air concentrations that were not from this study population/location.
Rafnsson et al. (1997)	Group-level exposure assignments were based on job tasks and duration of job, not chromium measurements.
Rosenman and Stanbury (1996)	Group-level exposure assignments were based on occupation, not chromium measurements. No air sampling was described.
Royle (1975a)	Inadequate exposure information. This article is part 1 of 2 articles. Air sampling was described in part 2, and concentrations were reported as exceeding certain values, but measured concentrations were not reported.
Shixiong (1994)	Categorical control data.
Sorahan and Harrington (2000)	Group-level exposure assignments were based on occupation, not chromium measurements. No air sampling was described.
Sorahan et al. (1987)	Group-level exposure assignments were based on occupation, not chromium measurements. No air sampling was described.
Sorahan et al. (1998)	Group-level exposure assignments were based on occupation, not chromium measurements. No air sampling was described.
Taylor (1966)	No chromium measurements.
van Wijngaarden et al. (2004)	Not an epidemiological study (meta-analysis).
TOMA (1987)	No chromium measurements.
Yang et al. (2013)	Not an epidemiological study (review).
Zhivin et al. (2013)	Exposure assignments were qualitative; based on time and numeric score for level, not chromium measurements.

[a]These studies were obtained via title/abstract screening and backward bibliography searches. Studies were excluded from consideration after full-text screening based on the rationale provided. In HERO (click here), these studies contain multiple inclusion/exclusion tags due to their potential relevance to other health effects. All were excluded from consideration for the lung cancer exposure-response.

[b]Laryngeal cancer (respiratory tract outside of the lung).

Table D-27. Overview of studies excluded for exposure-response analysis of lung cancer in humans based on screening the most recent analyses

Reference	Reason for exclusion
Mancuso (1997) Mancuso and Hueper (1951) Crump et al. (2003) Luippold et al. (2003)	Painesville Ohio cohort studies superseded by Proctor et al. (2016)

Reference	Reason for exclusion
Hayes et al. (1979) Braver et al. (1985) Park et al. (2004) Park and Stayner (2006)	Baltimore Maryland cohort studies superseded by Gibb et al., (2020; 2015; 2000b)
Korallus et al. (1982) Korallus et al. (1993)	German cohort studies superseded by Birk et al. (2006)
Pastides et al. (1994)	Castle Hayne, North Carolina cohort superseded by Luippold et al. (2005)
Machle and Gregorius (1948)	Baltimore and Painesville cohort studies superseded by Proctor et al. (2016) and Gibb et al. (2020; 2015)

Table D-28. Overview of studies excluded for exposure-response analysis of lung cancer in humans

Reference	Reason for exclusion
Luippold et al. (2005)	SMR analysis conducted where no slope or standard error were produced or could be calculated based on published data.
AEI (2002)	

Note: These studies had passed the initial full-text screening (despite inadequacies in exposure data) because they contained quantitative analyses that warranted further review for consideration. Studies were excluded from consideration after review of the quantitative methods and their utility for the exposure-response assessment.

D.5. INDIVIDUAL-LEVEL ANALYSIS OF NEOPLASTIC AND NONNEOPLASTIC LESIONS IN MICE FROM NTP (2008)

Table D-29. Individual-level overview of neoplastic and nonneoplastic lesions in male mice from NTP (2008)

		Tumors			Hyperplasia		
ID	Cr(VI) (mg/L)	Duod	Jej	Il	Duod	Jej	Il
11	0	A	--	--	--	--	--
55	5	--	C (multi)	--	--	--	--
64	5	--	--	A	--	--	--
81	5	--	C	--	DE	LT	--
105	10	--	--	C	DE	LT	CY
140	10	A	--	--	--	--	--
155	30	A	--	--	DE	--	--
161	30	A, C	--	--	DE	LT	--
162	30	--	C	--	DE	--	--
165	30	A	--	--	DE	LT	--
167	30	A	--	--	DE	--	--
172	30	C	--	--	DE	LT	
173	30	A	--	--	DE	--	--
202	90	--	C	--	DE	DE	--
203	90	--	A	--	--	--	No eval
205	90	C	--	--	DE	--	--
206	90	A	--	--	DE	--	--
211	90	--	C	--	DE	--	--
214	90	A (multi)	--	--	DE	--	--
215	90	A, C	A	--	DE	--	--
217	90	A	--	--	--	--	--
218	90	A (multi)	--	--	--	--	--
219	90	A (multi)	--	--	DE	--	LT
222	90	A	--	--	DE	--	--
223	90	A	--	--	DE, FE	--	--
227	90	A	No eval	--	--	No eval	--
234	90	--	A	--	DE	--	--
235	90	A (multi)	--	--	DE	LT	--
238	90	A (multi)	--	--	DE	--	--
240	90	A	--	--	--	No eval	No eval
242	90	A, C	--	--	--	--	--
245	90	A	--	--	--	--	--
249	90	A (multi)	--	--	DE	--	--

Duod = duodenum, Jej = jejunum, Il = ileum; A = adenoma, C = carcinoma, LT = lymphoid tissue hyperplasia, DE = diffuse epithelial hyperplasia, FE = focal epithelial hyperplasia, CY = cyst. Shaded rows correspond to exposed animals with no observed intestinal hyperplasia.

Table D-30. Individual-level overview of neoplastic and nonneoplastic lesions in female mice from NTP (2008)

		Tumors			Hyperplasia		
ID	Cr(VI) (mg/L)	Duod	Jej	Il	Duod	Jej	Il
268	0	--	C	--	--	--	--
317	5	--	A	--	--	--	--
351	20	--	C	--	DE	LT	--
371	20	A	--	--	DE, FE	DE	--
379	20	A	--	--	DE	--	--
380	20	--	C	--	DE	--	--
408	60	A	--	--	DE	--	--
411	60	A	--	--	--	--	--
412	60	A	--	--	DE	LT	--
413	60	A (multi)	--	--	DE	--	--
415	60	A	--	--	DE, CY	LT	--
416	60	--	A	--	--	--	--
420	60	--	A	--	DE, FE	--	--
421	60	A	C	--	DE	--	--
423	60	A	--	--	DE	--	--
427	60	A	--	--	--	--	--
428	60	A	--	--	--	--	--
431	60	A	--	--	DE	--	--
438	60	C	--	--	DE	--	--
439	60	--	C	--	DE	--	--
440	60	A	--	--	DE	--	--
446	60	A	--	--	DE	--	--
450	60	A	--	--	--	--	--
451	180	A	--	--	DE	--	--
452	180	A (multi)	--	--	DE	--	--
454	180	--	A	--	DE	DE	--
455	180	A (multi)	A	--	DE	DE	
458	180	A	--	--	DE	--	--
459	180	C	--	--	--	--	--
461	180	--	A	--	DE	DE	--
466	180	--	C	--	DE, LT	--	--
470	180	C	--	--	DE	--	--
472	180	--	A	--	DE	DE	--
474	180	C	--	--	DE	DE	--
475	180	A (multi)	--	--	DE	--	--
486	180	--	A (multi)	--	DE	--	--

		Tumors			Hyperplasia		
ID	**Cr(VI) (mg/L)**	**Duod**	**Jej**	**Il**	**Duod**	**Jej**	**Il**
488	180	A (multi)	--	--	DE	--	--
489	180	A	--	--	DE	--	--
490	180	A	--	--	DE	--	--
492	180	C	--	--	DE	--	--
495	180	A (multi)	--	--	DE	--	--
496	180	A, C	--	--	DE	DE	--
497	180	A	--	--	DE	--	--
498	180	A (multi)	--	--	DE	--	--
499	180	C	--	--	[dilation]	--	--

Duod = duodenum, Jej = jejunum; Il = ileum, LT = lymphoid tissue hyperplasia, DE = diffuse epithelial hyperplasia, FE = focal epithelial hyperplasia, CY = cyst.

Table D-31. Summary of neoplastic and nonneoplastic lesions in mice from NTP (2008)

Concentration (mg/L)	Sex	Total # animals with tumors in the small intestine	# animals with tumors in the small intestine and no nonneoplastic lesions[a] in the small intestine	Animal IDs
0	M + F	2	2 (100%)	11, 268
5	M + F	4	3 (75%)	55, 64, 317
10	M	2	1 (50%)	140
20	F	4	0	
30	M	7	0	
60	F	17	5 (29.4%)	411, 416, 427, 428, 450
90	M	20	7 (35%)	203, 217, 218, 227, 240, 242, 245
180	F	22	2 (9.1%)	459, 499
All (excluding control)	M + F	76	18 (23.7%)	

[a]Nonneoplastic lesions considered: lymphoid tissue hyperplasia, diffuse epithelial hyperplasia, focal epithelial hyperplasia, cyst. Full individual-level datasets are available from NTP (2007e).

D.6. PROBABILITY DISTRIBUTIONS OF HUMAN EQUIVALENT DOSE FOR CANCER AND NONCANCER PODS DERIVED FROM TOXICOKINETIC MODELING

D.6.1. Noncancer Model Outputs

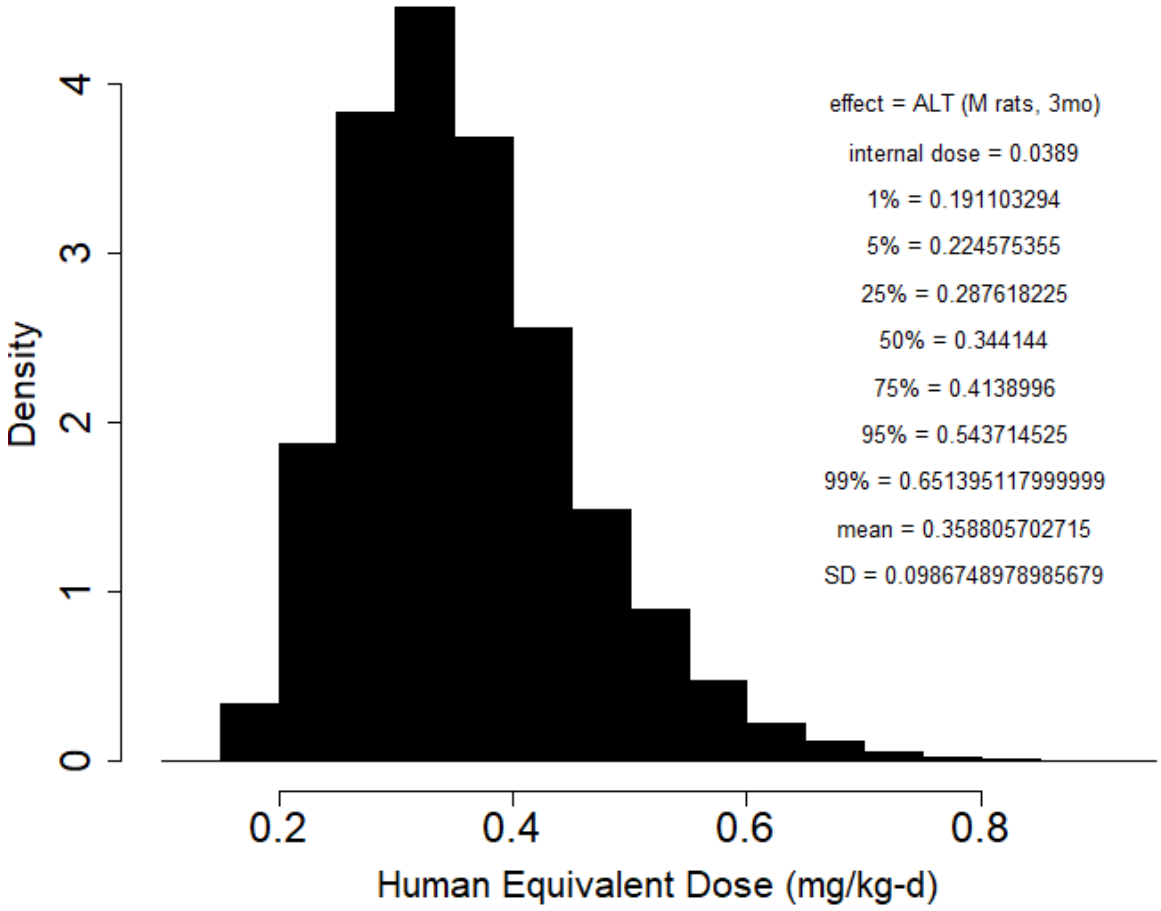

Figure D-4. Model outputs and distribution for rat (M) liver ALT (3 months) (NTP, 2008).

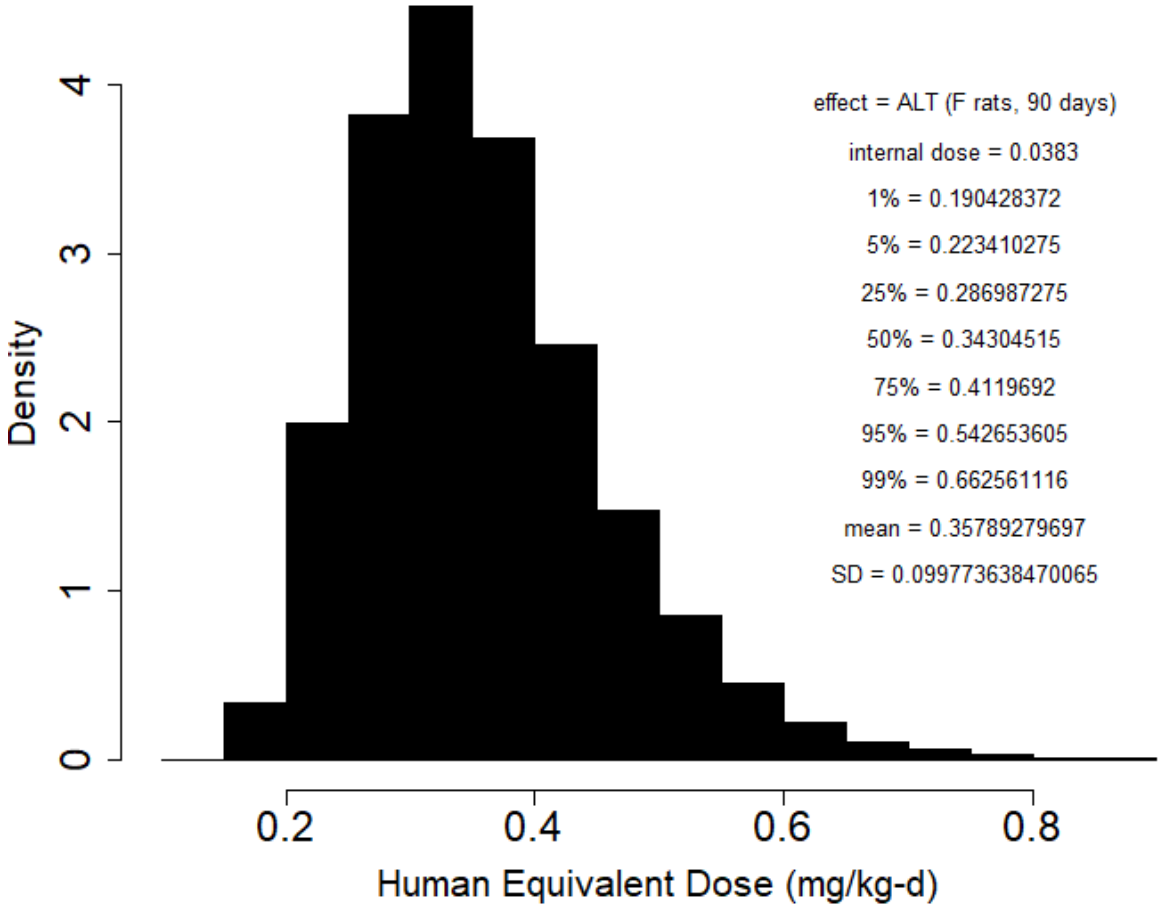

Figure D-5. Model outputs and distribution for rat (F) liver ALT (90 days) (NTP, 2007f).

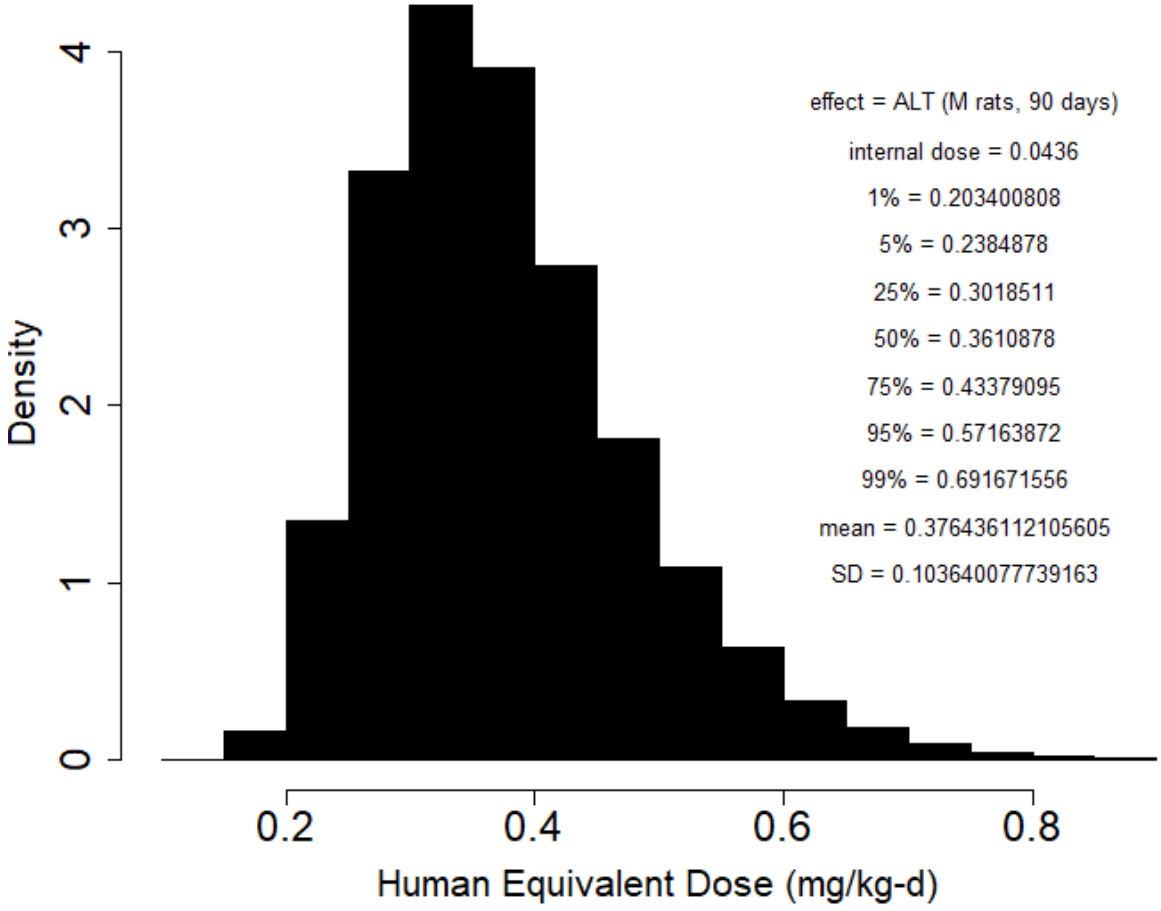

Figure D-6. Model outputs and distribution for rat (M) liver ALT (90 days) (NTP, 2007f)

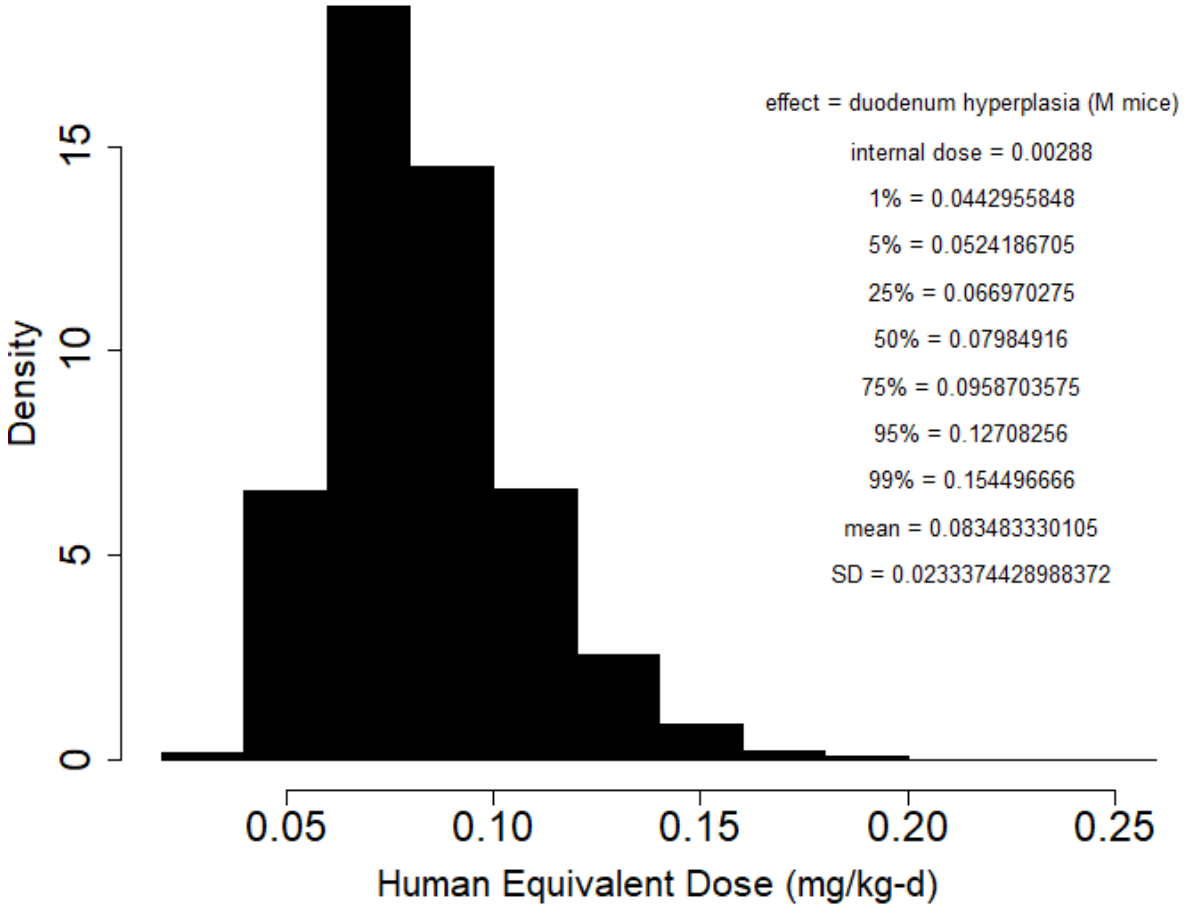

Figure D-7. Model outputs and distribution for mouse (M) hyperplasia (NTP, 2008).

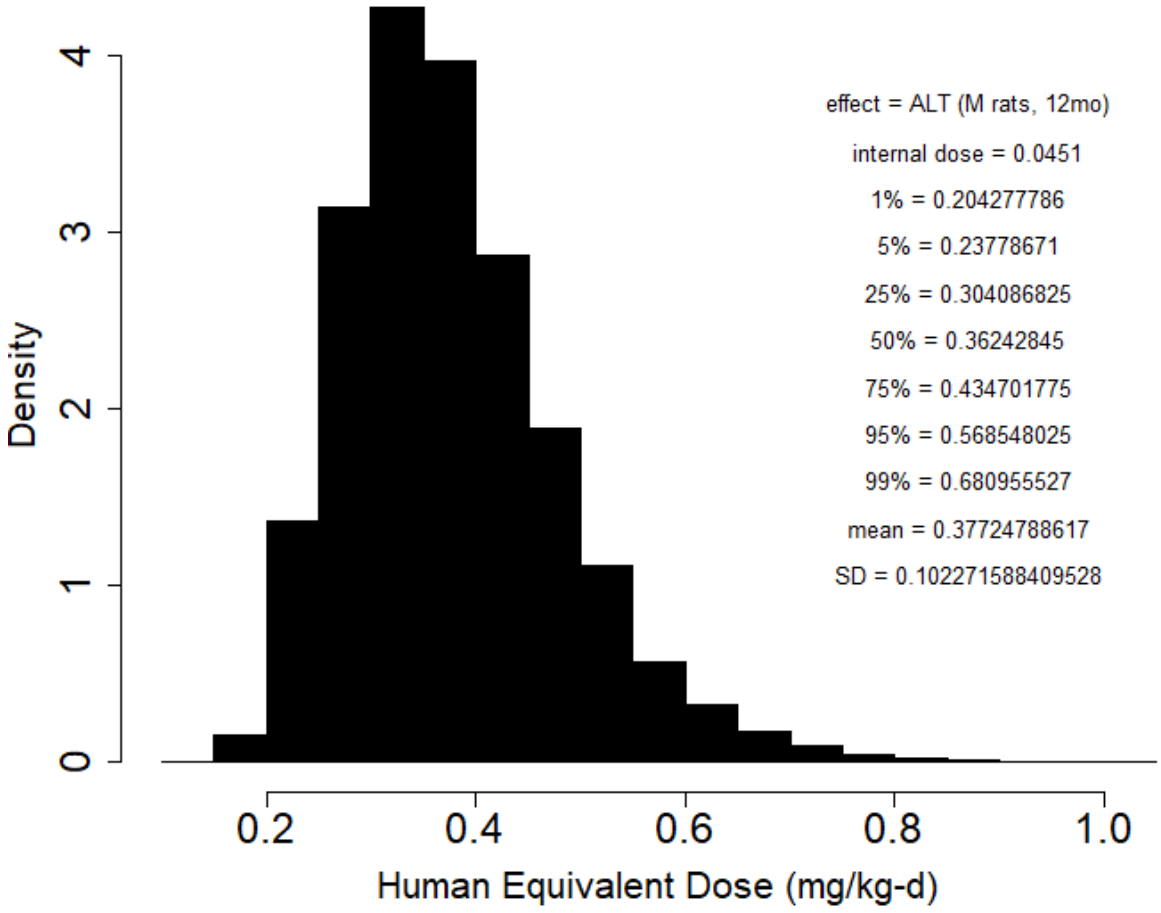

Figure D-8. Model outputs and distribution for rat (M) liver ALT (12 months) (NTP, 2008).

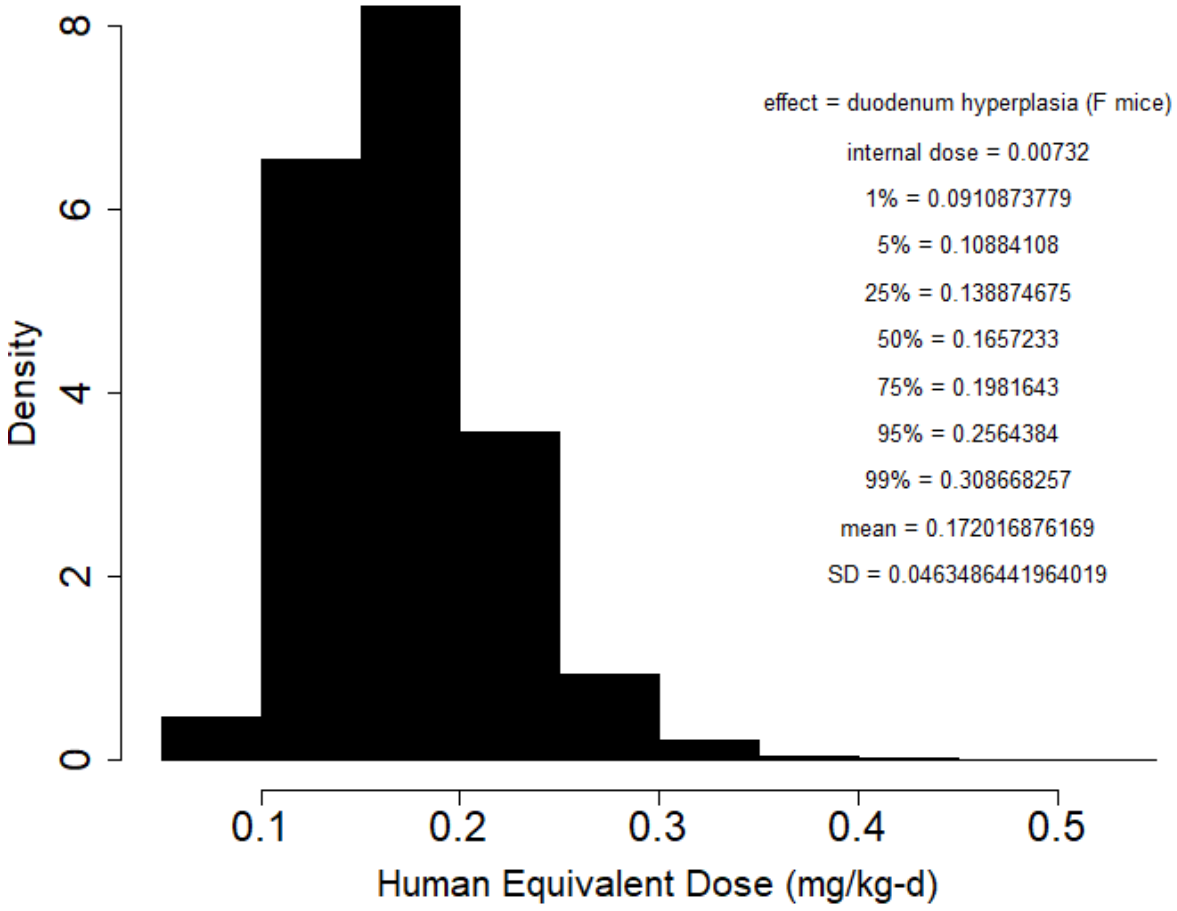

Figure D-9. Model outputs and distribution for mouse (F) hyperplasia (NTP, 2008).

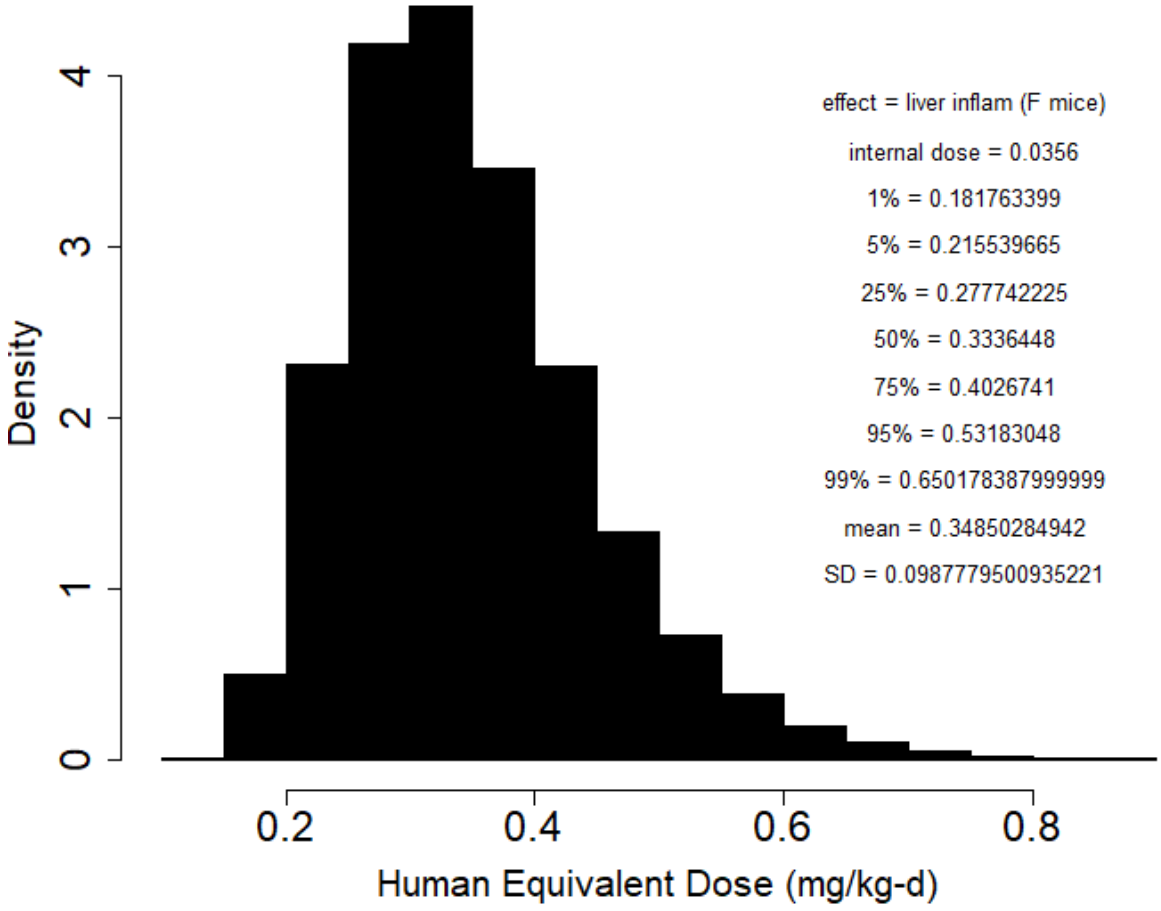

Figure D-10. Model outputs and distribution for mouse (F) liver chronic inflammation (2 years) (NTP, 2008).

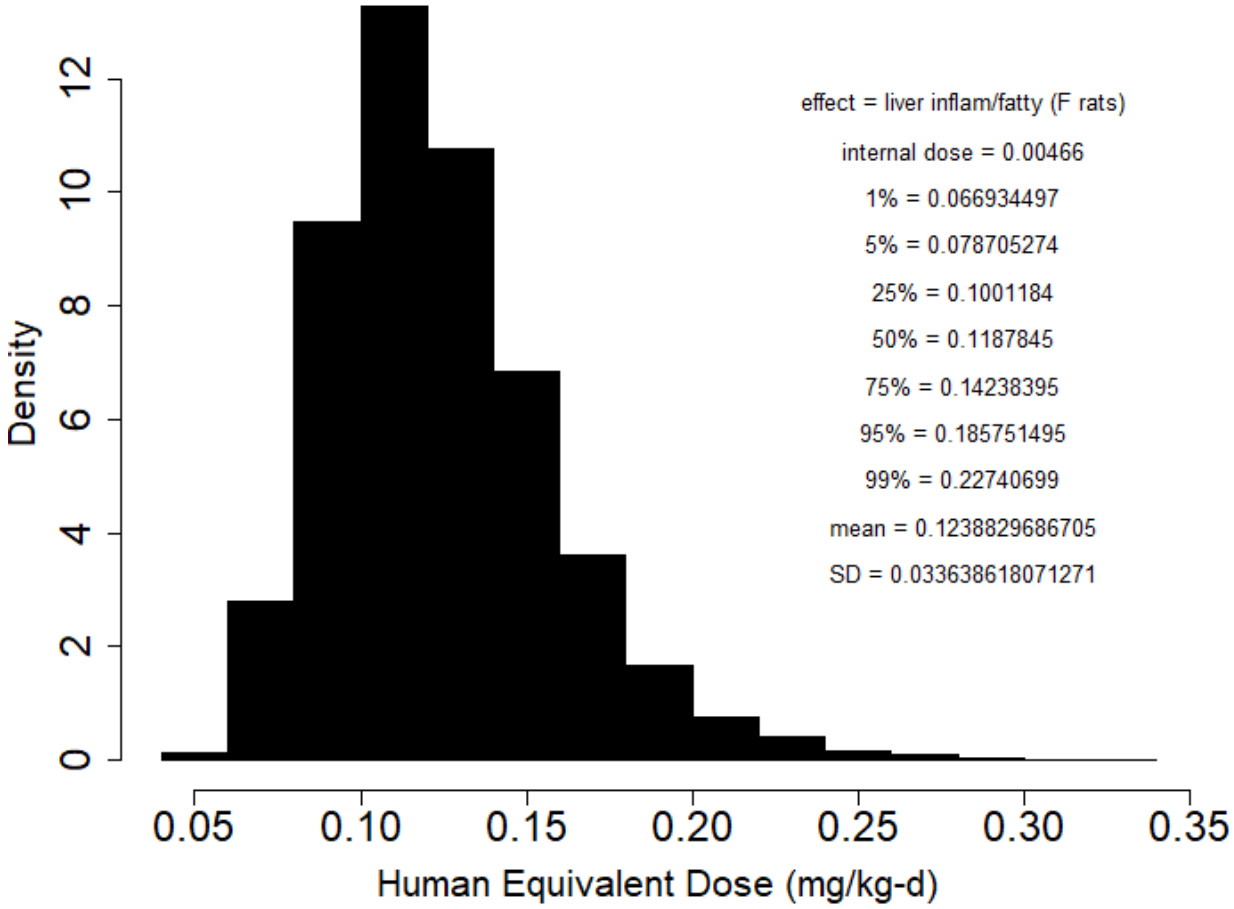

Figure D-11. Model outputs and distribution for rat (F) liver chronic inflammation (2 years) (NTP, 2008).

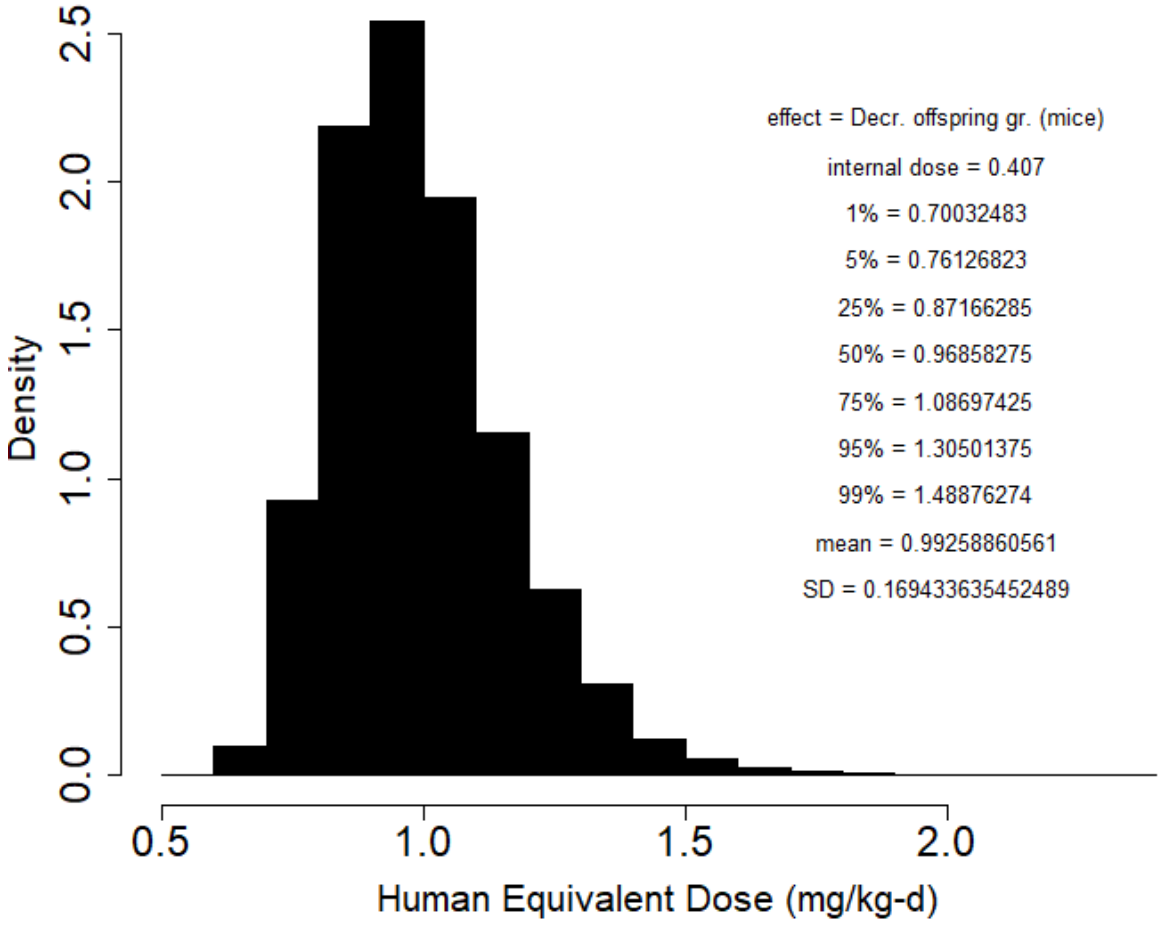

Figure D-12. Model outputs and distribution for mouse (F) Decreased F1 postnatal growth (NTP, 1997).

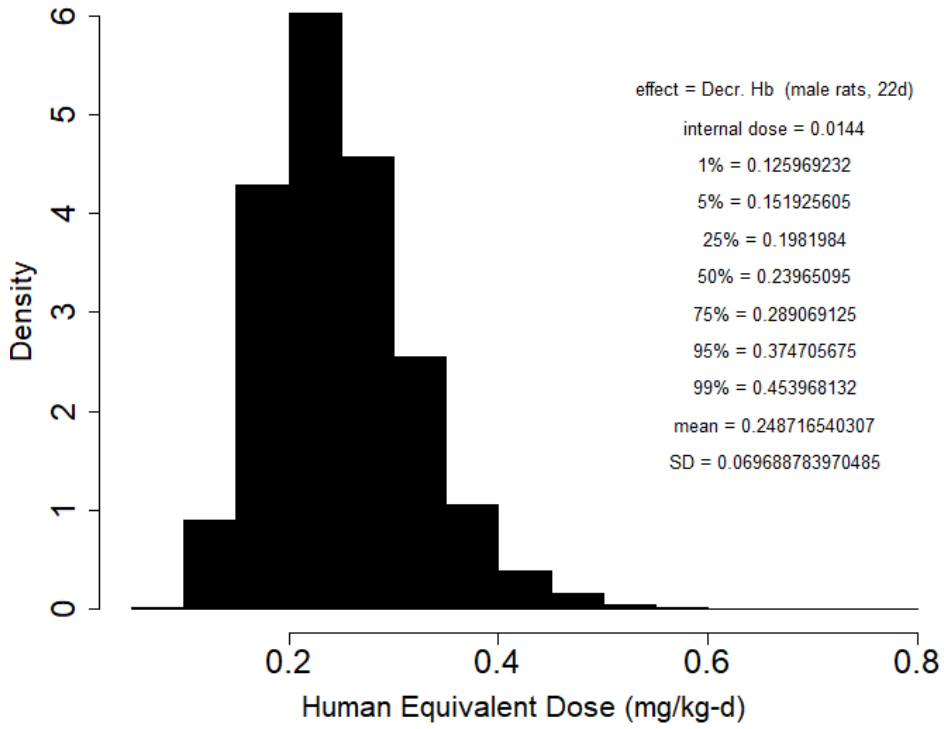

Figure D-13. Model outputs and distribution for rat (M) decreased Hb at 22 days (NTP, 2008)

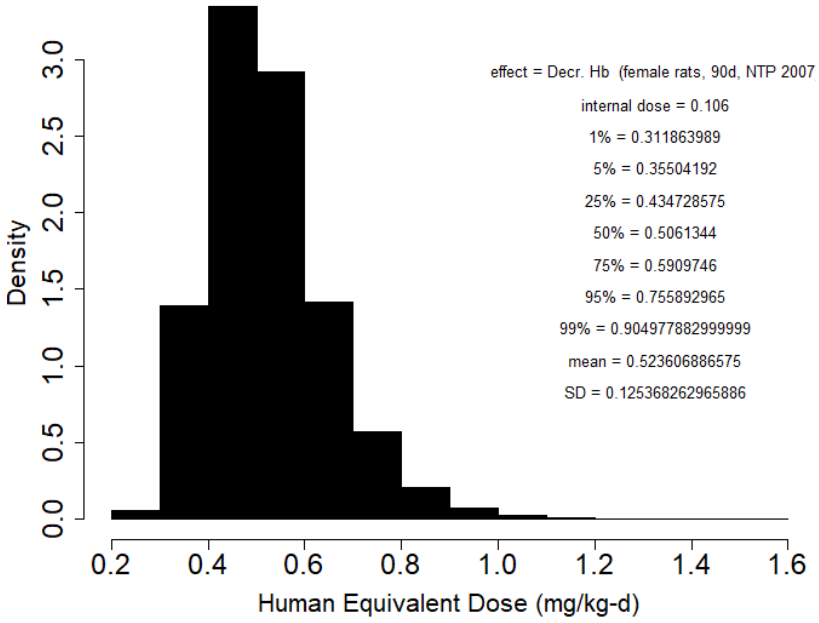

Figure D-14. Model outputs and distribution for rat (F) decreased Hb at 90 days (NTP, 2007f)

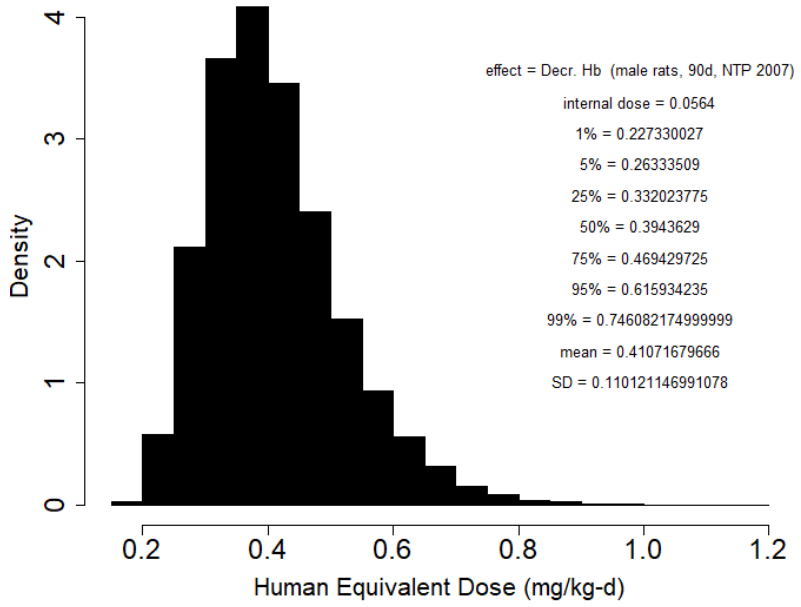

Figure D-15. Model outputs and distribution for rat (M) decreased Hb at 90 days (NTP, 2007f)

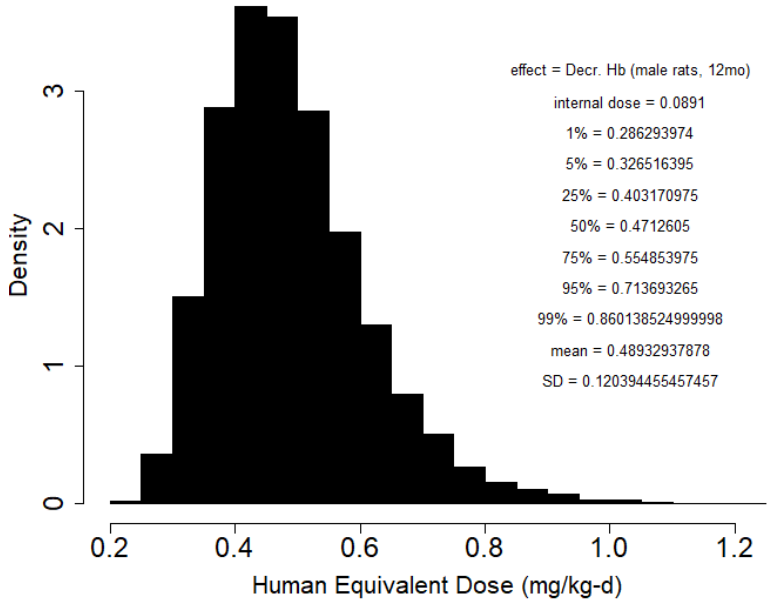

Figure D-16. Model outputs and distribution for rat (M) decreased Hb at 12 months (NTP, 2008)

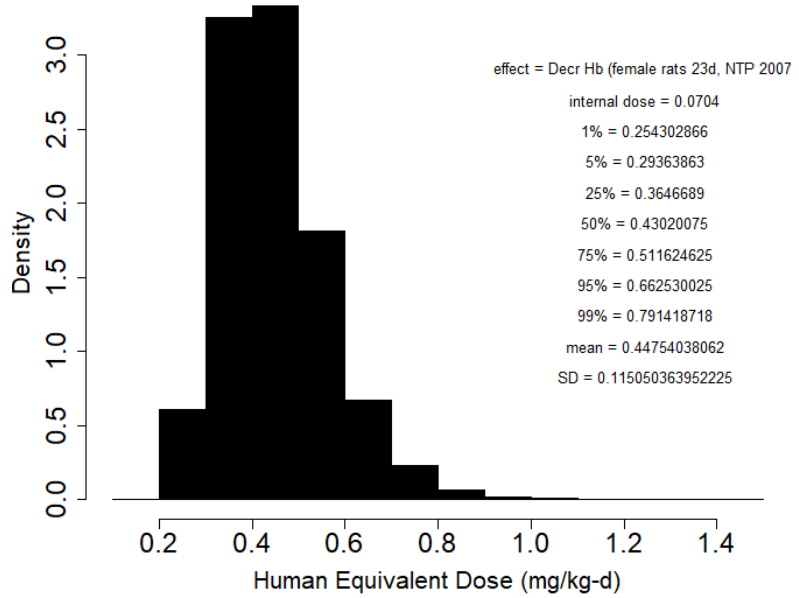

Figure D-17. Model outputs and distribution for rat (F) decreased Hb at 23 days (NTP, 2007f)

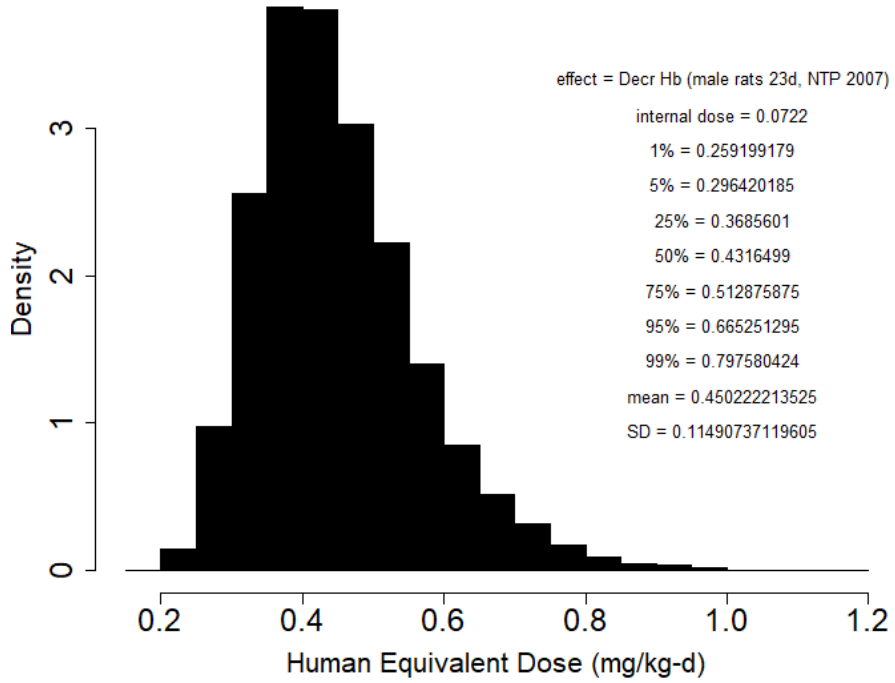

Figure D-18. Model outputs and distribution for rat (M) decreased Hb at 23 days (NTP, 2007f)

D.6.2. Cancer Model Outputs

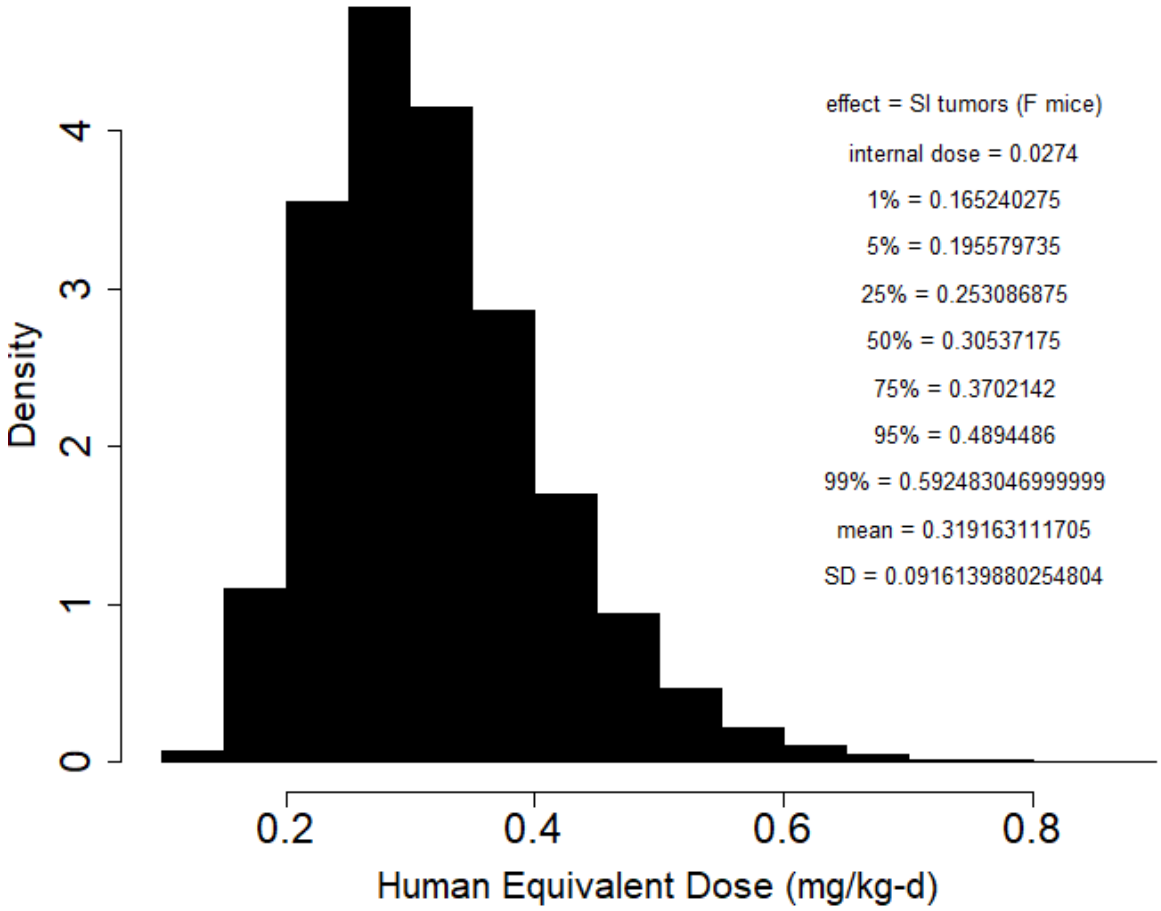

Figure D-19. Model outputs and distribution for adenomas or carcinomas in the female mouse small intestine (NTP, 2008).

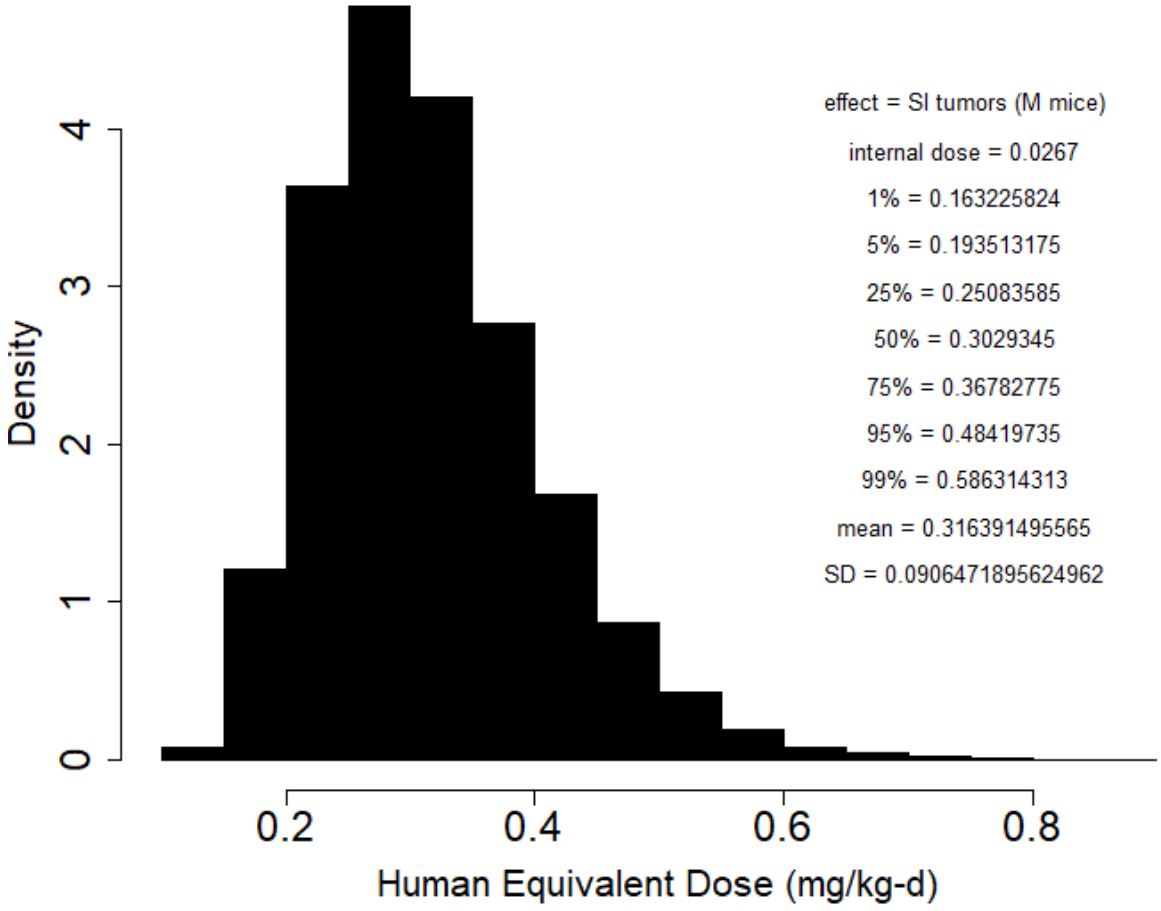

Figure D-20. Model outputs and distribution for adenomas or carcinomas in the male mouse small intestine (NTP, 2008).

APPENDIX E. SAS CODE FOR LIFE-TABLE ANALYSIS

1 The following pages contain the SAS programs for life-table analysis.

```
OPTIONS NODATE NONUMBER orientation=landscape linesize=max;  *BT added 7/3/19;
/*
This program calculates the risk of lung cancer from inhalation exposure to Cr(VI),
using a lifetable approach based on BEIR IV.  The basic exposure-response model is RR = exp(beta
* CE5).

The basic code for the lifetable calculations were developed and provided to EPA
by Randall Smith at NIOSH.  The code from NIOSH calculates the baseline risk (R0) and the exposed
risk (Rx)
from exposure to an exposure concentration of X_Level using NIOSH Model 1:  Rx = R0 * exp(COEF *
X_Level).

EPA has modified the NIOSH as follows:
1)  The all-cause and cause-specific (lung cancer) mortality data tables have been updated
2)  The equation for calculation of X_Time has been revised so all values are based on mid-point
of year:
       XTime   = min(max(0,(age+0.5-&Age1st_x-&Lag)),&Duration-0.5)
3)  An equation has been added to calculate extra risk:  Extra_Risk = (Rx - R0) / ( 1 - R0)
3)  A macro has been added to find the exposure level (X_Level) that yields an extra risk of 0.01
(1%).
    This is referred to as EC1%, which may then be used to calculate the unit risk:  UR = 0.01 /
EC1%
*/
/* .\Beta Version.sas  19jan00, 26jul00, 25oct01, 06dec05, 30nov18
-------------------------------------------------------------------------
Experimental version
------------------------------------------------------------------------- */
title  "Lifetable calculation of lung cancer risk";
title2 "under a non-linear relative rate model";

  /*--------------------------------------------------------------------+
   | Compute excess risk by the BEIR IV method using SAS datasteps.     |
   |                                                                    |
   | These programs compute the risk of a cause-specific                |
   | death in the presence of competing risks, where the cause-         |
   | specific death-rate is modeled either as a relative rate           |
   | [h=h0*f(Coef*X)] or as an absolute rate [h=h0+f(Coef*X)]           |
   | where                                                              |
   |     h denotes the cause-specific death-rate,                       |
   |     X denotes cumulative occupational exposure (with Lag)          |
   |     Coef denotes the coefficient for the effect of exposure and    |
   |     h0 is the corresponding rate at baseline (X=0).                |
   |     (Except for Coef,  these are functions of age.)                |
   |                                                                    |
   | A few simple models of f(Coef*X) are easily specified as           |
   | described below.  More complicated models can be specified with    |
   | a little more work. (For a more complicated example,               |
   | see \_GENERAL.LIB\PROGRAMS\SAS\BEIR-4.Method\BEIR4ex2.SAS).        |
   |                                                                    |
   +Reference:                                                          +
   |  Health Risks of Radon and Other Internally Deposited Alpha-       |
   |  Emitters   (BEIR IV).  Commitee on the Biologic Effects of        |
   |  Ionizing Radiations.  National Academy Press.  Wash. DC (1988).   |
   |  See especially pages 131-136.                                     |
   |                                                                    |
   |                                                                    |
   +USER-SUPPLIED ASSIGNMENTS:                                          +
   |                                                                    |
   |> The following macro variables are assigned using "%LET" state-    |
   |  ments:  MODEL, COEF,  LAG, AGE1ST_X, DURATION, LASTAGE.           |
   |  Further information appears below.                                |
   |> Exposure concentrations for computing risk are defined            |
   |  in the datastep "X_LEVELS."                                       |
   |> All-cause mortality information is entered as a life-table in     |
   |  the data step "ALLCAUSE," and converted to rates per individual.  |
   |> Cause-specific mortality information for unexposed referents is   |
   |  entered as rates per 100,000 and converted to rates per           |
   |  individual in the data step "CAUSE."                              |
   |                                                                    |
   |                                                                    |
```

```
+NOTES:                                                          +
   |> Datastep "EX_RISK" is where the desired risks are computed.     |
   |                                                                  |
   |> If the unexposed(referent) cause-specific mortality rate is from|
   |  a model then datastep "CAUSE" with variables AGE and RATE as    |
   |  modeled can be modified to incorporate this.  However, care     |
   |  must be taken in calculating confidence limits since imprecision|
   |  in the estimates of all of the parameters of the model          |
   |  contributes to the imprecision of excess risk estimates.        |
   |                                                                  |
   |> This program is currently set up to apply the Linear Rel. Rate  |
   |  model (Lag= 0) and accumulation of excess risk is over the      |
   |  rates in ALLCAUSE and CAUSE unless truncated at a younger age.  |
   |  (See LASTAGE below.)                                            |
   |                                                                  |
   |                                                                  |
   + SAS Programmer: Randall Smith                                   +
   |                 The Nat'l Inst. for Occupational Safety & Health |
   |                 26jul2000, 23jul2001, 25oct2001, 18nov2018       |
   + Modifications:                                                  +
   | 26jul00 Fix the procedure bug causing it to report incorrectly   |
   |             the age at which accumulation of risk was stopped    |
   |             whenever the age-specific rates included ages        |
   |             before the value of &Age1st_X.  (&Age1st_X is a macro|
   |             expression defining the age exposure begins.)        |
   |                                                                  |
   | 23jul01 Make changes to facilitate multiple applications of      |
   |         BEIR4 algorithm, i.e., MLE(Excess Risk), UCL(ExcessRisk),|
   |         searching for concentrations for a fixed risk. These     |
   |         changes involve defining Macros named BEIR4 and SEARCH   |
   |         given below with code illustrating these uses for the    |
   |         linear relative rate model.                              |
   |                                                                  |
   | 25oct01 Modified to add Macro variable EnvAdj for whether to     |
   |         increase inhaled dose from intermittent occupational     |
   |         exposures to continuous environmental exposures          |
   |         and update US rates for Gibb et al. cohort.              |
   |                                                                  |
   | 30nov18 A bug that prevented the calculation of excess risks     |
   |         after incorporating an adjustment from intermittent      |
   |         occupational exposures to continuous exposures is fixed. |
   +---                                                               |
   | March 2019: BT (SRC) Added maxro CONVERGE_BEIR4 which iteratively    |
   | runs macro BEIR4 until the EXPOSURE_CONCENTRATION corresponds to an  |
   |extra_risk=0.01 (the point of departure [POD]).                       |
   |

   | Macro CONVERGE_BEIR4 works with one value for the exposure          |
   |  variable XLevel (i.e., when the data C_Levels includes one record.) |
   |
                              |
   | The intent was to make as few changes to BEIR4 as possible. The data |
   | X_LEVELS and variable XLevel are retained but the initial value of   |
   | XLevel is provided in the call to macro CONVERGE_BEIR4 (the value    |
   | of Xlevel in the cards statement is not used in the calculations.    |
   | Changes to the BEIR4 macro are in Part III and Part IV, and are      |
   | indicated by the letters BT.                                         |
   | In addition to the parameter values that are specified by the user   |
   | in PART 1, and the user-provided data entered in Part II, parameters |
   | for the new macro CONVERGE_BEIR4 are specified in the call to the    |
   | macro CONVERGE_BEIR4 (see end of this SAS program file below).       |
   +----------------------------------------------------------------------*/
```

```
/* PART I.  USER-SUPPLIED ASSIGNMENTS (Macro variables):
  /*-----------------------------------------+
   | Model of cumulative exposure effects:   |
   |            1 => Loglinear Relative rate |
   |                  R=R0*exp(COEF*X)       |
   |            2 => Linear Relative rate,   |
   |                  R=R0*(1+COEF*X)        |
   |            3 => Absolute rate,          |
   |                  R=R0+COEF*X            |
   |            4 => Power relative rate     |
   |                  R=R0*(1+X)^COEF        |
   |            0 => User Defined & programmed |
   |                 in datastep Ex_Risk below |
   |                                       */  %Let Model    = 1;
  /*                                       |
   | Cumulative exposure parameter:        */  %Let COEF     = 0.001298;
  /*                                       |
   | Lag or delay between exposure and effect: */  %Let Lag      = 5;
  /*                                       |
   | Age exposure begins:                  */  %Let Age1st_x = 16;
  /* Exposure duration (years):             */  %Let Duration = 85;
  /* Adjust dose from occupational to       |
   | continuous environmental exposures (Y/N)? */  %Let EnvAdj = Yes;
  /* Age to stop accumulating excess risk   |
   | (supposing rates are available for     |
   | ages >= &LastAge); otherwise use all of |
   | the supplied rate information:        */  %Let LastAge  =85;
  /*-----------------------------------------*/


 * PART II.  USER-SUPPLIED ASSIGNMENTS (Datesets AllCause, Cause, X_Levels ): */

  data AllCause (label="Unexposeds' age-spec mortalty rates (all)"
                 drop=Lx  rename=(BLx=Lx) );
  /*-------------------------------------------------------------------+
   | Input lifetable and calculate the corresponding age-specific      |
   | (all-causes) mortality rate (AllCause) and conditional survival   |
   | probability for each year of age (qi) together with               |
   | the corresponding values of age (Age).                            |
   +-------------------------------------------------------------------*/
       Label Age      = "Age at start of year (Age=i)"
             BLx      = "Number alive at start of year"
             Lx       = "Number alive at end of year"
             CndPrDth = "Pr[Death before age i+1 | alive at age i]"
             qi       = "Pr[Survive to age i+1 | Alive at age i]"
             AllCause = "Age-spec mortality rate (all causes)";

       if _n_=1 then input age  //// @1 BLx @; /* //// => skip next 4 lines  */
       input Lx @@;
       CndPrDth = (BLx - Lx)/BLx;

       qi       = 1-CndPrDth;
       if qi <= 0 then AllCause = 1e+50;
                  else AllCause = - log(qi);

       if age < &LastAge then output; else STOP;
       BLx=Lx;
       age+1;
       retain age BLx;
  cards;
```

```
     0   = Life-table starting age.  (Required: Values must begin 4 lines down!)
          The following are 2017 Life-table values of US population
          starting at birth and ending at age 85.
          (Source: Nat.Vital Statistics Reports 2019 Vol 68 No 7, Table 1,
https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_07-508.pdf)
      100000 99422 99384 99360 99341 99326 99312 99299 99288 99278
       99268 99259 99249 99236 99217 99191 99158 99116 99066 99006
       98937 98858 98770 98674 98573 98466 98355 98241 98122 97999
       97872 97740 97603 97461 97314 97163 97006 96843 96674 96501
       96321 96135 95939 95732 95511 95275 95023 94753 94461 94144
       93797 93419 93008 92560 92070 91538 90963 90345 89684 88978
       88226 87424 86570 85664 84706 83696 82632 81507 80315 79048
       77697 76265 74715 73064 71296 69418 67402 65245 62933 60462
       57839 55053 52123 49035 45771 42382
   ;
*run;*BT 7/3/19 added Run statement here;

   data CAUSE (label="Unexposeds' age-cause-spec mortalty rates");
  /*-------------------------------------------------------------+
   | Specify unexposeds' age-specific mortality rates (per year)  |
   | from specific cause.                                         |
   +-------------------------------------------------------------*/
        label Age      = "Age"
              Rate_e5  = "Age,cause-specific rate per 100,000"
              Rate     = "Age,cause-specific rate per individual";

        if _n_ = 1 then input age    /* input starting age       */
                           ///;     /* /// => skip next 3 lines  */
        input Rate_e5  @@;

        Rate = Rate_e5 * 1e-5; /* Convert to rate per individual */

        if age <= 4
           then DO; output; age+1; END;
           else DO i = 0,1,2,3,4;     /*-----------------------------------------*/
                   if age < &LastAge  /* Fill out into yearly intervals from     */
                      then output;    /* inputted five year intervals after age 4*/
                   age+1;             /*-----------------------------------------*/
                END;
   cards;
    0  = Start age of cause-specific rate (Required: Rates begin 3 lines down!)
         The following are 2017 ICD10 = 113, (C33-C34) death rates per 100,000 for US pop'n
starting at birth.
         For ages 5 and above, each rate holds for the age thru age+4 years.
       Source: CDC Wonder, https://wonder.cdc.gov/ucd-icd10.html
0 0.038 0.038 0.038 0.038 0.010 0.019 0.033 0.045 0.120 0.382 1.074 3.131 8.506 24.321 54.508
87.599 131.875 198.108 265.763 309.625
;
*run; *BT 7/3/19 added Run statement here;

   data X_LEVELS (label=   "Exposure levels (e.g., concentrations)" );
  /*-------------------------------------------------------------------+
   | Specify environmental exposure levels                             |
   | and update label for the variable, XLevel, if necessary:          |
   +-------------------------------------------------------------------*/
   /*-------------------------------------------------------------------+
   | BT 3/8/19: Add maxro CONVERGE_BEIR4 which iteratively runs macro   |
   | BEIR4 until the EXPOSURE_CONCENTRATION corresponds to extra_risk=0.01|
                |
   | The intent was to make as few changes to BEIR4 as possible. The data |
   | X_LEVELS and variable XLevel are retained but the initial value of  |
   | XLevel is provided in the call to macro CONVERGE_BEIR4 (the value   |
   | of Xlevel in the cards statement is not used in the calculations.   |
   +-------------------------------------------------------------------*/
        input XLevel @@;
        label XLevel= "Cr(VI) exposure (µg Cr(VI)/m3)";
   cards;
   1
   ;
run;
```

```
%Macro BEIR4;
/* March 2019 - BT (SRC): Macro BEIR4 is now called by macro CONVERGE_BEIR4.
*/
/* 23jul01 modification */
/* Enclose the actual calculations and printed results in a macro       */
/* to facilitate multiple applications of the algorithm.                */

/* PART III. Perform calculations:                                      */

   data EX_RISK  (label = "Estimated excess risks [Method=BEIR IV]"
                  /*keep = XLevel Rx ex_risk RskRatio R0 extra_Risk */
                 rename= (Rx=Risk));
  /*-----------------------------------------------------------------+
   | Calculate risk and excess risk for each exposure concentration|
   | in work.X_Level by BEIR IV method using information in        |
   | work.AllCause and work.Cause to define referent population:   |
   +-----------------------------------------------------------------*/
              format hi F15.8; *BT 7/3/19: added the format statement;
        length XLevel 8.;
        label Age      = "Age at start of year (i)"
              XTime    = "Exposure duration midway between i & i+1"
              XDose    = "CE5(adj) (µg Cr(VI)/m3-yrs)"

              R0       = "Cumulative Risk of lung cancer (unexposed) (R0)"
              Rx       = "Cumulative risk of lung cancer (exposed) (Re)"
              Ex_Risk  = "Excess risk (Rx-Ro)"
              RskRatio = "Ratio of risks (Rx/Ro)"

              hi       = "Lung Cancer hazard (unexposed) (hi)"
              hix      = "Lung Cancer hazard (exposed) (hei)"
              hstari   = "All cause hazard (unexposed) (h*i)"
              hstarix  = "All cause hazard (exposed) (he*i)"
            qi       = "Probability of surviving year i assuming alive at start (unexposed) (qi)"
              S_1i     = "Probability of surviving to end of year i (unexposed) (S1,i)"
              S_1ix    = "Probability of surviving to end of yeari  (exposed) (Se1,i)";

/* BT 3/8/19: Calculation of unexposed's risk (following DO LOOP) could be omitted  from the
iteration
                              but may require further changes to BEIR4(?).
               *e.g.,  %if i=1 %then %do;*/

               if _n_=1 then DO;
                  /* Calculate unexposed's risk (R0) to be retained           */
                  /* based on equation 2A-21 (pg. 131) of BEIR IV:            */

                  /* Initialize:  */  S_1i = 1;  R0 = 0;

                  DO  pointer = 1 to min(n_all,n_cause) until (age>=&LastAge-1);
                      set allcause (keep=age AllCause  rename=(AllCause=hstari))
                             point=pointer nobs=n_all;
                      set cause    (keep=age Rate rename=(age=ageCause Rate=hi))
                             point=pointer nobs=n_cause;

                      if Age NE AgeCause then
                       put "** WARNING: Age values in datasets ALLCAUSE and CAUSE don't conform **"
                                /        @13 "Rates misaligned on age could give incorrect results"
                                /        @13  Pointer=
                                          +2 "Age(ALLCAUSE)=" Age +2 "Age(CAUSE)=" AgeCause /;

                      qi = exp(-hstari);
                      R0 = R0 + ( hi/hstari * S_1i * (1-qi) );
                      S_1i = S_1i * qi;
                  END;
               END;                 /* End of 'if _n_=1 then DO;' stmt */

               retain R0;
```

```
/* Calculate exposed's risk (Rx, renamed to Risk) for each exposure level        */
/* ultimately based on equation 2A-22 (pg. 132) of BEIR IV      */
/* but re-expressed in a form similar to equation  2A-21:       */

* BT 3/20/19. This version of CONVERGE_BEIR4 will work when there is one concentration in data
set x_levels - i.e., one value for xlevel.
                      The Do loop for X_levels is commented out;
                      DO pointX = 1 to No_of_Xs;
* set x_levels point=pointX nobs=No_of_Xs; /* BT 3/8/19: determines when to end the loop. Nobs is
set at compilation, so the value of nobs is available at first run through loop -  just one
record and one variable (XLevel) in dataset x_levels. */

/* BT 3/20/19: added the next lint to set the exposure concentration = current value of
&exposure_conc. */
                                                  xlevel = &exposure_conc;


                          /* Initialize :  */  S_1ix = 1; Rx = 0;S_1i=1; R0=0;

                          DO  pointer = 1 to min(n_all,n_cause) until (age>=&LastAge-1);
                              set allcause (keep=age AllCause  rename=(AllCause=hstari))
                                  point=pointer nobs=n_all;
                              set cause    (keep=Rate rename=(Rate=hi))
                                  point=pointer nobs=n_cause;

                              XTime   = min( max(0,(age+0.5-&Age1st_x-&Lag))
                                           , &Duration - 0.5 );

if UpCase("&EnvAdj") = "YES"
/* Occupational to Environmental Conversion */
                                then XDose = XLevel
                                             * 365/240      /* Days per year           */
                                             * 20/10        /* Ventilation (L) per day */
/*                     * 1/0.52       Converting Beta(CrO3) to Beta(Cr(VI)) */
/*                     * 1/1000       Converting mg/m3 to ug/m3  */
                                             * XTime;
                             ELSE if UpCase("&EnvAdj") = "NO"   /* 30nov2018 ('ELSE') */
                                then XDose = XLevel*XTime;
                                else DO; put //"Macro variable ENVADJ incorrectly specified."
                                /"It should be either YES or NO.  Value specified is: &ENVADJ"
                                             /;
                                        STOP;
                                   END;
                              hix=.;
                              if &Model = 1 then hix = hi * exp(&COEF*XDose);    else
                              if &Model = 2 then hix = hi * (1 + &COEF*XDose);   else
                              if &Model = 3 then hix = hi + &COEF*XDose;         else
                              if &Model = 4 then hix = hi * (1 + XDose)**&COEF;  else
                              if &Model = 0 then DO;
                                 hix = -99999; /* Code for user-defined model goes here. */
                              END;

                              hstarix =  hstari        /* hi=backgrd rate is included in hstari
*/
                                       + (hix - hi);   /*    so that adding in the excess
*/
                                                       /*    from exposure (hix-hi) gives the
*/
                                                       /*    total rate of the exposed.
*/
                              qix   = exp(-hstarix);
                              Rx    = Rx + ( hix/hstarix * S_1ix * ( 1-qix )  );
                              S_1ix = S_1ix * qix;

                                        qi = exp(-hstari);
                                        R0 = R0 + ( hi/hstari * S_1i * (1-qi) );
                                        S_1i = S_1i * qi;
                                        output;

                          END;
```

```
                                Ex_Risk  = Rx - R0;* Rx = risk in exposed population;
                                RskRatio = Rx / R0;    * R0 = from cancer;
                                Extra_risk = Ex_Risk/(1-R0);

                                        /* BT 3/20/19 added:*/
                                        call symput('Extra_Riskm',Extra_Risk);

                                        /*BT 4/24/19 replaced the next line
                                        Diff_Ex_Risk = abs(&ex_risk_target-Ex_Risk);  */
                                        Diff_Ex_Risk = abs(&ex_risk_target-Extra_Risk);
                                        call symput('Delta_Ex_Risk',Diff_Ex_Risk);

                                         output;

                             * END;  * corresponds to X_Levels;
                        STOP;

                        run;

%Mend BEIR4;



/* ------------------------------------------------------------------
                BT: March 2019: parameters for the convergence that are used
                in the modified version of the BEIR4 macro.
  ----------------------------------------------------------*/

%macro Converge_BEIR4 (init_exposure_conc=, ex_risk_target=, conv_criterion=, max_iteration=);

        %Let Delta_Ex_Risk = 1; * initial high value to make sure loop is run at least once
                                                        (i.e., macro BEIR4 is called at least once);

        /* BT 4/15/19: added next line to avoid error during compiling of BEIR4*/
        %Let Extra_Riskm = 1;

        %Let i=1; * first time through loop;

        %Do %Until (%sysevalf(&Delta_Ex_risk < &conv_criterion) OR %sysevalf(&i >
&max_iteration));

                        * first time through loop, set expsosure_conc=init_exposure_conc;
                %If &i=1 %Then
                        %Do;
                                %Let exposure_conc=&init_exposure_conc;

                        %End;
                %If &i>1 %Then
                        %Do;
                                data tempBEIRCONVERGE;
                                        *BEIR4 has run at least once. Adjust exposure_conc
                                                Extra_Riskm is created in BEIR4 (=Extra_Risk);
                                        NumLoops=&i;
                                        thisExposureConc=&exposure_conc;

        /* BT 4/15/19: replaced all of the convergence code with the same code that we used
                                                 in the meso code.*/
                                        numvar=&ex_risk_target;
                                        denvar=&Extra_Riskm;
                                        thisexposureconc = thisexposureconc * (numvar/denvar);
*update the concentration;
                                        call symput('exposure_conc',thisexposureconc);
                                        output;
                                Run;

                        %End; *Corresponds to If i>1 statement;
                %BEIR4;
                %Let i=%eval(&i+1);
        %End;
```

```
   stop;
run;
* rename variables to enable overwriting the values of S_1i and S_lix in ex_risk with the values
in newSRCData;
* Data file tempSRCData has age=0-85 while the ex_Risk file has age 0-84, with last two records
                both having age=84.;
Data tempSRCData; Set newSRCData(rename=(SRC_Age=age SRC_S_1i=S_1i SRC_S_1ix=S_1ix));
       if age=&LastAge then age=%sysevalf(&Lastage-1); Else age=age;
Run;

* there are duplicate values for age in both ex_risk and tempSRCData
                which may produce too many records. if that happens, then we use two set
statements;
Data ex_risk; merge ex_risk tempSRCData; By Age; Run;

/* BT 7/5/19: End of code that was added to merge variables for unexposed risk
                              (S_1i and S_1ix) to the rest of the output, by age;
*/

   *BT 7/3/19: made the these changes to the following Proc Print procedure:
                - commented out the label option and added the split, uniform and width= options
                - included all variables to the format statement;
   proc print data=ex_risk /*label*/ noobs split='/' width=FULL;
        format age F4. Xdose E11. hi E11. hstari E11. hix E11. hstarix E11. qi E11. qix E11.
                              S_1i E11. S_1ix E11. R0 E11. Risk E11. Ex_Risk E11. ;
                label   Age             = "Age at start of year (i)"
                              XDose    = "CE5(adj) (µg Cr(VI)/m3-yrs)"

            R0         = "Cumulative Risk of lung cancer (unexposed) (R0)"
            Risk       = "Cumulative risk of lung cancer (exposed) (Re)"
            Ex_Risk    = "Excess risk/[Rx-Ro]/ /(Ex_Risk)"
            hi         = "Lung Cancer hazard (unexposed) (hi)"
            hix        = "Lung Cancer hazard (exposed) (hei)"
            hstari     = "All cause hazard (unexposed) (h*i)"
            hstarix    = "All cause hazard (exposed) (he*i)"
            qi    = "Probability of surviving year i assuming alive at start (unexposed) (qi)"
            qix   = "Probability of surviving year i assuming alive at start (exposed) (qei)"
              S_1i             = "Probability of surviving to end of year i (unexposed) (S1,i)"
              S_1ix            = "Probability of surviving to end of yeari  (exposed) (Se1,i)";

                Var Age Xdose hi hstari hix hstarix qi qix S_1i S_1ix R0 Risk Extra_risk; *BT
7/3/19: Var statement added;
                label Extra_risk="Extra Risk (Re â€“ R0)\(1 â€“ R0)";
   run;

%End; *end of the If statement that tests if convergence was met;

%Mend Converge_BEIR4;

/* ---------------------------------------------------------------------+
   | March 2019: BT (SRC) Added maxro CONVERGE_BEIR4 which iteratively    |
   | runs macro BEIR4 until the EXPOSURE_CONCENTRATION corresponds to an  |
   | extra_risk=0.01 (the point of departure [POD]).                      |
   |
   | In addition to the parameter for CONVERGE_BEIR4, the user should also|
   | review parameters and data that are assigned/entered in Part 1 and   |
   | Part II (see above). Parameters for CONVERGE_BEIR4 are defined below |
   +---------------------------------------------------------------------*/

        *%BEIR4; * originally called macr BEIR4 directly. Now BEIR4 is called by Converge_BEIR4;

        %Converge_BEIR4(init_exposure_conc=1, /* initial exposure concentration (initial guess) */
                ex_risk_target=0.01000000, /*the point of departure (POD)-the target extra risk */
                conv_criterion=0.00000001,
                max_iteration=200);     /* to avoid excessively long run times */


Run;
```

```
        %Let EC_1Percent = &exposure_conc;

/*-----------------------------------------------------------------+
   | Report results if convergence criterion met:                                 |
   +-----------------------------------------------------------------*/
%If  %sysevalf(&Delta_Ex_risk < &conv_criterion) %then %do;
title5 "based on beta=&COEF, Concentration=&EC_1Percent, and LastAge=&LastAge";

  data _null_;          /* Modified 26-july-00  */
        pointer=1;
        set allcause (keep=age
                      rename=(age=ageall0)) point=pointer nobs=n_all;
        set cause    (keep=age
                      rename=(age=ageCs0)) point=pointer nobs=n_cause;
        pointer=n_all;
        set allcause (keep=age
                      rename=(age=ageall1)) point=pointer nobs=n_all;
        pointer=n_cause;
        set cause    (keep=age
                      rename=(age=ageCs1)) point=pointer nobs=n_cause;
        Tmp = sum(min(AgeAll1,AgeCs1,(&Lastage-1)),1);
        file PRINT;
        if ageall0 NE ageCs0 then DO;
           put /"ERROR: The initial age for all-causes rate differs from the"
               /"       initial age for the cause-specific rate.";
        END;
        else DO;
            put  / "Values of macro variables used in this computation:      "
                 // @3 "Value"     @17 "Macro_Var" @29 "Description"
                  / @3 "-----"     @17 "---------" @29 "----------------------------"
                 // @3 "&Model   " @17 "MODEL"     @29 "1 = Loglinear Relative Rate,"
                  /                                @29 "2 = Linear Relative Rate,    "
                  /                                @29 "3 = Linear Absolute Rate,    "
                  /                                @29 "4 = 'Power' Relative Rate,   "
                  /                                @29 "0 = User defined.            "
                  / @3 "&Coef    " @17 "COEF"      @29 "Exposure parameter estimate"
                 // @3 "&Lag     " @17 "LAG"       @29 "Exposure Lag "
                 // @3 "&Age1st_x" @17 "AGE1ST_X"  @29 "Age exposure begins"
                  / @3 "&Duration" @17 "DURATION"  @29 "Duration of exposure"
                  / @3 "&EnvAdj"   @17 "ENVADJ"    @29 "Adjust dose from intermittent"
                  /                                @29 "occupational exposures to "
                  /                                @29 "continuous environmental exposures"
                / @3 "-----"     @17 "---------" @29 "----------------------------"
                  // "-------------------------------------------------------------"
                // @3 "EC1% = " @10 "&EC_1Percent" @25 "(µg Cr(VI)/m3); Rx = " @39 "&Extra_Riskm"
                // "-------------------------------------------------------------"
                  /"The risks are calculated from age " ageall0 " up to age " Tmp "."
                 // ;

        if ageall1 NE ageCs1 then
           put /"WARNING: The last age for the all-causes rates differs from"
               /"         the last age for the cause-specific rates, suggesting"
               /"         the possibility that the rates weren't entered as desired."
               /;
        END;
   Stop;
   run;
/* BT 7/5/19: Start of code that was added to merge variables for unexposed risk
                            (S_1i and S_1ix) to the rest of the output, by age;
Data newSRCData(keep=SRC_age SRC_S_1i SRC_S_1ix);
               set ex_Risk;
               SRC_age=0; SRC_S_1i=1; SRC_S_1ix=1;
               output;

               do obsnum=1 to last-1;
               set ex_Risk point=obsnum nobs=last;
               if _error_ then abort;
                      SRC_age=age+1; SRC_S_1i=S_1i; SRC_S_1ix=S_1ix;
               output;
               end;
```

```
Values of macro variables used in this computation:
Value Macro_Var Description
----- --------- ----------------------------
1 MODEL 1 = Loglinear Relative Rate,
2 = Linear Relative Rate,
3 = Linear Absolute Rate,
4 = 'Power' Relative Rate,
0 = User defined.
0.001298 COEF Exposure parameter estimate
5 LAG Exposure Lag
16 AGE1ST_X Age exposure begins
85 DURATION Duration of exposure
Yes ENVADJ Adjust dose from intermittent
occupational exposures to
continuous environmental exposures
----- --------- ----------------------------
---------------------------------------------------------------
EC1% = 1.1795769661 (f/ml); Rx = 0.0099999947
---------------------------------------------------------------
The risks are calculated from age 0 up to age 85 .
```

Age at start of year (i)	CE10(adj) (f\cc-yrs)	Lung Cancer hazard (unexposed) (hi)	All cause hazard (unexposed) (h*i)	Lung Cancer hazard (exposed) (hei)	All cause hazard (exposed) (he*i)	Probability of surviving year i assuming alive at start (unexposed) (qi)	Probability of surviving year i assuming alive at start (exposed) (qei)	Probability of surviving to end of year i (unexposed) (S1,i)	Probability of surviving to end of yeari (exposed) (Se1,i)	Cumulative Risk of lung cancer (unexposed) (R0)	Cumulative risk of lung cancer (exposed) (Re)	Extra Risk (Re-R0)\(1-R0)
0	0.0000E+00	0.0000E+00	5.7968E-03	0.0000E+00	5.7968E-03	9.9422E-01	9.9422E-01	1.0000E+00	1.0000E+00	0.0000E+00	0.0000E+00	.
1	0.0000E+00	3.8000E-07	3.8228E-04	3.8000E-07	3.8228E-04	9.9962E-01	9.9962E-01	9.9422E-01	9.9422E-01	3.7773E-07	3.7773E-07	.
2	0.0000E+00	3.8000E-07	2.4152E-04	3.8000E-07	2.4152E-04	9.9976E-01	9.9976E-01	9.9384E-01	9.9384E-01	7.5534E-07	7.5534E-07	.
3	0.0000E+00	3.8000E-07	1.9124E-04	3.8000E-07	1.9124E-04	9.9981E-01	9.9981E-01	9.9360E-01	9.9360E-01	1.1329E-06	1.1329E-06	.
4	0.0000E+00	3.8000E-07	1.5101E-04	3.8000E-07	1.5101E-04	9.9985E-01	9.9985E-01	9.9341E-01	9.9341E-01	1.5103E-06	1.5103E-06	.
5	0.0000E+00	1.0000E-07	1.4096E-04	1.0000E-07	1.4096E-04	9.9986E-01	9.9986E-01	9.9326E-01	9.9326E-01	1.6097E-06	1.6097E-06	.
6	0.0000E+00	1.0000E-07	1.3091E-04	1.0000E-07	1.3091E-04	9.9987E-01	9.9987E-01	9.9312E-01	9.9312E-01	1.7090E-06	1.7090E-06	.
7	0.0000E+00	1.0000E-07	1.1078E-04	1.0000E-07	1.1078E-04	9.9989E-01	9.9989E-01	9.9299E-01	9.9299E-01	1.8083E-06	1.8083E-06	.
8	0.0000E+00	1.0000E-07	1.0072E-04	1.0000E-07	1.0072E-04	9.9990E-01	9.9990E-01	9.9288E-01	9.9288E-01	1.9075E-06	1.9075E-06	.
9	0.0000E+00	1.0000E-07	1.0073E-04	1.0000E-07	1.0073E-04	9.9990E-01	9.9990E-01	9.9278E-01	9.9278E-01	2.0068E-06	2.0068E-06	.
10	0.0000E+00	1.9000E-07	9.0668E-05	1.9000E-07	9.0668E-05	9.9991E-01	9.9991E-01	9.9268E-01	9.9268E-01	2.1954E-06	2.1954E-06	.
11	0.0000E+00	1.9000E-07	1.0075E-04	1.9000E-07	1.0075E-04	9.9990E-01	9.9990E-01	9.9259E-01	9.9259E-01	2.3840E-06	2.3840E-06	.
12	0.0000E+00	1.9000E-07	1.3099E-04	1.9000E-07	1.3099E-04	9.9987E-01	9.9987E-01	9.9249E-01	9.9249E-01	2.5726E-06	2.5726E-06	.
13	0.0000E+00	1.9000E-07	1.9148E-04	1.9000E-07	1.9148E-04	9.9981E-01	9.9981E-01	9.9236E-01	9.9236E-01	2.7611E-06	2.7611E-06	.
14	0.0000E+00	1.9000E-07	2.6209E-04	1.9000E-07	2.6209E-04	9.9974E-01	9.9974E-01	9.9217E-01	9.9217E-01	2.9496E-06	2.9496E-06	.
15	0.0000E+00	3.3000E-07	3.3275E-04	3.3000E-07	3.3275E-04	9.9967E-01	9.9967E-01	9.9191E-01	9.9191E-01	3.2769E-06	3.2769E-06	.
16	0.0000E+00	3.3000E-07	4.2366E-04	3.3000E-07	4.2366E-04	9.9958E-01	9.9958E-01	9.9158E-01	9.9158E-01	3.6040E-06	3.6040E-06	.
17	0.0000E+00	3.3000E-07	5.0459E-04	3.3000E-07	5.0459E-04	9.9950E-01	9.9950E-01	9.9116E-01	9.9116E-01	3.9310E-06	3.9310E-06	.
18	0.0000E+00	3.3000E-07	6.0584E-04	3.3000E-07	6.0584E-04	9.9939E-01	9.9939E-01	9.9066E-01	9.9066E-01	4.2578E-06	4.2578E-06	.
19	0.0000E+00	3.3000E-07	6.9717E-04	3.3000E-07	6.9717E-04	9.9930E-01	9.9930E-01	9.9006E-01	9.9006E-01	4.5844E-06	4.5844E-06	.
20	0.0000E+00	4.5000E-07	7.9881E-04	4.5000E-07	7.9881E-04	9.9920E-01	9.9920E-01	9.8937E-01	9.8937E-01	5.0295E-06	5.0295E-06	.
21	1.7939E+00	4.5000E-07	8.9056E-04	4.5105E-07	8.9056E-04	9.9911E-01	9.9911E-01	9.8858E-01	9.8858E-01	5.4741E-06	5.4752E-06	.

Age at start of year (i)	CE10(adj) (f\cc-yrs)	Lung Cancer hazard (unexposed) (hi)	All cause hazard (unexposed) (h*i)	Lung Cancer hazard (exposed) (hei)	All cause hazard (exposed) (he*i)	Probability of surviving year i assuming alive at start (unexposed) (qi)	Probability of surviving year i assuming alive at start (exposed) (qei)	Probability of surviving to end of year i (unexposed) (S1,i)	Probability of surviving to end of yeari (exposed) (Se1,i)	Cumulative Risk of lung cancer (unexposed) (R0)	Cumulative risk of lung cancer (exposed) (Re)	Extra Risk (Re-R0)\(1-R0)
22	5.3818E+00	4.5000E-07	9.7243E-04	4.5315E-07	9.7243E-04	9.9903E-01	9.9903E-01	9.8770E-01	9.8770E-01	5.9184E-06	5.9225E-06	.
23	8.9697E+00	4.5000E-07	1.0241E-03	4.5527E-07	1.0241E-03	9.9898E-01	9.9898E-01	9.8674E-01	9.8674E-01	6.3622E-06	6.3715E-06	.
24	1.2558E+01	4.5000E-07	1.0861E-03	4.5739E-07	1.0861E-03	9.9891E-01	9.9891E-01	9.8573E-01	9.8573E-01	6.8055E-06	6.8222E-06	.
25	1.6145E+01	1.2000E-06	1.1279E-03	1.2254E-06	1.1280E-03	9.9887E-01	9.9887E-01	9.8466E-01	9.8466E-01	7.9865E-06	8.0281E-06	.
26	1.9733E+01	1.2000E-06	1.1597E-03	1.2311E-06	1.1598E-03	9.9884E-01	9.9884E-01	9.8355E-01	9.8355E-01	9.1660E-06	9.2383E-06	.
27	2.3321E+01	1.2000E-06	1.2120E-03	1.2369E-06	1.2121E-03	9.9879E-01	9.9879E-01	9.8241E-01	9.8241E-01	1.0344E-05	1.0453E-05	.
28	2.6909E+01	1.2000E-06	1.2543E-03	1.2427E-06	1.2544E-03	9.9875E-01	9.9875E-01	9.8122E-01	9.8122E-01	1.1521E-05	1.1671E-05	.
29	3.0497E+01	1.2000E-06	1.2968E-03	1.2485E-06	1.2968E-03	9.9870E-01	9.9870E-01	9.7999E-01	9.7999E-01	1.2696E-05	1.2894E-05	.
30	3.4085E+01	3.8200E-06	1.3496E-03	3.9928E-06	1.3498E-03	9.9865E-01	9.9865E-01	9.7872E-01	9.7872E-01	1.6432E-05	1.6799E-05	.
31	3.7673E+01	3.8200E-06	1.4027E-03	4.0114E-06	1.4029E-03	9.9860E-01	9.9860E-01	9.7740E-01	9.7740E-01	2.0163E-05	2.0717E-05	.
32	4.1261E+01	3.8200E-06	1.4559E-03	4.0302E-06	1.4561E-03	9.9855E-01	9.9854E-01	9.7603E-01	9.7603E-01	2.3889E-05	2.4648E-05	.
33	4.4848E+01	3.8200E-06	1.5094E-03	4.0490E-06	1.5097E-03	9.9849E-01	9.9849E-01	9.7461E-01	9.7461E-01	2.7609E-05	2.8591E-05	.
34	4.8436E+01	3.8200E-06	1.5529E-03	4.0679E-06	1.5531E-03	9.9845E-01	9.9845E-01	9.7314E-01	9.7314E-01	3.1324E-05	3.2547E-05	.
35	5.2024E+01	1.0740E-05	1.6171E-03	1.1490E-05	1.6179E-03	9.9838E-01	9.9838E-01	9.7163E-01	9.7163E-01	4.1751E-05	4.3702E-05	.
36	5.5612E+01	1.0740E-05	1.6817E-03	1.1544E-05	1.6825E-03	9.9832E-01	9.9832E-01	9.7006E-01	9.7006E-01	5.2160E-05	5.4891E-05	.
37	5.9200E+01	1.0740E-05	1.7466E-03	1.1598E-05	1.7475E-03	9.9825E-01	9.9825E-01	9.6843E-01	9.6843E-01	6.2552E-05	6.6113E-05	.
38	6.2788E+01	1.0740E-05	1.7911E-03	1.1652E-05	1.7920E-03	9.9821E-01	9.9821E-01	9.6674E-01	9.6674E-01	7.2926E-05	7.7367E-05	.
39	6.6376E+01	1.0740E-05	1.8670E-03	1.1706E-05	1.8680E-03	9.9813E-01	9.9813E-01	9.6501E-01	9.6501E-01	8.3280E-05	8.8653E-05	.
40	6.9964E+01	3.1310E-05	1.9329E-03	3.4286E-05	1.9359E-03	9.9807E-01	9.9807E-01	9.6321E-01	9.6320E-01	1.1341E-04	1.2165E-04	.
41	7.3552E+01	3.1310E-05	2.0409E-03	3.4447E-05	2.0440E-03	9.9796E-01	9.9796E-01	9.6135E-01	9.6134E-01	1.4348E-04	1.5473E-04	.
42	7.7139E+01	3.1310E-05	2.1600E-03	3.4607E-05	2.1632E-03	9.9784E-01	9.9784E-01	9.5939E-01	9.5938E-01	1.7348E-04	1.8789E-04	.
43	8.0727E+01	3.1310E-05	2.3112E-03	3.4769E-05	2.3147E-03	9.9769E-01	9.9769E-01	9.5732E-01	9.5731E-01	2.0342E-04	2.2114E-04	.

Age at start of year (i)	CE10(adj) (f\cc-yrs)	Lung Cancer hazard (unexposed) (hi)	All cause hazard (unexposed) (h*i)	Lung Cancer hazard (exposed) (hei)	All cause hazard (exposed) (he*i)	Probability of surviving year i assuming alive at start (unexposed) (qi)	Probability of surviving year i assuming alive at start (exposed) (qei)	Probability of surviving to end of year i (unexposed) (S1,i)	Probability of surviving to end of yeari (exposed) (Se1,i)	Cumulative Risk of lung cancer (unexposed) (R0)	Cumulative risk of lung cancer (exposed) (Re)	Extra Risk (Re-R0)\(1-R0)
44	8.4315E+01	3.1310E-05	2.4740E-03	3.4931E-05	2.4776E-03	9.9753E-01	9.9753E-01	9.5511E-01	9.5509E-01	2.3329E-04	2.5446E-04	.
45	8.7903E+01	8.5060E-05	2.6485E-03	9.5341E-05	2.6588E-03	9.9736E-01	9.9734E-01	9.5275E-01	9.5273E-01	3.1422E-04	3.4517E-04	.
46	9.1491E+01	8.5060E-05	2.8455E-03	9.5786E-05	2.8562E-03	9.9716E-01	9.9715E-01	9.5023E-01	9.5020E-01	3.9494E-04	4.3606E-04	.
47	9.5079E+01	8.5060E-05	3.0865E-03	9.6233E-05	3.0976E-03	9.9692E-01	9.9691E-01	9.4753E-01	9.4749E-01	4.7541E-04	5.2710E-04	.
48	9.8667E+01	8.5060E-05	3.3615E-03	9.6682E-05	3.3731E-03	9.9664E-01	9.9663E-01	9.4461E-01	9.4456E-01	5.5562E-04	6.1826E-04	.
49	1.0225E+02	8.5060E-05	3.6927E-03	9.7133E-05	3.7047E-03	9.9631E-01	9.9630E-01	9.4144E-01	9.4138E-01	6.3555E-04	7.0953E-04	.
50	1.0584E+02	2.4321E-04	4.0381E-03	2.7903E-04	4.0739E-03	9.9597E-01	9.9593E-01	9.3797E-01	9.3790E-01	8.6322E-04	9.7070E-04	.
51	1.0943E+02	2.4321E-04	4.4092E-03	2.8033E-04	4.4464E-03	9.9560E-01	9.9556E-01	9.3419E-01	9.3408E-01	1.0899E-03	1.2320E-03	.
52	1.1302E+02	2.4321E-04	4.8284E-03	2.8164E-04	4.8669E-03	9.9518E-01	9.9514E-01	9.3008E-01	9.2994E-01	1.3156E-03	1.4932E-03	.
53	1.1661E+02	2.4321E-04	5.3079E-03	2.8295E-04	5.3477E-03	9.9471E-01	9.9467E-01	9.2560E-01	9.2542E-01	1.5401E-03	1.7544E-03	.
54	1.2019E+02	2.4321E-04	5.7950E-03	2.8427E-04	5.8360E-03	9.9422E-01	9.9418E-01	9.2070E-01	9.2049E-01	1.7634E-03	2.0153E-03	.
55	1.2378E+02	5.4508E-04	6.3014E-03	6.4009E-04	6.3964E-03	9.9372E-01	9.9362E-01	9.1538E-01	9.1513E-01	2.2608E-03	2.5992E-03	.
56	1.2737E+02	5.4508E-04	6.8172E-03	6.4307E-04	6.9151E-03	9.9321E-01	9.9311E-01	9.0963E-01	9.0930E-01	2.7549E-03	3.1819E-03	.
57	1.3096E+02	5.4508E-04	7.3433E-03	6.4607E-04	7.4443E-03	9.9268E-01	9.9258E-01	9.0345E-01	9.0303E-01	3.2455E-03	3.7632E-03	.
58	1.3455E+02	5.4508E-04	7.9032E-03	6.4909E-04	8.0072E-03	9.9213E-01	9.9202E-01	8.9684E-01	8.9633E-01	3.7325E-03	4.3427E-03	.
59	1.3813E+02	5.4508E-04	8.4874E-03	6.5212E-04	8.5945E-03	9.9155E-01	9.9144E-01	8.8978E-01	8.8919E-01	4.2154E-03	4.9200E-03	.
60	1.4172E+02	8.7599E-04	9.1319E-03	1.0529E-03	9.3088E-03	9.9091E-01	9.9073E-01	8.8226E-01	8.8158E-01	4.9848E-03	5.8439E-03	.
61	1.4531E+02	8.7599E-04	9.8165E-03	1.0578E-03	9.9983E-03	9.9023E-01	9.9005E-01	8.7424E-01	8.7341E-01	5.7468E-03	6.7633E-03	.
62	1.4890E+02	8.7599E-04	1.0521E-02	1.0628E-03	1.0707E-02	9.8953E-01	9.8935E-01	8.6570E-01	8.6472E-01	6.5012E-03	7.6773E-03	.
63	1.5248E+02	8.7599E-04	1.1246E-02	1.0677E-03	1.1438E-02	9.8882E-01	9.8863E-01	8.5664E-01	8.5551E-01	7.2474E-03	8.5856E-03	.
64	1.5607E+02	8.7599E-04	1.1995E-02	1.0727E-03	1.2192E-02	9.8808E-01	9.8788E-01	8.4706E-01	8.4578E-01	7.9850E-03	9.4873E-03	.
65	1.5966E+02	1.3188E-03	1.2794E-02	1.6224E-03	1.3098E-02	9.8729E-01	9.8699E-01	8.3696E-01	8.3553E-01	9.0817E-03	1.0834E-02	.

Age at start of year (i)	CE10(adj) (f\cc-yrs)	Lung Cancer hazard (unexposed) (hi)	All cause hazard (unexposed) (h*i)	Lung Cancer hazard (exposed) (hei)	All cause hazard (exposed) (he*i)	Probability of surviving year i assuming alive at start (unexposed) (qi)	Probability of surviving year i assuming alive at start (exposed) (qei)	Probability of surviving to end of year i (unexposed) (S1,i)	Probability of surviving to end of yeari (exposed) (Se1,i)	Cumulative Risk of lung cancer (unexposed) (R0)	Cumulative risk of lung cancer (exposed) (Re)	Extra Risk (Re-R0)\(1-R0)
66	1.6325E+02	1.3188E-03	1.3708E-02	1.6300E-03	1.4019E-02	9.8639E-01	9.8608E-01	8.2632E-01	8.2466E-01	1.0164E-02	1.2169E-02	.
67	1.6684E+02	1.3188E-03	1.4733E-02	1.6376E-03	1.5051E-02	9.8538E-01	9.8506E-01	8.1507E-01	8.1318E-01	1.1231E-02	1.3491E-02	.
68	1.7042E+02	1.3188E-03	1.5901E-02	1.6453E-03	1.6228E-02	9.8422E-01	9.8390E-01	8.0315E-01	8.0103E-01	1.2282E-02	1.4798E-02	.
69	1.7401E+02	1.3188E-03	1.7239E-02	1.6529E-03	1.7573E-02	9.8291E-01	9.8258E-01	7.9048E-01	7.8814E-01	1.3315E-02	1.6089E-02	.
70	1.7760E+02	1.9811E-03	1.8603E-02	2.4947E-03	1.9116E-02	9.8157E-01	9.8107E-01	7.7697E-01	7.7441E-01	1.4840E-02	1.8003E-02	.
71	1.8119E+02	1.9811E-03	2.0533E-02	2.5063E-03	2.1059E-02	9.7968E-01	9.7916E-01	7.6265E-01	7.5974E-01	1.6336E-02	1.9887E-02	.
72	1.8478E+02	1.9811E-03	2.2345E-02	2.5180E-03	2.2882E-02	9.7790E-01	9.7738E-01	7.4715E-01	7.4391E-01	1.7799E-02	2.1739E-02	.
73	1.8836E+02	1.9811E-03	2.4496E-02	2.5298E-03	2.5044E-02	9.7580E-01	9.7527E-01	7.3064E-01	7.2708E-01	1.9229E-02	2.3556E-02	.
74	1.9195E+02	1.9811E-03	2.6694E-02	2.5416E-03	2.7255E-02	9.7366E-01	9.7311E-01	7.1296E-01	7.0910E-01	2.0623E-02	2.5333E-02	.
75	1.9554E+02	2.6576E-03	2.9472E-02	3.4255E-03	3.0239E-02	9.7096E-01	9.7021E-01	6.9418E-01	6.9004E-01	2.2441E-02	2.7662E-02	.
76	1.9913E+02	2.6576E-03	3.2525E-02	3.4415E-03	3.3309E-02	9.6800E-01	9.6724E-01	6.7402E-01	6.6948E-01	2.4204E-02	2.9928E-02	.
77	2.0272E+02	2.6576E-03	3.6079E-02	3.4575E-03	3.6879E-02	9.6456E-01	9.6379E-01	6.5245E-01	6.4755E-01	2.5907E-02	3.2126E-02	.
78	2.0630E+02	2.6576E-03	4.0056E-02	3.4737E-03	4.0872E-02	9.6074E-01	9.5995E-01	6.2933E-01	6.2410E-01	2.7546E-02	3.4250E-02	.
79	2.0989E+02	2.6576E-03	4.4352E-02	3.4899E-03	4.5184E-02	9.5662E-01	9.5582E-01	6.0462E-01	5.9911E-01	2.9118E-02	3.6294E-02	.
80	2.1348E+02	3.0963E-03	4.9367E-02	4.0849E-03	5.0356E-02	9.5183E-01	9.5089E-01	5.7839E-01	5.7264E-01	3.0865E-02	3.8576E-02	.
81	2.1707E+02	3.0963E-03	5.4690E-02	4.1039E-03	5.5698E-02	9.4678E-01	9.4582E-01	5.5053E-01	5.4452E-01	3.2524E-02	4.0749E-02	.
82	2.2065E+02	3.0963E-03	6.1072E-02	4.1231E-03	6.2099E-02	9.4076E-01	9.3979E-01	5.2123E-01	5.1502E-01	3.4090E-02	4.2808E-02	.
83	2.2424E+02	3.0963E-03	6.8884E-02	4.1423E-03	6.9930E-02	9.3344E-01	9.3246E-01	4.9035E-01	4.8401E-01	3.5557E-02	4.4745E-02	.
84	2.2783E+02	3.0963E-03	7.6927E-02	4.1617E-03	7.7992E-02	9.2596E-01	9.2497E-01	4.5771E-01	4.5132E-01	3.6921E-02	4.6552E-02	.
84	2.2783E+02	3.0963E-03	7.6927E-02	4.1617E-03	7.7992E-02	9.2596E-01	9.2497E-01	4.2382E-01	4.1746E-01	3.6921E-02	4.6552E-02	0.0099999947

1

APPENDIX F. QUALITY ASSURANCE FOR THE IRIS TOXICOLOGICAL REVIEW OF HEXAVALENT CHROMIUM

This assessment is prepared under the auspices of the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) Program. The IRIS Program is housed within the Office of Research and Development (ORD) in the Center for Public Health and Environmental Assessment (CPHEA). EPA has an agency-wide quality assurance (QA) policy that is outlined in the *EPA Quality Manual for Environmental Programs* (see CIO 2105-P-01.1) and follows the specifications outlined in EPA Order CIO 2105.1.

As required by CIO 2105.1, ORD maintains a Quality Management Program, which is documented in an internal Quality Management Plan (QMP). The latest version was developed in 2013 using Guidance for Developing Quality Systems for Environmental Programs (QA/G-1). An NCEA/CPHEA-specific QMP was also developed in 2013 as an appendix to the ORD QMP. Quality assurance for products developed within CPHEA is managed under the ORD QMP and applicable appendices.

The IRIS Toxicological Review of Hexavalent Chromium is designated as Highly Influential Scientific Information (HISA) and is classified as QA Category A. Category A designations require reporting of all critical QA activities, including audits. The development of IRIS assessments is done through a seven-step process. Documentation of this process is available on the IRIS website: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process.

Specific management of quality assurance within the IRIS Program is documented in a Programmatic Quality Assurance Project Plan (PQAPP). A PQAPP is developed using the EPA Guidance for Quality Assurance Project Plans (QA/G-5), and the latest approved version is dated June 2022. All IRIS assessments follow the IRIS PQAPP, and all assessment leads and team members are required to receive QA training on the IRIS PQAPP. During assessment development, additional QAPPs may be applied for quality assurance management. They include:

Title	Document number	Date
Program Quality Assurance Project Plan (PQAPP) for the Integrated Risk Information System (IRIS) Program	L-CPAD-0030729-QP-1-5	June 2022
An Umbrella Quality Assurance Project Plan (QAPP) for Dosimetry and Mechanism-Based Models (PBPK)	L-CPAD-0032188-QP-1-2	January 2021
Quality Assurance Project Plan (QAPP) for Enhancements to Benchmark Dose Software (BMDS)	L-HEEAD-0032189-QP-1-2	October 2020

During assessment development, this project undergoes quality audits during assessment development including:

Date	Type of audit	Major findings	Actions taken
Augusts 2018	Technical system audit	None	None
August 2019	Technical system audit	None	None
August 2020	Technical system audit	None	None
July 2021	Technical system audit	None	None
August 2022	Technical system audit	None	None

During Step 3 and Step 6 of the IRIS process, the IRIS toxicological review is subjected to external reviews by other federal agency partners, including the Executive Offices of the White House. Comments during these IRIS process steps are available in the docket *EPA-HQ-ORD-2014-0313* on http://www.regulations.gov.

During Step 4 *[include this section AFTER Step 4]* of assessment development, the IRIS Toxicological Review of [chemical X] undergoes public comment from [insert date of public comment]. Following this comment period, the toxicological review undergoes external peer review by [SAB/NAS/contractor peer-review panel] on [insert date of ERD]. The peer-review report is available on the [NAS/SAB website—include the URL]. All public and peer-review comments are available in the docket *[insert chemical docket number—make sure that the ERD public comments are available in the docket as well]*.

[Include this section AFTER Step 6] Prior to release (Step 7 of the IRIS process), the final toxicological review is submitted to management and QA clearance. During this step the CPHEA QA Director and QA Managers review the project QA documentation and ensure that EPA QA requirements are met.

APPENDIX G. RESPONSE TO EXTERNAL COMMENTS

1 *[Template placeholder]*

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