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

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EXECUTIVE SUMMARY

Summary of Occurrence and Health Effects

Chromium is a ubiquitous element present in soil, water, air, and food that can originate from both natural and anthropogenic sources. This toxicological review restricts its focus to hexavalent chromium compounds, which are a group of substances that contain chromium in the hexavalent (+6) oxidation state, denoted as Cr(VI). Cr(VI) compounds have many industrial applications, including pigment manufacturing, corrosion inhibition and metal finishing. Because many Cr(VI) compounds are water soluble, they are highly mobile in soil and may contaminate drinking water. Cr(VI) may be emitted into air by industries using Cr(VI) compounds, and by various other sources such as the burning of fossil fuels.

The systematic review (see Appendix A for methods) conducted to support this assessment evaluated all cancer outcomes, and noncancer effects for the following potential target systems: respiratory, gastrointestinal (GI) tract, hepatic, hematological, immune, reproductive, and developmental. For cancer and nasal effects via the inhalation route (which are well established), the systematic review focused on data that may inform the quantitative dose-response analysis.

Evidence indicates that Cr(VI) is likely to cause GI tract, liver, developmental, and lower respiratory toxicity in humans. Evidence suggests that Cr(VI) may cause male reproductive effects, immune effects, and hematological toxicity in humans. Evidence is inadequate to assess whether Cr(VI) causes female reproductive toxicity in humans. Organ/system-specific reference values were derived for GI tract, liver, developmental, hematological, and nasal effects. The overall chronic RfD is 9×10^{-4} mg/kg-day, and the overall chronic RfC is 3×10^{-5} mg/m^3.

For cancer via the oral route of exposure, Cr(VI) is *likely to be carcinogenic* to the human GI tract. Because a mutagenic mode-of-action (MOA) for Cr(VI) carcinogenicity 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, 2005a). The Cr(VI) oral slope factor (OSF) estimated for exposure to adults (i.e., without ADAF application) is 0.16 (mg/kg-day)$^{-1}$, based on tumors in the oral cavity of female rats. Furthermore, in the absence of chemical-specific data to evaluate differences in age-specific susceptibility, increased early-life susceptibility to Cr(VI) is assumed and EPA applied ADAFs in accordance with the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The total lifetime exposure OSF for Cr(VI) is 0.27 (per mg/kg-day).

For cancer via the inhalation route of exposure, quantitative exposure-response data were evaluated, and an inhalation unit risk (IUR) was developed for human lung cancer. Linear low dose extrapolation and application of ADAFs were performed for the inhalation route of exposure. The Cr(VI) IUR estimated for exposure to adults (i.e.,

without ADAF application) is 1.1×10^{-2} [μg Cr(VI)/m^3]$^{-1}$. The total lifetime exposure IUR for Cr(VI) is 1.8×10^{-2} [μg Cr(VI)/m^3]$^{-1}$.

ES.1 EVIDENCE FOR HAZARDS OTHER THAN CANCER: ORAL EXPOSURE

The evidence indicates that Cr(VI) is likely to cause gastrointestinal (GI) tract toxicity in humans following oral ingestion (see Section 3.2.2). The evidence also indicates that Cr(VI) is likely to cause hepatic and developmental toxicity in humans via either the oral or inhalation routes (see Sections 3.2.4 and 3.2.9), though hepatic effects are more likely to occur following oral exposures due to the first-pass effect. The determination that evidence indicates that Cr(VI) is likely to cause GI toxicity in humans was based on toxicology studies in rodents reporting histological effects in the GI tract. For the determination of hepatic toxicity, toxicology studies in rodents reported histological effects in the liver and serum indicators of hepatotoxicity. The determination for developmental effects was based on the observation of decreased offspring growth across most animal studies. For the hazards listed above, mechanistic evidence supported the human relevance of the effects observed in animals.

The evidence suggests that Cr(VI) may cause immune, hematological, and male reproductive toxicity in humans via the oral or inhalation routes (see Sections 3.2.5, 3.2.6, 3.2.7). Male reproductive effects on sperm parameters and testosterone were observed in both human and animal studies, however most studies were considered *low* confidence, and effects were inconsistent among the *high* confidence rodent studies. For hematological effects, *high* confidence studies in rodents reported changes in hematological parameters that suggested a pattern consistent with regenerative microcytic hypochromic anemia, but the confidence in this judgment was diminished due to uncertainty regarding the apparent transient nature of the effects. The conclusion for immune effects was primarily based on coherent evidence of effects on 1) ex vivo WBC function across human and animal studies, 2) antibody responses to T cell-dependent antigen measured in animals, and 3) reduction in host resistance to bacterial infection reported in animal studies; however, confidence in the evidence was reduced due to primarily *low* confidence studies reporting findings that were often inconsistent across studies.

The evidence is inadequate to assess whether Cr(VI) causes female reproductive toxicity in humans via the oral or inhalation routes (see Section 3.2.8). Although an association with female reproductive toxicity was demonstrated in a single *low* confidence epidemiology study and a series of *low* confidence animal toxicology studies, effects were not observed in *medium* or *high* confidence studies aside from a moderate decrease in maternal body weight.

ES.1.1. Oral Reference Dose (RfD)

Hyperplasia in the small intestine of female B6C3F1 mice was selected as the basis for the overall chronic RfD of 9×10^{-4} mg/kg-day. A LOAEL analysis was used to derive an organ/system-specific point of departure (POD) for GI tract effects. Human equivalent doses (HEDs) were calculated using PBPK modeling to account for species differences and human variability in

detoxification of Cr(VI) in the stomach. A composite uncertainty factor of 100 was applied. This uncertainty factor incorporated: an interspecies uncertainty (UF_A) of 3 to account for animal-to–human extrapolation (pharmacodynamic differences); an intraspecies uncertainty (UF_H) of 3 to account for variation in susceptibility across the human population, and the possibility that the available data may not be representative of individuals who are most susceptible to the effects; and a LOAEL-to-NOAEL uncertainty (UF_L) of 10 to account for extrapolation from the LOAEL. The remaining uncertainty factors were equal to 1.

The confidence in the overall chronic RfD is medium-high. The RfD is based on a *high* confidence chronic 2-year drinking water study by NTP (2008) that exposed rats and mice of both sexes to Cr(VI) as sodium dichromate dihydrate (see Section 3.2.2). Multiple *high* confidence subchronic studies also support these data, and mechanistic studies support the involvement of oxidative stress in Cr(VI)-induced cytotoxicity in a variety of tissues, including the GI tract. However, overall confidence in this osRfD is somewhat reduced because the data for this endpoint are not amenable to BMD modeling, resulting in the reliance on a LOAEL as the POD. Organ/system-specific RfDs (osRfDs) are listed in Table ES-1.

Table ES-1. Organ/system-specific RfDs and overall RfD for Cr(VI)

Hazard	Basis	osRfD mg/kg-d	Study exposure description	Confidence
Gastrointestinal system (GI tract)	Hyperplasia in small intestine of female mice	9×10^{-4}	Chronic drinking water	Medium-High
Hepatic system	Chronic inflammation in female rats	7×10^{-4}	Chronic drinking water	Medium-High
Developmental toxicity	Decreased F1 offspring postnatal growth	0.07	Continuous breeding	Low
Hematological toxicity	Decreased Hgb (male rats)	0.01	Subchronic drinking water	Medium
Overall RfD	**GI tract effects**	**9×10^{-4}**	**Chronic drinking water**	**Medium-High**

The osRfD for hepatic effects was based on chronic inflammation in female F344 rats reported in NTP (2008). An osRfD of 7×10^{-4} mg/kg-day was derived using a LOAEL analysis. Human equivalent doses (HEDs) were calculated using pharmacokinetic modeling to account for species differences and human variability in detoxification of Cr(VI) in the stomach. A composite uncertainty factor of 100 was applied. This uncertainty factor incorporated: an interspecies uncertainty (UF_A) of 3 to account for animal-to-human extrapolation (pharmacodynamic differences); an intraspecies uncertainty (UF_H) of 3 to account for variation in susceptibility across the human population, and the possibility that the available data may not be representative of

individuals who are most susceptible to the effects; and a LOAEL-to-NOAEL uncertainty (UF_L) of 10 to account for extrapolation from the LOAEL. The remaining uncertainty factors were equal to 1. There is medium-high confidence in this osRfD. It is based on a *high* confidence chronic study in rats and there are other subchronic data and mechanistic evidence to support the liver endpoints (see Section 3.2.4). However, overall confidence in this value is reduced due to the minimal severity of the chronic inflammation, and because the data for the endpoint were not amenable to BMD modeling, a LOAEL was used as the POD (see Section 4.1.2.3).

The osRfD for developmental toxicity was based on decreased F1 offspring postnatal growth from the continuous breeding study in BALBC mice (NTP, 1997). The osRfD was 0.07 mg/kg-day and was based on extrapolation from a NOAEL. A human equivalent dose (HED) was calculated using PBPK modeling to account for species differences and human variability in detoxification of Cr(VI) in the stomach. A composite uncertainty factor of 10 was applied. This uncertainty factor incorporated: an interspecies uncertainty (UF_A) of 3 to account for animal-to-human extrapolation (pharmacodynamic differences); an intraspecies uncertainty (UF_H) of 3 to account for variation in susceptibility across the human population, and the possibility that the available data may not be representative of individuals who are most susceptible to the effects. The remaining uncertainty factors were equal to 1. There is low confidence in this osRfD. While it is based on a *high* confidence continuous breeding study and similar effects on decreased offspring growth observed in multiple other studies (see Section 3.2.9), this effect only occurred in high dose groups where other toxicological effects (as indicated by the lower points of departure in Table ES-2) may be occurring. Lower confidence in this osRfD was assigned due to the possibility that other toxicities could be affecting the animals in the high dose groups where developmental effects were observed.

The osRfD for hematological toxicity was based on decreased Hgb in male F344 rats at 22 days reported in NTP (2008). Hematological effects were observed to have the highest magnitude at short time periods and ameliorate over time. As a result, short-term/low-dose data from NTP (2008) were used, and a subchronic-to-chronic uncertainty factor was not applied. An osRfD of 0.01 mg/kg-day was derived using BMD analysis and PBPK modeling. A composite uncertainty factor of 10 was applied. This uncertainty factor incorporated: an interspecies uncertainty (UF_A) of 3 to account for animal-to-human extrapolation (pharmacodynamic differences); an intraspecies uncertainty (UF_H) of 3 to account for variation in susceptibility across the human population, and the possibility that the available data may not be representative of individuals who are most susceptible to the effects. There is medium confidence in this osRfD. It is based on a *high* confidence study in rats and there are other subchronic data and mechanistic evidence to support the endpoint. However, confidence is somewhat diminished due to the apparent transient nature of the observed hematological effects (see Section 3.2.5).

Table ES-2. Summary of reference dose (RfD) derivation

Critical effect	Point of departure mg/kg-d	UF	Candidate Value (mg/kg-d)	osRfD (mg/kg-d)
GI TRACT TOXICITY				
Mice (M) diffuse epithelial hyperplasia of duodenum[a] NTP (2008)	$BMDL_{10\%ER\text{-}HED}$: 0.0443	10	4.43×10^{-3}	**9×10^{-4}**
Mice (F) diffuse epithelial hyperplasia of duodenum[a] NTP (2008)	$LOAEL_{HED}$: 0.0911	100	9.11×10^{-4}	
HEPATIC TOXICITY				
Rat (M) liver ALT (12 mo) NTP (2008)	$BMDL_{1RD\text{-}HED}$: 0.204	10	0.0204	**7×10^{-4}**
Rat (M) liver ALT (3 mo) NTP (2008)	$NOAEL_{HED}$: 0.191	30	6.37×10^{-3}	
Rat (M) liver ALT (90 d) NTP (2007)	$LOAEL_{HED}$: 0.203	300	6.77×10^{-4}	
Rat (F) liver ALT (90 d) NTP (2007)	$LOAEL_{HED}$: 0.190	300	6.33×10^{-4}	
Rat (F) liver chronic inflammation (2 yr) NTP (2008)	$LOAEL_{HED}$: 0.0669	100	6.69×10^{-4}	
Mouse (F) liver chronic inflammation (2 yr) NTP (2008)	$BMDL_{10\%ER\ HED}$: 0.182	10	0.0182	
Rat (F) liver fatty change (2 yr) NTP (2008)	$NOAEL_{HED}$: 0.0669	10	6.69×10^{-3}	
DEVELOPMENTAL TOXICITY				
Mouse (F) Decreased F1 postnatal growth NTP (1997)	$NOAEL_{HED}$: 0.700	10	0.0700	**0.07**
HEMATOLOGICAL TOXICITY				
Rat (M) decreased Hgb (22 d) NTP (2008)	$BMDL_{1SD\ HED}$: 0.126	10	0.0126	**0.01**

[a]Duodenum: the most proximal subsection of the small intestine, immediately distal to the stomach.

ES.2 EVIDENCE FOR HAZARDS OTHER THAN CANCER: INHALATION EXPOSURE

As stated in the Cr(VI) IRIS Assessment Protocol (see Appendix A), EPA did not re-evaluate the qualitative evidence for an association between inhalation Cr(VI) exposure and nasal effects. On the basis of EPA's 1998 evaluation of the literature and the determination that the effects of Cr(VI) on the nasal cavity have been well established [e.g., OSHA (2006) and U.S. EPA (2014b)], hazard identification was not performed for nasal effects. Rather, the review of the evidence for nasal effects focused on identifying studies that might improve the quantitative dose-response analysis for this outcome.

EPA evaluated qualitative evidence for an association between inhalation Cr(VI) exposure and lower respiratory toxicity. EPA determined that Cr(VI) is likely to cause lower respiratory tract toxicity, based on evidence in six *medium* confidence animal studies examining lung cellular responses and/or histopathology. Because histopathological and cellular changes occurred together, and in combination with serum biomarkers indicating an inflammatory response, these were considered indicators of adverse responses. The human evidence for Cr(VI)-induced lower respiratory effects is limited in terms of number and confidence of studies. However, three of the available five studies provide some indication of exposure-related decrements in lung function assessed using spirometry. Mechanistic evidence supports the respiratory tract effects observed in animals. As discussed in Section ES.1, several other hazards (hepatic, developmental, immune, hematological, and male reproductive toxicity) were identified from evidence bases that included inhalation studies in animals and/or in humans exposed primarily via inhalation, but the inhalation data for these effects outside of the respiratory system were limited and composed primarily of *low* confidence studies.

ES.2.2. Inhalation Reference Concentration (RfC)

The overall RfC was based on effects in the upper respiratory tract (ulceration of the nasal septum) reported by *medium* confidence studies (see Section 4.2). Effects of Cr(VI) on the nasal cavity have been well established to occur in humans, and this was also the most sensitive effect. Therefore, this RfC is considered protective of the other noncancer effects. Organ/system-specific RfCs are listed in Table ES-3.

Table ES-3. Organ/system-specific RfCs and overall RfC for Cr(VI)

Hazard	Basis	osRfC mg/m^3	Study exposure description	Confidence
Respiratory (upper tract)	Ulcerated nasal septum in humans	3×10^{-5}	Occupational longitudinal study	Medium
Overall RfC	**Respiratory effects**	**3×10^{-5}**	**Occupational longitudinal study**	**Medium**

Effects in the nasal cavity included irritation/ulceration of the nasal mucosa or septum, perforation of the septum, and bleeding nasal septum. The osRfC (for the upper respiratory tract, see Table ES-4) was derived using data of nasal septum ulceration in humans from Gibb et al. (2000a). LOAEL analyses were used to derive the upper respiratory tract related points of departure (POD) (see Section 4.2.2). A composite uncertainty factor of 100 was applied. This uncertainty factor incorporated: an intraspecies uncertainty factor (UF_H) of 3 to account for variation in susceptibility across the human population and the possibility that the available data may not be representative of individuals who are most susceptible to the effect; a LOAEL-to-NOAEL uncertainty factor (UF_L) of 10 because this endpoint had a high incidence at the lowest

concentration across multiple studies; and a subchronic-to-chronic uncertainty factor (UF_S) of 3 because data were not from chronic lifetime exposures (however, the effects had a short onset time) (see Section 4.2.3).

Table ES-4. Summary of reference concentration (RfC) derivation

Critical effect	Point of departure mg/m³	UF	Candidate value mg/m³	osRfC mg/m³
UPPER RESPIRATORY TRACT TOXICITY				
Ulceration of the nasal septum Gibb et al. (2000a)	LOAEL: 3.4×10^{-3}	100	3.4×10^{-5}	**3×10^{-5}**
Nasal mucosal pathology Cohen et al. (1974)	LOAEL: 9.5×10^{-4}	100	9.5×10^{-6}	
Ulceration of the nasal septum Lindberg and Hedenstierna (1983)	LOAEL: 6.6×10^{-4}	100	6.6×10^{-6}	

ES.3 EVIDENCE FOR HUMAN CARCINOGENICITY

Under EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), Cr(VI) is **likely to be carcinogenic** to humans by the oral route of exposure. The evidence of carcinogenicity to the GI tract from animal studies is *robust*, and the evidence of carcinogenicity from human studies is *slight*. There is strong supporting mechanistic evidence for Cr(VI) involvement in biological pathways contributing to carcinogenesis. See Section 3.2.3 for more details.

As noted in the Protocol (see Appendix A), this assessment maintains the previous determination that Cr(VI) is **carcinogenic to humans** by the inhalation route of exposure based on long-standing evidence of a causal relationship between inhalation of Cr(VI) and increased incidence of lung cancer in humans in occupational settings.

ES.4 QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK: ORAL EXPOSURE

The animal database for cancer by oral exposure consisted of a high confidence chronic 2-year drinking water bioassay which found "clear evidence of carcinogenic activity" of Cr(VI) in male and female rats and mice (NTP, 2008). These results were based on increased incidences of squamous cell neoplasms in the oral cavity of rats, and increased incidences of neoplasms in the small intestine of mice. Using these data, benchmark dose (BMD) modeling was applied to derive points of departure (PODs) for small intestinal tumors in mice and oral tumors in rats (see Section 4.3). For mice, human equivalent doses (HEDs) were calculated using PBPK modeling to account for species differences in detoxification of Cr(VI) in the stomach because tumors occurred in the small intestine (after stomach reduction to Cr(III)). For rats, HEDs were calculated using $BW^{3/4}$ scaling in accordance with U.S. EPA (2011), because tumors occurred in the oral cavity (prior to stomach reduction to Cr(III)). 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, 2005a, 2011).

The lifetime oral cancer slope factor for humans is defined as the slope of the line from the lower 95% bound on the exposure at the POD to the control response (slope factor = 0.1/HED($BMDL_{10}$) or 0.01/HED($BMDL_{01}$)). Specifically, using dosimetric extrapolation from the $BMDL_{10}$ or $BMDL_{01}$, human equivalent oral slope factors were derived for each sex/species/tumor site combination and are listed in Table ES-5. The Cr(VI) oral slope factor estimated for exposure to adults (i.e., without ADAF application) is 0.16 (per mg/kg-day), based on tumors in the oral cavity of female rats.

Table ES-5. Summary of oral slope factor (OSF) derivation

Critical effect	Point of departure mg/kg-d[a]	Human equivalent dose mg/kg-d	Adult exposure OSF[b] $(mg/kg\text{-}d)^{-1}$	Confidence
Adenomas or carcinomas in the mouse small intestine of male mice NTP (2008)	$BMDL_{01\%ER}$: 0.0208	0.0931[c]	0.107	High
Adenomas or carcinomas in the mouse small intestine of female mice NTP (2008)	$BMDL_{01\%ER}$: 0.0232	0.102[c]	0.0980	High
Squamous cell carcinoma or squamous cell papilloma in oral mucosa or tongue of male rats NTP (2008)	$BMDL_{10\%ER}$: 3.37	0.923[d]	0.108	High
Squamous cell carcinoma or squamous cell papilloma in oral mucosa or tongue of female rats NTP (2008)	**$BMDL_{10\%ER}$: 2.70**	**0.645[d]**	**0.155**	**High**
Adult exposure OSF[b]: 0.16 $(mg/kg\text{-}d)^{-1}$ (rounded from 0.155) **Lifetime exposure OSF for squamous cell carcinomas or squamous cell papillomas in the female rat tongue or oral mucosa, after application of the age-dependent adjustment factors at constant dose: 0.27 $(mg/kg\text{-}d)^{-1}$ (see Section 4.3.4 for derivation)**				

[a]For intestinal tumors the point of departure is for the gastric PBPK-predicted internal dose (dose escaping reduction in the stomach) while for oral cavity tumors it is the ingested dose.
[b]OSF values without application of the age-dependent adjustment factors.
[c]Estimated by PBPK modeling after application of $BW^{3/4}$ scaling adjustment (internal dose multiplied by $(BW_A/BW_H)^{1/4}$, where BW_H = 80 kg (human body weight) and BW_A (animal body weight) is set to a study-specific value.
[d]Estimated by $BW^{3/4}$ scaling adjustment (ingested dose multiplied by $(BW_A/BW_H)^{1/4}$, where BW_H = 80kg and BW_A is set to a study-specific value.

The OSF for intestinal tumors was estimated using mouse internal doses calculated using the gastric PBPK model in the low-dose region, using a BMR of 1%, to account for nonlinearity in the intestinal dosimetry in mice and to obtain a POD in the range where the human

pharmacokinetic model indicates that humans are more effective at detoxifying Cr(VI) (see Section 3.1.2.2). The resulting OSF values extrapolated from male and female mice for tumors of the small intestine at low doses have an average of 0.10 $(mg/kg\text{-}day)^{-1}$. This value represents a population mean slope factor for adult exposures at low doses. Specifically, while the value is based on the lower 95% confidence limit (BMDL) of the dose estimated to cause a 1% tumor response in mice, the median HED obtained from probabilistic sampling of gastric dosimetry was used (details in Appendix C.1.5.2), so the result is presumed to represent the average cancer risk for the healthy adult population described by the PBPK model.

Likewise, the OSF values for oral cavity tumors are presumed to represent a population mean slope factor for adult exposures because the $BW^{3/4}$ scaling used for animal-human extrapolation provides a prediction of the extent to which Cr(VI) reduction in the oral epithelial tissues is expected to be lower in an average human adult compared with an average adult rat. In particular, the intestinal and oral cavity OSF estimates do not specifically address interindividual variability in susceptibility. Because a mutagenic MOA for Cr(VI) carcinogenicity (see Section 3.2.3) is "sufficiently supported in (laboratory) animals" and "relevant to humans," and as there are no chemical-specific data to evaluate the differences between adults and children, increased early-life susceptibility should be assumed. If there is early-life exposure, age-dependent adjustment factors (ADAFs) should be applied, as appropriate, in accordance with the EPA's *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* (U.S. EPA, 2005b).

The total lifetime exposure OSF for Cr(VI) derived from the oral cavity tumor response in female rats by application of the ADAFs is **0.27 $(mg/kg\text{-}day)^{-1}$** (rounded from 0.265 $(mg/kg\text{-}day)^{-1}$). Partial oral slope factors for different age groups are provided in Section 4.3.4.

ES.5 QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK: INHALATION EXPOSURE

In 1998, the EPA IRIS Toxicological Review of Hexavalent Chromium classified Cr(VI) as a "known human carcinogen by the inhalation route of exposure" based on consistent evidence that inhaled Cr(VI) causes lung cancer in humans and supporting evidence of carcinogenicity in animals (U.S. EPA, 1998). The same conclusion has since been reached by other authoritative federal and state health agencies and international organizations and the carcinogenicity of Cr(VI) is well established for inhalation exposures (TCEQ, 2014; OSHA, 2006; NTP, 2011; NIOSH, 2013; IPCS, 2013; IARC, 2012; CalEPA, 2011). As stated in the 2014 preliminary packages (U.S. EPA, 2014a, b) and the Systematic Review Protocol (see Appendix A), the review of cancer by the inhalation route focused on data that may improve the quantitative exposure-response analysis conducted in EPA's 1998 IRIS assessment. An overview of the literature screening for exposure-response data is contained in Section 4.4.1.

The IUR was based on an occupational cohort by Gibb et al. (2000b); (2020); of chromate production workers at a facility in Baltimore, MD. Details of the cohort are contained in Section 4.4.

Because a mutagenic MOA for Cr(VI) carcinogenicity is "sufficiently supported in (laboratory) animals" and "relevant to humans," and as there are no chemical-specific data to

evaluate the differences between adults and children, increased early-life susceptibility should be assumed. If there is early-life exposure, age-dependent adjustment factors (ADAFs) should be applied, as appropriate, in accordance with the EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

Partial unit risks for different age groups are provided in Section 4.4.4. Table ES-6 summarizes the derivation of the IUR.

Table ES-6. Summary of inhalation unit risk (IUR) derivation

Critical effect	Basis	Adult exposure IUR $[\mu g\ Cr(VI)/m^3]^{-1}$	Study exposure description	Confidence
Cancer	Lung cancer Gibb et al. (2020)	1.11×10^{-2}	Occupational cohort	High
Adult exposure IUR: 1.1×10^{-2} $[\mu g\ Cr(VI)/m^3]^{-1}$ (rounded from 1.11×10^{-2}) **Lifetime exposure IUR for human lung cancer, after application of ADAFs: 1.8×10^{-2} $[\mu g\ Cr(VI)/m^3]^{-1}$**				

ES.6 SUSCEPTIBLE POPULATIONS AND LIFE STAGES

Susceptible populations and life stages refers to groups of people who may be at increased risk for negative health consequences following chemical exposures due to factors such as life stage, genetics, race/ethnicity, sex, health status and disease, lifestyle factors, and other co-exposures. Populations susceptible to increased risks for negative health consequences of Cr(VI) exposure include:

- Individuals with preexisting health effects that overlap with those caused by Cr(VI) exposure may be at increased risk. Health conditions that may be exacerbated by Cr(VI) exposure include gastrointestinal diseases, liver diseases, respiratory diseases, and anemia.

- Individuals with chronically high stomach pH are expected to detoxify Cr(VI) less effectively, leading to increased uptake of Cr(VI) in the gastrointestinal tract following oral exposure. High stomach pH can be caused by a number of factors, such as low gastric acid (hypochlorhydria), usage of medications to treat gastroesophageal reflux disease (GERD), and population variability.

- Individuals with genetic polymorphisms conveying deficiencies in DNA repair capacity may have increased susceptibility to Cr(VI)-induced cancer.

- Carriers of a mutated cystic fibrosis transmembrane conductance regulator (CFTR) allele may be at higher risk of Cr(VI)-induced cancers of the gastrointestinal tract. Suppression of the CFTR gene was shown to enhance intestinal tumorigenesis in animal models. CFTR was shown to be inactivated in mice exposed to Cr(VI). Thus, individuals with an impaired CFTR due to genetics may suffer an even further reduction in CFTR expression levels following oral exposure to Cr(VI).

Life stages susceptible to increased risks for negative health consequences of Cr(VI) exposure include:

- The developmental life stage (in utero) is considered susceptible because Cr(VI) was determined to likely cause developmental toxicity in humans.
- Neonates, infants, and young toddlers less than 30 months old, which exhibit elevated stomach pH and therefore cannot effectively detoxify Cr(VI).
- Elderly populations (aged 65 and older) may be at higher risk because they exhibit some preexisting health conditions associated with aging that may be exacerbated by oral or inhalation exposure to Cr(VI). This includes conditions that cause elevated stomach pH.

ES.7 ORAL ABSORPTION UNCERTAINTIES AND ASSUMPTIONS APPLIED IN HAZARD IDENTIFICATION AND MODE-OF-ACTION ANALYSES

Even under controlled rodent pharmacokinetic studies, assessing the oral absorption and whole-body distribution of orally administered Cr(VI) at low doses involves uncertainty. Only the total chromium concentration, which includes the trivalent and hexavalent oxidation states, can be reliably measured in tissues in vivo, and most total chromium is likely to be Cr(III). Total chromium measured in tissues of animals orally exposed to Cr(VI) results from:

- Rapid cellular uptake of administered Cr(VI) that was absorbed into the body as Cr(VI), and subsequently reduced to Cr(III) within that tissue.
- Slow cellular uptake of Cr(III) that was absorbed into the body as Cr(III), formed from administered Cr(VI) that reduced to Cr(III) extracellularly and outside of systemic circulation (e.g., gastric juices).
- Slow cellular uptake of Cr(III) that was absorbed into the body as administered Cr(VI) and reduced by other components within systemic circulation (e.g., plasma, liver, red blood cells). For example, plasma can reduce Cr(VI) extracellularly, and the resulting Cr(III) absorbed into other tissues. RBCs can reduce Cr(VI) intracellularly, and the resulting Cr(III) can be released to systemic circulation (to be absorbed by other tissues) after RBCs are broken down.
- Background uptake and distribution of dietary and drinking water chromium (Cr(III) and/or Cr(VI)) not administered or controlled in the bioassay.

Additional details are provided in Section 3.1 (Pharmacokinetics) and Appendix C.1. Elevated chromium concentrations in red blood cells (RBCs) are a strong indicator that Cr(VI) was absorbed in the GI tract unreduced and was not subsequently reduced by the liver during first-pass metabolism. Uptake and reduction of Cr(VI) by RBCs is rapid, and the resulting Cr(III) in red blood cells is bound to hemoglobin and/or diffuses out of the RBC slowly. Therefore, elevated RBC chromium persists longer relative to plasma chromium levels following systemic Cr(VI) absorption. On the basis of analyses of the RBC:plasma ratios of exposed and unexposed rodents from the(NTP,

2007, 2008) studies (see Appendix C.1.2), general assumptions, summarized in Figure ES-1, were made when interpreting animal studies for hazard identification and MOA:

- At oral *ad libitum* doses below 1 mg/kg-day, Cr(VI) is absorbed by the GI tract, but most Cr(VI) absorbed by the GI tract is reduced to Cr(III) by the liver (and to a lesser extent, plasma and RBCs in the portal vein). At these low doses, the GI tract and liver are exposed to Cr(VI), but exposure to other systems may be low and highly variable. There is high uncertainty as to whether other systemic tissues receive consistent exposure to Cr(VI) at these doses across all the studies. Therefore, inconsistent pharmacokinetic and toxicological results among studies for doses below 1 mg/kg-day are to be expected.

- At oral *ad libitum* doses greater than or equal to 1 mg/kg-day, Cr(VI) is absorbed by the GI tract, exceeds the reducing capacity of the liver, and is widely distributed to systemic tissues (e.g., kidney, lung, brain). Exposure to systemic tissues may still be highly variable, and there may be some inconsistencies in dose-response between studies.

- For oral gavage doses at any level, Cr(VI) is widely distributed to systemic tissues, and results in significantly higher internal doses than dietary and drinking water exposure. This is because the gavage route greatly condenses the timescale of an exposure, surpassing gastric reduction capacity (ad libitum exposures are distributed over a 24-hour period, whereas gavage occurs over a very short period).

- Injection studies (intravenous or intraperitoneal) will expose systemic tissues to significantly greater levels of Cr(VI) than oral gavage studies because there is not a first-pass effect (reduction of Cr(VI) in the stomach and liver). Following injection, there will also be (temporarily) more Cr(VI) available in the plasma prior to uptake to RBCs.

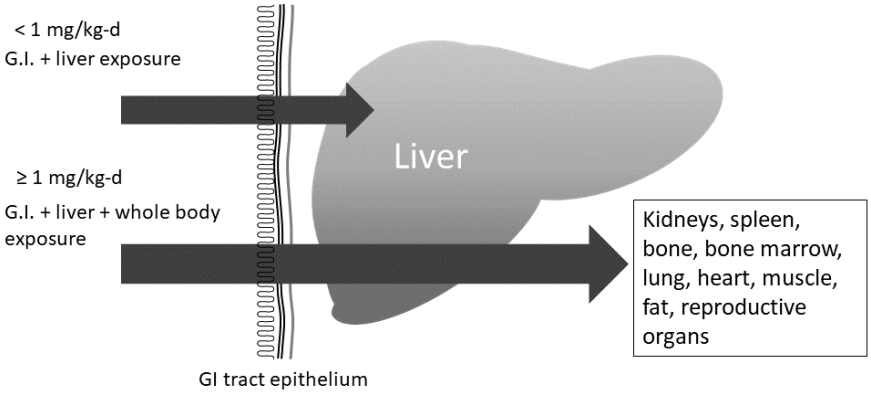

Figure ES-1. General assumptions regarding absorption and distribution of Cr(VI) ingested by rodents during ad libitum drinking water or dietary bioassays. At doses <1 mg/kg-d, it is assumed that Cr(VI) is absorbed by the small intestine, and most of the absorbed Cr(VI) is reduced by the liver. At doses ≥1 mg/kg-d, it is assumed that systemic absorption and distribution of Cr(VI) throughout the whole body will occur.

Despite uncertainties below 1 mg/kg-day, these assumptions were adequate for interpreting the current Cr(VI) database because most studies were conducted using doses greater than 1 mg/kg-day. The 1 mg/kg-day dose level was not used as a cutoff for the inclusion of data or to make inferences about low-dose extrapolation, but instead was used to generally evaluate the uncertainties of results. For studies in which the daily oral ad libitum dose was much greater than 1 mg/kg-day, there is higher certainty that Cr(VI) reaches target tissues. For studies in which the daily oral ad libitum doses were lower than 1 mg/kg-day, there is added uncertainty when analyzing data outside of the GI or liver, because it cannot be assumed that Cr(VI) reaches other target systemic tissues at high enough doses that can induce observable effects. In general, it can be assumed that ingested Cr(VI), even at low doses, will expose at least the surface GI epithelial cells if not the liver. For chronic exposure collection periods of the NTP (2008) distribution study (collection days 182 and 371, with 2-day washout period), liver chromium concentrations were significantly elevated at all dose groups (including <1 mg/kg-day) in rats and mice. Human radiolabeled-Cr studies performed by Donaldson and Barreras (1966) demonstrated that very low concentrations of Cr(VI) (1.3×10^{-5} mg/L, or 0.013 ppb) can be absorbed by the small intestine and distributed systemically (see Section 3.1.2.2).