**Table 1. Summary of Key Pharmacokinetic Data Sets for Chromium in Humans**

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| **Valence** | **Form** | **Reference** | **n** | **Exposure** | **Plasma** | **Erythrocytes** | **Urine** | **Note** |
| Cr(III) | Dichromate (reduced in OJ) | Kerger et al.[31] | 4 | 1x  (5 mg) | X | NU | X |  |
|  | Chloride | Kerger et al.[31] | 5 | 1x  (5 mg) | X | NU | X |  |
|  | Chloride | Anderson et al.[27,28,29] | 17-76 | 3 months  (0.2 mg/d) | X |  | X |  |
|  | Chloride | Mohamedshah et al.[30] | 6 | 3 d  (0.4 mg/d) | X |  | X |  |
|  | Picolinate | Lukaski et al.[33] | 83 | 12 weeks  (0.2 mg/d) | X |  | X |  |
|  | Picolinate | Volpe et al.[32] | 44 | 12 weeks  (0.4 mg/d) | X | X | X |  |
|  | Chloride | Rubin et al.[34] | 10 | 1x  (0.3 mg) |  |  | X |  |
|  | Picolinate | Gargas et al.[35] | 8 | 3x  (0.4 mg/d) |  |  | X |  |
| Cr(VI) | Chromate | Finley et al.[26] | 5 | 3x3d  (0.1, 0.5, 1, 5, 10 mg/d) | X | NU | X |  |
|  | Dichromate | Paustenbach et al.[36] | 1 | 17 d  (4 mg/d) | X | NU | X | Background levels for Cr in plasma from Finley et al. (1997) were used to calculate |
|  | Dichromate | Kerger et al.[31] | 5 | 1x  (5 mg/d) | X | NU | X |  |
|  | Dichromate | Goullé et al.[42] | 1 | 1x  (~800 mg) | X | X | X | Background levels from Anderson et al. (1982, 1983, 1985) and Volpe et al. (2001) used o calculate added Cr |

NU = not used due to concerns that erythrocytes were not sufficiently rinsed to remove Cr from the erythrocyte cell membrane (personal communication, B.Kerger).

**Table 2. GI Model Parameters**

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| **Group** | **Description** | **Symbol** | **Units** | **Adult** | **Source** |
| Tissue Volumes | Duodenum  Ileum  Jejunum  Stomach | vdc  vic  vjc  vsc | Unitless (fraction of body weight) | 0.00077  0.0042  0.0038  0.0021 | Tissue volumes for all GI tissues reflect values for adults from ICRP[45]. |
| Blood Flows | Duodenum  Ileum  Jejunum  Stomach | qdc  qic  qjc  qsc | Unitless (fraction of portal flow or cardiac output) | 0.07  0.39  0.35  0.19 | Fractions of portal blood flows were assumed to be proportionate to tissue fractions of body weight. |
| Transit | Stomach to Duodenum  Duodenum to Jejunum  Jejunum to Ileum  Ileum to Large Int.  Large Int. to Feces | klsd  kldj  klji  klil  kfx | hr-1 | 1.2  4.3  0.94  0.63  0.039 | GI transit rates for total diet in adult males were adopted as constants for simulations fit to data[45]. Transit rate constants for each GI section were calculated as ln(2) divided by the transit halftime (estimates as ICRP transit times divided by 2). Transit rates for the small intestines sections were apportioned by relative length of the duodenum, jejunum, and ileum as reported in ICRP[45]. |
| Lumen Content Rates | Food Intake  Water Intake  Saliva Production  Gastric Fluid Production | rfood  rdrink  rsal  rgif | L/hr\*kg | 0.00067  0.00057  0.00063  0.0010 | Average intake rates were assumed for food (16 g/kg-day) and water (1.1 L/d), normalized to average body weight of 80 kg[69]. Salivation and gastric fluid production rates were calculated from ICRP[45]. |
| Lumen Volumes | Stomach lumen volume  Duodenum lumen volume  Jejunum lumen volume  Ileum lumen volume | vslc  vdlc  vjlc  vilc | Fraction body weight | 0.0034  0.00038  0.0018  0.0026 | GI lumen volumes are from ICRP[45]. Lumen volumes for the small intestines sections were apportioned by relative length of the duodenum, jejunum, and ileum. |
| Lumen  pH | Stomach pH  Duodenum pH  Jejunum pH  Ileum pH | pHs  pHd  pHj  pHi | Unitless | 2.5  6  6.5  7 | A gastric pH of 2.5 was considered to reflect a daily time-weighted average value over fed and fasted states based on review of data on diurnal variation in humans[24,47,65,67,68] |
| Reduction | Reducing equivalents in gastric fluid  pH-Dep 2nd Order Rate Constant  Tissue 1st Order Rate Constant | cre0  kredgifc  kredgit | mg/L  L/mg\*hr  hr-1 | 20  44.5  71 | The value for reducing equivalents value is considered to be a representative of a daily average value based upon the range estimated for fasting conditions (4-10 mg/L; range estimated from individual samples this study) fed conditions (approximately 30 mg/L estimated from the data of De Flora et al.[24]. The pH-dependent rate of Cr(VI) reduction in GI lumen is based on fits to *ex vivo* data collected in this study. Intracellular reduction values based on reduction rates fit to data for rat erythrocytes[58] |
| GI Absorption | Rate constant Cr(III) abs., stomach  Rate constant Cr(VI) abs., stomach  Rate constant Cr(III) absorption, SI  Rate constant Cr(VI) absorption, SI  Rel uptake by duodenum of Cr(III)  Rel uptake by duodenum of Cr(VI)  Rel uptake by jejunum of Cr(III)  Rel uptake by jejunum of Cr(VI)  Rel uptake by ileum of Cr(III)  Rel uptake by ileum of Cr(VI)  SI Cell sloughing  Duodenum length  Jejunum length  Ileum length | kabs3s  kabs6s  kabs3  kabs6  rad3  rad6  raj3  raj6  rai3  rai6  kslough  dl  jl  il | L/ hr  L/hr  L/cm\*hr  L/cm\*hr  unitless  unitless  unitless  unitless  unitless  unitless  hr-1  cm  cm  cm | 0.  0.  4.2E-05a  1.04E-03b  1  1  0.1  0.3  0.024  0.022  0.029  22.4  104  154 | Assumed negligible based on relative surface area and transit time.  Assumed negligible based on relative surface area and transit time.  Parameter values for absorption were adjusted for each data set to match Cr mass measured at the last cumulative urine data point.  Basis of comparison for other sections (duodenum defined as 1)  Rodent values for relative uptake in SI sections[16] were assumed for humans.  Sloughing rates are based on cell turnover rates, which range from approximately 1-5 days (Creamer et al.). Using 2 days as representative value for this range, a halftime of 24 hours was assumed to calculate the rate constant for SI (rate constant = ln(2)/halftimes). Small intestines section lengths are from ICRP[45]. |
| Blood: Tissue Transfer | T-Cr(III): GI tissue to plasma  Cr(VI): GI tissue to plasma | kout3  kout6 | Unitless | 0.03  0.11 | Value adjusted to achieve a fraction of Cr body burden in SI (~3%) to match that measured in pigs exposed to Cr(III)[70]  Calculated from kout3 assuming proportionality to rodent values[16] |

aArithmetic mean of values estimated for each Cr(III) data set: Anderson et al.[27,28,29] (1.9E-05), Mohamedshah et al. [30](4.2E-05), Rubin et al.[34](8.8E-05), Kerger et al.[31](1.1E-05, 3.6E-05), Lukaski et al.[33](3.3E-05), Volpe et al.[32](2.0E-05), Gargas et al.[35](8.3E-05)

bArithemetic mean of values estimated for each Cr(VI) data set: Paustenbach et al.[36](1.3E-03), Kerger et al.[31](7.8E-04)

**Table 3. Systemic Model Parameters**

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| **Group** | **Description** | **Symbol** | **Units** | **Adult** | **Source** |
| Tissue Volumes | Bone  Blood  Fraction portal  Hematocrit  Kidney  Liver  Other tissues | vbc  vblc  fpt  hct  vkc  vlc  votc | Unitless (fraction of body weight) | 0.14  0.073  0.205  0.434  0.0042  0.025  calc | Tissue volumes for adult males were obtained from ICRP[45]. Fractional volume of other tissue compartment calculated as 1–vbc-vlc-vkc-vsc-vdc-vjc-vic-vblc. |
| Tissue Blood Flows | Bone  Kidney  Liver (excluding portal)  Other tissues | qbc  qkc  qlc  qotc | Unitless (fraction of cardiac output) | 0.05  0.19  0.065  calc | Tissue blood flows for adults were obtained from ICRP[45]. |
| Blood Tissue Transfer Coefficients | Cr(VI): plasma to tissue  C-Cr(III): plasma to kidney  T-Cr(III): plasma to kidney  T-Cr(III): plasma to bone  T-Cr(III): plasma to liver  T-Cr(III): plasma to other  C-Cr(III): bone to plasma  C-Cr(III): liver to plasma  C-Cr(III): other to plasma  Scaling factors for plasma to tissue, tissue to plasma  Cr(VI): plasma to erythrocyte  T-Cr(III): plasma to erythrocyte  C-Cr(III): erythrocyte to plasma | kin6  kinccr  kintcrk  kintcrb  kintcrl  kintcrot  koutccrb  koutccrl  koutccrot  SFin  SFout  krbcin6  krbcin3  krbcout3 | Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  Unitless  L/hr  L/hr  L/hr | 4.6  0.03a  0.15b  0.25  0.081  0.016  0.000057  0.0004  0.0002  0.15  40  6.  0.0018  0.002 | Based on the average value estimated for rodents[16]  Model parameters for (kinccr, kintcrk) to adjusted to fit plasma and urine data for Cr(III) and Cr(VI) data sets (see Table 1), with early time points being dependent on kintcrk and late time points being dependent on kinccr.  Based upon the similarity in liver:kidney tissue ratios in mice and humans (i.e., greater than 1 in both species), human parameter values for distribution of Cr(III) in liver, bone, and other tissues were scaled from mice rather than rats[16], where the scaling factor was adjusted to provide fits to plasma data. Mouse plasma-to-tissue parameter values were multiplied by a factor of 0.15. Mouse tissue-to-plasma parameter values were multiplied by a scaling factor of 40.  Values adjusted based upon fits to data sets with multiple time points for plasma[30,31,36,42]  Parameter values for distribution to erythrocytes (krbcin6, krbcin3, krbcout3) were adjusted to fit data from Volpe et al.[32] and Goullé et al.[42]. |
| Reduction in Tissues | Cr(VI) reduction in tissues  Cr(VI) reduction in plasma  Cr(VI) reduction in erythrocytes | kred  kredbp  kredrc | /hr | 71  0.66  71 | For rats, rates for reduction in erythrocytes and plasma are based on the data of Richelmi and Baldi[58]. Intracellular rate for erythrocytes was adopted for all tissues. All rat values were adopted for the mouse. |
| Excretion | Urinary excretion rate | kurcc | /hr | 0.03 | Value obtained by adjusting parameter to provide fits to all Cr(III) and Cr(VI) urinary excretion data (Table 1), while maintaining a liver:kidney tissue concentration ratio above 1 during exposure. |
| General | Body weight  Cardiac output | wbody  qcc | kg  L/hr | 80  15.6 | Values for adult males were obtained from ICRP[45] |

aData set of Mohamedshah et al.[30] required a slower clearance from plasma (kinccr=0.012). Data set of Paustenbach et al.[36] required a more rapid clearance from plasma (kinccr=0.06).

bData set of Mohamedshah et al.[30] required a slower clearance from plasma (kintcrk=0.06).

**Table 4. Sensitivity Analysis**

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| **Dose Measure** | **Units** | **Parameter (symbol: sensitivity\*)** |
| Cr(VI) flux from stomach lumen per kg SI tissue | mg/kg-day | Stomach lumen pH (phs: 12.8%)  Stomach lumen transit (klsd: 10.6%)  Lumen reducing equivalents (cre0: 5.1%)  Volume stomach lumen (vslc: 4.8%)  Lumen reduction rate (kredgifc: 4.6%)  Volume ileum (vic: 2.3%)  Volume jejunum (vjc: 2.1%)  Regeneration of gastric reducing equivalents (rfoodc, rgifc, rdrinkc, rsalc: 1.3%) |
| Cr(VI) flux into SI tissue | mg/kg-day | Stomach lumen pH (phs: 12.9%)  Duodenum lumen pH (phd: 12.2%)  Stomach lumen transit (klsd: 10.6%)  Lumen reducing equivalents (cre0: 8.1%)  Lumen reduction rate (kredgifc: 7.5%)  Jejunum lumen pH (6.3%)  Volume stomach lumen (vslc: 4.8%)  SI absorption rate (kabs6: 4.4%) |
| Fraction absorbed | Unitless | SI absorption rate (kabs3: 3.8%)  Stomach lumen pH (phs: 3.1%)  Length duodenum (ld: 3.0%)  Duodenum lumen pH (phd: 3.0%)  Stomach lumen transit (2.6%)  Volume duodenum lumen (vdlc: 2.6%)  Relative absorption duodenum (rad3: 2.3%)  Duodenum lumen transit (kldj: 2.7%) |
| Liver:Kidney tissue concentration ratio | Unitless | Urinary excretion (kurcc: 5.0%)  Scaling factor, systemic tissue to plasma (SFout: 4.9%)  Cardiac output (qcc: 4.4%)  Hematocrit (hct: 4.2%)  Scaling factor, plasma to systemic tissue (SFin: 3.9%)  Kidney blood flow (qkc: 3.6%)  Transfer plasma to kidney (kintcrk: 3.3%)  Stomach lumen pH (phs: 2.2%) |
| Erythrocyte:Plasma concentration ratio | Unitless | Stomach lumen pH (phs: 8.4%)  Duodenum lumen pH (phd: 7.9%)  Stomach lumen transit (klsd: 6.8%)  Transfer erythrocyte to plasma (krbcout3: 4.4%)  Lumen reducing equivalents (cre0: 4.1%)  Kidney blood flow (qkc: 4.0%)  Lumen reduction rate (kredgifc: 3.7%)  Transfer plasma to erythrocyte (krbcin3: 2.8%)  Volume stomach lumen (vslc: 2.6%) |

\*Sensitivity measured by reporting the percent change in the dose measure value when the model parameter value is increased by 5%. (for example, in the first line a 5% change in phs results in a 12.8% change in predicted Cr(VI) flux). The top eight parameters are presented for each internal dose. Simulations for the sensitivity analysis were for 0.1 mg Cr(VI)/kg-day, assuming the dose is spread over 5 exposure events per day.