NAVAL MEDICAL RESEARCH UNIT DAYTON

AVAILABILITY OF ACUTE AND/OR SUBACUTE TOXICOKINETIC DATA FOR SELECT COMPOUNDS FOR THE RAT AND PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELS FOR RATS AND HUMANS FOR THOSE COMPOUNDS

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14. ABSTRACT

US Army Center for Environmental Health Research (USACEHR) has expressed a need for support for the physiologically based pharmacokinetic (PBPK) modeling efforts. Specifically, information has been requested regarding the availability of acute and/or subacute toxicokinetic data and PBPK models for arsenic, cadmium, chromium, cobalt, lead, nickel, allyl alcohol, bromobenzene, and carbon tetrachloride, in the rat. As the interest in these models pertains to data development in the rat and extrapolation to humans, PBPK models for humans were also of interest. Short-term toxicokinetic data in the rat were identified for all compounds of interest. Toxicokinetic/biokinetic models for at least one species (rat or human) exist for all compounds of interest except nickel and bromobenzene.
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Availability of acute and/or subacute toxicokinetic data for select compounds for the rat and physiologically based pharmacokinetic (PBPK) models for rats and humans for those compounds

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EXECUTIVE SUMMARY

US Army Center for Environmental Health Research (USACEHR) has expressed a need for support for the physiologically based pharmacokinetic (PBPK) modeling efforts. Specifically, information has been requested regarding the availability of acute and/or subacute toxicokinetic data and PBPK models for arsenic, cadmium, chromium, cobalt, lead, nickel, allyl alcohol, bromobenzene, and carbon tetrachloride, in the rat. As the interest in these models pertains to data development in the rat and extrapolation to humans, PBPK models for humans were also of interest.

Arsenic: Available PBPK models primarily address long-term human exposure, but a model for rats has been developed. Toxicokinetic data not previously considered in rat PBPK model development are available for various forms of arsenic.

Cadmium: Human "biokinetic" models of cadmium exist, but are not generally amenable to interspecies extrapolation. Cadmium mass balance and tissue time course data are available for the rat.

Chromium: PBPK models for rats and humans exist, but primarily address long-term exposure. Most of the available rat toxicokinetic data have been used in model validation/calibration.

Cobalt: No PBPK models of cobalt disposition in the rat were identified in the literature. The existing cobalt models for humans are not generally amenable to interspecies extrapolation. Many mass balance and tissue time course data sets pertaining to cobalt are available for the rat.

Lead (Pb): PBPK models emphasizing long-term exposure have been developed for rats and humans have been developed. Limited evaluation suggests that they are also consistent with short-term exposure data.

Nickel: No PBPK model of nickel exist. Mass balance and tissue time course data were identified for rats.

Allyl alcohol: A single PBPK model was identified for rats, and none for humans, but the model was not validated and has deficiencies. Limited toxicokinetic data for rats were identified.

Bromobenzene: No PBPK models were identified for bromobenzene for any species. Mass balance and tissue time course were identified for rats.

Carbon tetrachloride: Validated/calibrated PBPK models were identified for rats and humans, primarily addressing the inhalation route. Additional rat toxicokinetic data addressing blood and tissue concentrations after oral and inhalation exposure were identified.

BACKGROUND

As delineated in Agreement NMR-9704/USAMRMC No. 11180578, US Army Center for Health Research (USACEHR) has expressed a need for support for the physiologically based pharmacokinetic (PBPK) modeling efforts. Specifically, information has been requested regarding the availability of acute and/or subacute toxicokinetic data and PBPK models for arsenic, cadmium, chromium, cobalt, lead, nickel, allyl alcohol, bromobenzene, and carbon tetrachloride, in the rat. As the interest in these models pertains to data development in the rat and extrapolation to humans, PBPK models for humans were also of interest.

METHODS

The primary literature searches were conducted using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed). In order to search broadly with in the available PBPK modeling literature, chemical names of interest were combined with the search "(((pbpk OR pbtk)) OR (((physiologic[Text Word] OR physiologically[Text Word] OR physiological[Text Word]) AND (pharmacokinetic[Text Word] OR pharmacokinetics[Text Word]) AND (model[Text Word] OR models[Text Word] OR modeling[Text Word]))) AND ((English[lang]))) OR (pbpk[All Fields] OR pbtk[All Fields] OR ((physiologic[Text Word] OR physiologically[Text Word] OR physiological[Text Word]) AND based[All Fields] AND (pharmacokinetic[Text Word] OR toxicokinetic[Text Word] OR pharmacokinetics[Text Word]) AND (model[Text Word] OR models[Text Word] OR modeling[Text Word])))". The lead author of this report (LMS) receives daily notifications of new database entries matching the above search strategy for PBPK models, so relevant new models will be identified. In addition, weekly notifications are received for search strategies of the chemical name in combination with "(pharmacokinetic* OR toxicokinetic*) AND rat" to identify new toxicokinetic data of potential interest (rat toxicokinetic data with single or short-term dosing). The lead author of the report reviewed abstracts and promising papers were retrieved and reviewed. Retrieved papers also had their references reviewed to identify relevant literature missed by the primary searches. Key papers were entered into Google Scholar (http://scholar.google.com/) to identify subsequent publications that cited these key papers. If appropriate, the citing papers were also retrieved as part of the literature review.

Key information from identified, relevant papers was extracted (test species, route of exposure, matrices in which test article was measured, model language), entered into tables, and provided below. For each chemical, findings pertaining to the available PBPK models were summarized.

RESULTS

Metals: Arsenic

Arsenic PBPK modeling

PBPK models of arsenic primarily address disposition of ingested inorganic arsenic in humans; one model has addressed the disposition of arsenic in rats. Most of the models derive from the work of Mann et al. (1996a), Yu (1993), or both.

Table A1. Diffusion-limited PBPK model of arsenic(V) (AsV), AsIII, methylarsonic acid (MMA), and dimethylarsinic acid (DMA) in hamsters, rabbits, humans, and mice (Mann et al., 1996a, b; Gentry et al., 2004)

Author(s)	Mann et al. (1996a, b); Gentry et al. (2004)
Species	Hamster and rabbit (Mann et al., 1996a), human (Mann et al., 1996b), mouse (Gentry et al., 2004)
Species details	Not stated for hamster, rabbit or human; female B6C3F1 and C57Bl/6N mice
Route(s)	Rabbit: intravenous (iv) injection; hamster: iv, intratracheal (it), by mouth (po); human: oral (single and repeated), inhalation (repeated) ; mouse: single oral (DMA), or drinking water (sodium arsenite)
Duration	Single bolus (iv, it); single or repeated bolus (po); 5 daily occupational inhalation exposures; 26 week drinking water (mouse)
Tissue dosimetry	Rabbit: amount of urinary AsV, AsIII, DMA, and total arsenic; plasma AsV, AsIII, and DMA amounts; liver, kidney, skin and other tissues total amounts of arsenic Hamster: amounts inorganic arsenic (iAs), MMA, and DMA in urine, feces, liver, and kidney; total arsenic in urine, feces, and body; total arsenic and DMA amounts in skin and lung Human: amounts or amounts per g creatinine of iAs, MMA, DMA, and total As in urine Mouse: radioactivity in feces, liver, kidneys, lungs, and carcass (DMA), DMA in urine; after arsenate dose, radioactivity in urine, feces, liver, kidneys, lungs, skin, carcass and blood and AsV, AsIII, MMA and DMA excreted in urine; after arsenite dose, AsV, AsIII, MMA, and DMA in blood, liver, and urine
Model language	Simusolv 2.1
Code availability	Not provided; some equations provided
Comments/ Narrative	In this model, AsV, AsIII, MMA, and DMA circulate and are described by linked multicompartmental PBPK models. Compartments in the model include the gastrointestinal (GI) tract lumen; plasma in equilibrium with red blood cells (RBC), liver, kidneys, lungs, skin, and other tissue; and nasopharyngeal, tracheobronchial, and pulmonary surfaces. In the model, arsenic deposited on airway surfaces is either absorbed into plasma, or cleared into the GI tract lumen. Arsenic absorbed from the GI tract lumen is transported to the liver, and unabsorbed GI tract arsenic is eliminated in feces; urinary elimination of arsenic is described as occurring from plasma. Arsenic in plasma may also be transported via plasma flow to tissues; tissue uptake of arsenic is assumed to be diffusion limited due to varying capillary properties (e.g., pore size, pore area, and capillary thickness). All arsenic species

	are modeled as being subject to biliary clearance. AsIII loss from skin via desquamation was also modeled as irreversible binding to keratin. Physiological parameters were scaled allometrically as functions of body weight. AsV reduction to AsIII and the reverse oxidation reaction were modeled as occurring in the plasma; AsV reduction, but not oxidation, was also assumed to occur in the kidney. Sequential methylation in the liver, governed by Michaelis-Menten kinetics, was assumed for metabolism of AsIII to MMA and MMA to DMA. Metabolic rate parameters and tissue affinity constants (partition coefficients) were determined by calibration to the available rat and hamster data. The last hamster parameters estimated were the absorption rates. For the human model, optimized hamster/rabbit partition coefficients were used directly, whereas the absorption rates and metabolic parameters were fitted to the available human data. The authors suggest that the model is useful primarily for comparison of urinary excretion of arsenic metabolites after oral or inhalation exposure. Further, they caution that, "The constants estimated within the model should not be used separately, due to the large number of estimated parameters." For the mouse model, the permeability coefficients were assumed to be the same as for the rabbit and hamster, but partition coefficients and metabolic parameters were estimated by fitting the model to the mouse-specific data. Preliminary results from the rabbit, hamster, and human models were also provided in Mann et al. (1994).

Table A2. Berthet et al. (2010) human compartmental based toxicokinetic (CBTK) model for inorganic arsenic (iAs), MMA, and DMA

Author(s)	Berthet et al. (2010)
Species	Humans
Species details	Adult workers at rest or at an activity level of 50 W
Route(s)	Inhalation
Duration	300 work weeks; 1500 exposure days
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Mathematical equations were presented in a prior publication.
Comments/ Narrative	The generic model structure (applied to 14 chemicals) consists of absorption into a central compartment, blood-flow mediated exchange of parent compound between the central compartment and a permeability-limited peripheral compartment, metabolism of the parent

	compound to up to 2 metabolites, excretion of parent compound from the central or peripheral compartments, and excretion of metabolites from the central compartment. For arsenic, the central compartment was equated to total body volume (TBV), with the peripheral compartment equated to liver. Sequential metabolism of iAs to MMA then DMA was assumed to proceed via Michaelis-Menten kinetics. Additional first order renal clearance was also assumed; it is not clear if renal clearance applied to all forms of arsenic, or only inorganic arsenic in this model. The oxidation/reduction reactions for AsV and AsIII included in Mann et al. (1996b) were not represented in the Berthet et al. (2010) arsenic model.

Table A3. PBPK model of iAs (Yu 1993, 1998)

Author(s)	Yu (1993, 1998)
Species	Rats, mice, human
Species details	16.3 kg human child
Route(s)	Oral
Duration	Single administration for rodent calibration data (measured at 24 or 48 h)
Tissue dosimetry	iAs in urine and feces and MMA and DMA excreted for rodents. No calibration or validation.
Model language	Not stated.
Code availability	Not provided. Mass balance equations are provided. The 4^{th} order Runge-Kutta method was used to generate solutions to the coupled differential equations
Comments/ Narrative	The sole circulating moiety in the model was iAs; the author acknowledged that this construct lumps AsIII and AsV, and neglects the circulation of the metabolites MMA and DMA. Compartments in the model include the stomach lumen, GI tract lumen, intestinal tissue, liver, kidney, lung, (other) vessel-rich tissue, fat (rat only), muscle, and skin. In the model, iAs is cleared from the kidney to urine (time-varying in rat), from the liver into feces via biliary excretion (time-varying in rat), and from the GI tract lumen into feces, and independently metabolized to MMA and DMA in the liver only (i.e., the methylation reactions are depicted as parallel, not sequential), via Michaelis-Menten kinetics. Partition coefficients were based on a human poisoning case for rodents and the human child, but the values used for the child model are different from the rodent model. Parameter values were supplied by a private communication from J.P. Brown, California Environmental Protection Agency. The human partition coefficients for the iAs PBPK model are the same as those for AsV and AsIII in further variants of the model (see below, **Table A4, Tables A6-8**). The work was described in a 1993 doctoral dissertation and 1998 publication.

Table A4. PBPK model of AsV, AsIII, MMA, and DMA in humans (Yu 1993, 1999a, b)

Author(s)	Yu (1993, 1999a, b)
Species	Human
Species details	16.3 kg child (1993, 1999a), 70 kg adult (1993, 1999 a, b)
Route(s)	Oral (AsV)
Duration	Single or multiple oral
Tissue dosimetry	No dose metrics used for calibration or validation
Model language	Not stated
Code availability	Not provided. Mass balance equations are provided. The 4th order Runge-Kutta method was used to generate solutions to the coupled differential equations.
Comments/ Narrative	In this version of the human model, the parent compound (AsV) and 3 metabolites circulate and are described by linked multicompartmental PBPK models. Compartments in the model include the stomach lumen (AsV only), GI tract lumen (AsV only), intestinal tissue, liver, kidney, lung, (other) vessel-rich tissue, fat (rat only), muscle, and skin. In the model, AsV is cleared from the liver via biliary excretion and from the GI tract lumen into feces. AsV was assumed to be reduced to AsIII in all tissues by nominally second order reaction of AsV with glutathione (GSH), but no depletion of GSH is considered, rendering the process effectively first order. All arsenic species are modeled as being cleared from the kidney to urine. AsIII was assumed to be metabolized via Michaelis-Menten kinetics directly to both MMA and DMA; MMA is further assumed to also be methylated to DMA. Methylation is assumed to take place in the liver and kidney. Vmax values for methylation were scaled allometrically with a body weight scaling factor of 0.7. Partition coefficients were based on a human poisoning case, but the iAs partition coefficients differ from the partition coefficients used by the author for a rodent model relying on the same partitioning data (see above, **Table A3**). No comparisons to calibration or validation data were shown, although some simulations were said to be "consistent" with some experimental observations, while underpredicting and overpredicting others. The work was described in a 1993 doctoral dissertation and in publications from 1999 (a and b).

Table A5. Bayesian PBPK model of AsV, AsIII, MMA, and DMA in humans (Dong et al., 2016)

Author(s)	Dong et al. (2016); Primarily based on Yu (1999a, b)
Species	Human
Species details	Age-dependent body weight to simulate birth through adulthood
Route(s)	Oral (AsV, AsIII, MMA, DMA)
Duration	At least 65 years (upper end of US National Health and Nutrition Examination Survey [NHANES] population not stated)
Tissue dosimetry	Urinary AsIII levels were used for optimization

Model language	MATLAB
Code availability	Provided as supplementary material
Comments/ Narrative	The structure and many of the parameter values for this model were taken from Yu (1999a, b) (**Table A4**), though the partition coefficients differ from Yu (1999a, b). The following parameters were optimized (using a Bayesian approach) based on fit to urinary AsIII data in reported in NHANES (2011-12): liver/blood partition coefficient for As III, Vmax for conversion of AsIII to MMA, and the urinary elimination rate of AsIII. The model used a liver blood flow rate that is not physiologically realistic (too low, as the value used reflects only the hepatic arterial flow, and omits the portal flow from the GI tract, spleen, and pancreas).

Table A6. PBPK-pharmacodynamic (PD) model of AsV in humans (Ling and Liao, 2007)

Author(s)	Ling and Liao (2007); partially based on Yu (1999a)
Species	Human
Species details	Children, adolescents and adults
Route(s)	Oral (AsV)
Duration	Chronic
Tissue dosimetry	No dose metrics used for calibration or validation
Model language	Not stated
Code availability	Not provided
Comments/ Narrative	In this modification of the Yu (1999a) model, only AsV is considered. The stomach and GI tract lumen are not explicitly modeled, replaced by an assumed absorption efficiency of 85 percent (based on human case studies) and blood dissolution fraction of 0.2 (based on a physiologically based biokinetic model of cesium). The AsV urinary elimination rate of Yu (1999a) is applied to a "bladder" compartment that receives almost 40% of the total blood perfusion (based on rates from Mann et al. 1996b—equivalent to the kidney blood flow). The fecal elimination rate (rather than the biliary elimination rate) of Yu (1999a) is applied to the gastrointestinal tissue concentration of arsenic (the liver appears to be lumped into the GI tract tissue compartment in this model). The other compartments in the model were the lung, skin, and blood. Partition coefficients were taken from Yu (1999a). No reduction or methylation of arsenic was incorporated into this version of the model. While sweat elimination was noted on the flow diagram, the rate was apparently set at zero. No calibration or validation of the model was noted. For the risk characterization, ingestion rates of and arsenic concentrations in various farmed seafood and groundwater were varied, as were body weight, bladder weight, urine elimination rate, and fecal elimination rate. Dose-response relationships (pharmacodynamic [PD]

	modeling) were fit to 3-parameter Hill equations based on target organ concentrations of arsenic. Further application of the PBPK model: Ling and Liao (2009) used a very similar PK model, though absorption efficiency was reduced from 85% (based on arsenic case studies, per Ling and Liao, 2007) to 35% based on studies of polychlorinated biphenyls in fish. (Exposure scenarios and some of the PD modeling parameters were quite different from Ling and Liao, 2007.)

Table A7. PBPK-PD models of AsV, AsIII, MMA and DMA in humans

Author(s)	Liao et al. (2008); partially based on Yu (1999b) and Mann et al. (1996b)
Species	Human
Species details	Children; follow on work addresses adults (see Narrative, below)
Route(s)	Oral (AsV, AsIII)
Duration	Chronic
Tissue dosimetry	No dose metrics used for calibration or validation of Liao et al. (2008) model; urinary DMA used to validate the Chen et al. (2010) variation of the model; urinary DMA and total arsenic were used to validate the Chou et al. (2016) variant of the model.
Model language	MATLAB (stated in some, but not all publications in this series)
Code availability	Not provided; equations provided as an appendix
Comments/ Narrative	The model first presented in this paper (and subsequently reutilized/extended in Liao et al., 2009; Chou et al., 2009; Chen et al., 2010; Liao et al., 2010; Ling et al. 2014) is a departure from the model previously used by Liao and coworkers (**Table A6**). This model combines elements of both the Mann et al. (1996b) and Yu (1999b) human models. As in those models, two species of iAs (AsV and AsIII) and two methylated forms (MMA and DMA) were described using compartmental models. The descriptions of the model structure in the text, the depictions in the diagrams, and the equations in the appendix often show inconsistencies. Referencing that is clearly in error is apparent. Non-physiological elements of model structure are depicted in diagrams or represented in equations. Since model code was not supplied, it is unclear if the errors were primarily transmission errors (present in the paper only) or whether they reflect errors that were part of the model and thus affect the presented results. Given the large level of effort that it would take to document the inconsistencies, only a limited number of examples are given. In some cases, portal blood flow exiting the GI tissues is depicted as returning to a common blood pool, and in others, it flows to the liver. Equations describing this relationship were consistently inaccurate, with GI mass

balance terms having hepatic blood flow returning to the GI. Biliary excretion was generally shown as systemic elimination, rather than elimination into GI tract contents. Oxidation/reduction reactions (AsV ↔ AsIII) stated in the text as occurring in blood, liver, and kidney, were present in the equations for all tissues present in the model (lung, skin, fat, muscle, kidney, liver, and GI tract, in Liao et al., 2008).

These oxidation/reduction reactions were described as first order, at the rate determined by Mann et al. (1996b). The sequential methylation of AsIII to MMA then DMA and the direct demethylation of AsIII to DMA were described as conforming to Michaelis-Menten kinetics, at rates consistent with those in Yu (1999b), with the modification of the MMA to DMA reaction based on the observed age-related variation of urinary DMA/MMA ratios in children and adults. MMA methylation is described on the figure and in the equations as saturable, but only a single rate parameter is reported in the table of metabolic rate constants. Possibly the Michaelis constant (KM) was the same as the AsIII methylation and demethylation KM, and was omitted from the table. Partition coefficients were also taken from Yu (1999b).

In addition to elimination via metabolism, elimination of all forms of arsenic were also described as occurring via losses of body water that sum to the water loss needed to balance daily water intake. Water loss was apportioned among the kidneys, skin, lungs, and GI tract at 60, 20, 12, and 8 percent, respectively, and presumably represent urine, sweat, conditioned exhaled breath, and fecal water content, respectively. Lung water elimination was listed in a table of parameter values, but not depicted in the model diagram or incorporated into the model equations.

Variations/extensions:

Liao et al. (2009). The adult model appears to differ from Liao et al. (2008) only with respect to the MMA methylation rate.

Chou et al. (2009). This model for occupationally-exposed adults adds a human respiratory tract model to describe arsenic exposure via the inhalation route. As in Liao et al. (2008), the MMA methylation is described on the figure and in the equations as saturable, but only a single rate parameter is reported in the table of metabolic rate constants. In this case, the rate is reported as a range (with no explanation) and the MMA methylation rate in the kidney is reported as being more than 3-fold faster than the rate in the liver. A 10-fold reduction in the kidney Vmax in the table would be more consistent with ratios in Liao et al. (2008, 2009) and Chen et al. (2010).

Chen et al. (2010). In this model for children and adults, the age-specific DMA/MMA ratios are computed based on a different data set than that used by Liao et al. (2008). This paper presents limited validation of

	urinary DMA estimates in 4 groups that ate arsenic-containing oysters, clams, seaweed, or shrimp. In the mass balance equation for AsIII in the liver, the term delivery of portal-derived arsenic in blood mistakenly includes the liver blood flow rate rather than the GI blood flow rate. The MMA methylation rate for adults was estimated by allometric scaling of the rate used by Yu (1999b). Units on the Michaelis constants are listed as μmol/h; presumably μmol/L were the intended units. Ling et al. (2014). In this publication, the authors apparently revert to the Liao et al. (2009) metabolism scheme and parameter values, rather than the adult metabolism parameter values in Chou et al. (2009) or Chen et al. (2010), or the altered metabolism scheme and values used in Liao et al. (2010)—see below, **Table A8**). The documentation was poor/incomplete. The mass balance equations in the supplementary material were incomplete, as the GI equations were omitted. The equations also contain several apparent typographical errors (e.g., C_{kin} for C_{skin} twice, Wbilizry for Wbiliary, K_3 and K_4 in place of K_1 and K_2) and the values of the reduction and oxidation first order rate constants (K_1 and K_2) were not provided or referenced. Chou et al. (2016). This most recent publication in the series retains the un-physiological description of blood flow to the GI in the equations, and has some of the same typographical errors seen in other versions (e.g., in the mass balance equation for AsIII in liver, the second instance of QL should be QGI). The model was said to be a modification of that in Chen et al. (2010), but modifications and reasons for making them were not explicitly delineated. Stated values of methylation and elimination parameters frequently differ from those in Chen et al. (2010). Some differences may reflect typographical errors (e.g., 100 μmol/L vs. 0.1 μmol/L), but others cannot be reconciled on the basis of misplaced decimal points or different units (e.g., Vmax values for all the methylation reactions and the urinary elimination constants for MMA and DMA). In this model, predictions of urinary DMA and total arsenic were validated against NHANES data.

Table A8. PBPK-PD model of AsV, AsIII, MMAV, MMAIII, DMAV and DMAIII in humans

Author(s)	Liao et al. (2010); partially based on Yu (1999b) and Mann et al. (1996b)
Species	Human
Species details	Children
Route(s)	Oral (AsV, AsIII)
Duration	Chronic
Tissue dosimetry	None
Model language	Not stated
Code availability	Not provided; equations provided as an appendix

Comments/ Narrative	For this model, a derivative of the Liao et al. 2008 model described in **Table A7**, the metabolism scheme was altered to include oxidation/reduction reactions of MMA (MMAV vs. MMAIII) and DMA (DMAV vs. DMAIII).

Table A9. PBPK model of AsV, AsIII, MMAV, MMAIII, DMAV and DMAIII in humans

Author(s)	El-Masri and Kenyon (2008)
Species	Human
Species details	Adults
Route(s)	Oral (AsV, AsIII)
Duration	Days or chronic
Tissue dosimetry	Urinary iAs, MMA, and DMA
Model language	MATLAB; recoded into Berkeley Madonna by Ruiz et al. (2010); an additional MATLAB implementation was mapped on to a Generalized Toxicokinetic Modeling System for Mixtures (GTMM) by Sasso et al. (2010).
Code availability	Equations provided as an appendix
Comments/ Narrative	This model, which was developed prior to that of Liao et al. (2010) (**Table A8**), includes oxidation/reduction reactions of iAs (AsV, AsIII), MMA (MMAV, MMAIII), and DMA (DMAV, DMAIII). Metabolism of AsIII to DMA is modeled as occurring both directly from AsIII and sequentially from AsIII to MMA to DMA. MMA is modeled as noncompetitively inhibiting AsIII methylation and AsIII is modeled as noncompetitively inhibiting MMA methylation. In this model, the oxidation/reduction reactions of MMA and DMA occur in the "lung" (pooled blood), liver, and kidney, with excretion to urine, but MMAIII and DMAIII are not described as circulating via blood flow. Tissues are described as perfusion limited, rather than diffusion limited. Pharmacokinetic parameter values were taken from a variety of sources, including animal studies (e.g., oral absorption rate), in vitro kinetic studies, and calibration to a human study. The model was validated against additional human data.

Table A10. PBPK model of DMA in mice

Author(s)	Garcia et al. (2015); based on Evans et al. (2008)
Species	Mice
Species details	None
Route(s)	Oral, iv
Duration	Not stated
Tissue dosimetry	Arsenic in urine, feces, blood, lung, liver, kidney, or bladder
Model language	Not stated
Code availability	Equations provided as an appendix

Comments/ Narrative	This model uses Bayesian approaches to update parameter values and assess parameter identifiability for partition coefficients, absorption rate, biliary excretion, and renal excretion.

Studies of arsenic kinetics in rats

Table A11. Arsenic kinetics in the presence and absence of lead (Pb) after AsV dosing

Author(s)	Diacomanolis et al. (2013)
Species details	Adult Sprague-Dawley rat
Test article	Sodium arsenate (AsV)
Route(s)	iv (arsenic only) or po in water (arsenic only or As + Pb)
Duration	240 h
Tissue dosimetry	Total arsenic in blood (iv: 0 [pre-dose], 15, 30, 60 minutes, 3, 6, 12, 24, 48, 72, 96, 10, 144, 192, 216, and 24 h post dose; po: 6, 24, 48, 72, 96, 120, 144, 192, 216, and 240 h post dose) shown in figures. Urinary As (As + Pb dosing: collected at 24, 48, 72, 96, 120, 144, 192, 216, and 240 h post dosing, reported as ng As/24 h urine, mean ± SD or SE). Liver, kidney, and spleen arsenic at 24 h post oral dosing (As alone, or As + Pb)
Comments/ Narrative	Arsenic "did not decline considerably over the experimental time" after reaching a peak early in the study period (10-70 h after dosing). Co-administration of Pb resulted in decreased blood arsenic concentrations, lower arsenic bioavailability, faster absorption of arsenic, and faster elimination of arsenic.

Table A12. Biliary and urinary excretion and tissue distribution of iAs in rats after iAs injection

Author(s)	Gregus and Klaassen (1986)
Species details	Adult male Sprague-Dawley rat (200-300 g)
Test article	Arsenic (III) trichloride
Route(s)	iv, in water
Duration	2 h (biliary excretion and tissue and plasma concentrations); 4 days (fecal and urinary excretion)
Tissue dosimetry	Radiolabel in liver, kidneys, spleen, lung, testes, brain, blood, and plasma.; biliary, fecal, and urinary excretion of radiolabel
Comments/ Narrative	The arsenic data were previously published; this publication represents a compilation of comparable data for 18 metals collected using a consistent protocol. The radiolabeled forms were arsenic trichloride, bismuth nitrate, cadmium chloride, cesium chloride, chromium chloride, cobaltous chloride, cupric nitrate, gold chloride, ferrous sulfate, lead nitrate, manganese chloride, methyl mercuric chloride, mercuric chloride, selenious acid, silver nitrate, thallium nitrate, stannous chloride, and zinc chloride. In urinary and fecal excretion studies, excreta were collected for 24-hr periods for 4 days. Biliary excretion in

	bile-cannulated rats was determined at 2 h after administration; tissue distribution was determined in the same rats upon completion of the biliary excretion assessment. Compared to other metals, AsIII exhibited relatively low total (fecal and urinary) excretion over four days (16.9 ± 0.37% mean ± standard error (SE) of 4-6 rats). After the first day, urinary excretion of AsIII was fairly consistent. Biliary excretion of arsenic was relatively high, compared to other metals. Likewise, bile:plasma ratios for AsIII were relatively high. Most metals had their highest concentrations in the liver or kidney.

Table A13. Biliary and urinary excretion and tissue distribution of iAs and its methylated metabolites in rats after iAs injection

Author(s)	Gregus et al. (2000), Csanaky et al. (2003)
Species details	Adult male Wistar rat
Test article	Sodium arsenite (AsIII), disodium hydrogen arsenate (AsV)
Route(s)	iv
Duration	2 h (urine and bile collection); 10 min or 2 h (tissue distribution)
Tissue dosimetry	AsIII, AsV (only in Gregus et al., 2000), monomethylarsonous acid (MMAsIII) in bile and urine (20 minute intervals). AsIII, AsV, MMAsIII, MMAsV, and DMAsV in blood, heart, liver, and kidney
Comments/ Narrative	AsIII, AsV, and MMAsIII were measured in the bile and urine of rats in which the urinary bladder had been exteriorized and the bile ducts had been cannulated. AsV (Gregus et al., 2000 only) or AsIII (one dose level in Gregus et al., 2000, 3 dose levels in Csanaky et al., 2003) was administered by iv injections, and urine flow was promoted by administration of mannitol in saline. Only AsIII and MMAsIII were detectable in bile, while AsV and AsIII were excreted in urine. Csanaky et al. (2003) observed that AsIII excretion increased "almost proportionately to dose", AsIII concentration increases in tissue were greater than proportionate to dose, and excretion and tissue concentration of methylated metabolites increased less than dose.

Table A14. Arsenic kinetics after a single oral dose of AsIII

Author(s)	Naranmandura et al. (2007)
Species details	Adult male Wistar rat
Test article	Sodium arsenite (AsIII)
Route(s)	Oral, in water
Duration	7 days
Tissue dosimetry	Total arsenic in plasma, RBC, liver, and kidney 1, 3, 5, and 7 days after administration. 24-hr urinary As for each of 7 days post-dosing. Qualitative speciation (DMAV, MMAV, iAsV, arsenobetaine [AsB],

	dimethylmonoarsonic acid [DMMTAV]) information in tissues and urine was presented.
Comments/ Narrative	As was primarily distributed to RBC as DMAV in the rat.

Table A15. Methylated arsenic distribution, excretion, and chemical forms after a single iv dose

Author(s)	Suzuki et al. (2004)
Species details	Adult male Wistar rat
Test article	Dimethylarsinic acid (DMAV) or monomethylarsonic acid (MMAV)
Route(s)	iv, in saline
Duration	Bile collection up to 3 h, tissue distribution at 10 minutes and 12 h
Tissue dosimetry	Total arsenic in bile (30-minute collections) up to 3 h; urine arsenic at 12 h; total arsenic in plasma, RBC, liver, kidneys, muscle, skin, and urine at 10 min and 12 h after administration; 24-h urinary arsenic for each of 7 days post-dosing; qualitative speciation (DMAV, MMAV, arsenobetaine [AsB]), information in plasma, RBC, liver, bile and urine was presented
Comments/ Narrative	MMA and DMA were both mostly excreted into the urine in the form in which they were administered.

Table A16. Methylated arsenic distribution, excretion, and chemical forms after a single oral or ip dose

Author(s)	Yoshida et al. (1997)
Species details	Adult male F344 rat
Test article	Dimethylarsinic acid (DMAV)
Route(s)	Oral or ip
Duration	Urine collection at 0, 2, 4, 6, 10, 24, and 48 h after administration.
Tissue dosimetry	Total As concentrations of DMA, MMA, AsIII, trimethylarsine oxide (TMAO), AsB, and an unidentified peak in urine, collected by forced urination
Comments/ Narrative	Initially, DMA was the predominant form of As excreted, but later, proportions of TMAO, then arsenite in urine increased.

Metals: Cadmium

Cadmium PBPK modeling

The available PBPK models for cadmium were all developed to describe disposition in humans. Most of these models are based on the Kjellström-Nordberg (KN) model (Kjellström and Nordberg, 1978; Nordberg and Kjellström, 1979), which is physiologically based in the sense that the intercomparmental transfers are based on physiological/biochemical processes, but these values are typically optimized, with little species-specific physiological or chemical-specific physicochemical information incorporated, making them less amenable to interspecies extrapolation.

Table B1. KN model for cadmium kinetics in humans (Kjellström and Nordberg, 1978; Nordberg and Kjellström, 1979)

Author(s)	Kjellström and Nordberg, 1978; Nordberg and Kjellström, 1979)
Species	Humans
Species details	Up to age 79. Conversions for tissue content (mg) to concentration (mg/g) provided for Swedes age 1-79; Japanese/Swedish body weight ratios provided at age 5, 15, 20-24, 30-39, 40-49, 50-59, 60-69, and 70-79 years of age.
Route(s)	Inhalation (including smoking) and ingestion
Duration	Up to 79 years.
Tissue dosimetry	Cd in kidney cortex, liver, blood, and urine
Model language	Basic
Code availability	Not provided with original publication. Mathematical difference equations for 1 time unit (1 day) provided. Subsequent authors have used different software (see Comments below).
Comments/ Narrative	Systemic uptake from inhalation and ingestion was described. A fraction of inhaled Cd is assumed to be available to lung tissue and another fraction of inhaled Cd is assumed to be available for GI uptake due to mucocilliary deposition and transport, with the remainder of the inhaled Cd exhaled. Of the Cd deposited in the lung, clearance is by first order transfer to the GI tract or first order systemic uptake. In addition to inhalation-derived Cd cleared to the GI tract, ingested Cd is also considered in the model. A fraction of the Cd from the oral tract is taken up into the intestinal tissue, from which it contributes to the daily systemic uptake, while the remainder is excreted unabsorbed via the feces. The combined uptake is initially split between two of the three "blood" compartments, one with a capacity limited fraction representing plasma metallothionein (B3) and the rest of the daily intake is apportioned to other plasma (B1). Cd in B1 is apportioned to other tissues, fecal excretion, the liver, and red blood cells (B2). The following processes are all assumed to be first order. Cd in red blood cells (B2) may be transferred to metallothionein (B3). Cd associated with plasma metallothionein (B3) is cleared into urine or into the kidney. Cd cleared from the kidney goes to urine or plasma (B1); the urinary excretion rate from the kidney increases after age 30, and continues to increase with age. Cd cleared from the liver goes to feces, plasma metallothionein (B3), or other plasma (B1). Cd in the other tissues may be cleared to blood (B1). In all, the kinetics of Cd in humans are described by 21 transfer coefficients. Simulations of the KN model using Berkeley Madonna software were conducted by Ju et al. (2012), with no further validation of the model. Sasso et al. (2010) mapped a MATLAB version of the KN model on to their Generalized Toxicokinetic Modeling System for Mixtures (GTMM), with no parameter changes and validated the model against

	the same kidney data as Diamond et al. (2001) (**Table B2**) and same NHANES 2003-2004 urinary data as Ruiz et al. (2010). Béchaux et al. (2014) developed triangular distributions for the parameters of the KN model and used Bayesian approaches to infer time dependent dietary exposure to Cd, as a means to explain observed trends in urinary Cd for 1900 individuals (ages 18-75) in the 2006-2007 French Nutrition and Health Survey.

Table B2. Diamond/Choudhury model for cadmium kinetics in humans

Author(s)	Choudhury et al. (2001), Diamond et al. (2001)
Species	Humans
Species details	Up to age 70
Route(s)	Oral (dietary ingestion)
Duration	Up to 70 years
Tissue dosimetry	Urinary and kidney Cd
Model language	ACSL 11
Code availability	Not provided; Berkeley Madonna code purported to be based on Diamond/Choudhury code provided by Amzal et al. (2009)
Comments/ Narrative	The authors report that their model is a modification of the KN model (Table B2) with difference equations for intercompartmental transfer changed to differential equations and growth algorithms (body weight and organ weight) added to the model. The model was validated against NHANES III (1988-1994) urinary Cd data and kidney data (mostly postmortem) from Canada, the United Kingdom, and Sweden. No equations or parameter values were provided for this model. Ruiz et al. (2010) report that they recoded the Diamond-Choudhury model for use with Berkeley Madonna software. They report that their model reproduced the simulations from Choudhury et al. (2001), and they further tested the model against the NHANES 2003-2004 data. However, of the 5 Cd model parameter values reported in Ruiz et al. (2010), 4 differ from the values in the originally published KN model. It is not clear when these values were changed or by which researchers. No model code was provided by Ruiz et al. (2010) Amzal et al. (2009) provide supplementary Berkeley Madonna code they report is "based on the works by Diamond …and others… who essentially combined the Kjellström and Nordberg cadmium model … with a model for lead biokinetics." Amzal et al. (2009) fitted two of the model's 29 parameters (absorption fraction and the fraction transferred from plasma to extravascular fluid) to urinary Cd data from a 2004-2007 subcohort of women enrolled in the Swedish Mammography Cohort. Parameter values in the Amzal et al. (2009) model appear to differ from the KN model.

Table B3. Fransson et al. (2014) cadmium model calibrated using data from living kidney donors

Author(s)	Fransson et al. (2014)
Species	Humans
Species details	Up to age 70
Route(s)	Systemic uptake via diet and smoking
Duration	Up to 70 years
Tissue dosimetry	Whole blood, plasma, urinary, and kidney Cd
Model language	acslX
Code availability	Not provided
Comments/ Narrative	The authors report that their model is a modification of the systemic portion of the KN model (Table B1) with difference equations for intercompartmental transfer changed to differential equations and growth algorithms (body weight and organ weight) added to the model. Furthermore, because low Cd intake was assumed, a term for capacity-limitations with respect to metallothionein were omitted. Systemic daily intake was modified to reflect 2 components, a body weight dependent dietary contribution and a pack-year dependent smoking term, with start and stop years. No equations or code were provided for this model. The calibration data consisted of blood, plasma, 24 h urinary data, and kidney cortex biopsy Cd concentrations from 82 kidney donors age 27-70 years old with complete data sets. Validation data were available from an additional 25 participants with incomplete data. In contrast, the original KN model was calibrated using disparate data sets, rather than paired data. The values of five parameters which were determined to be structurally globally identifiable were estimated using a Bayesian approach; the others were left fixed at the values for the baseline KN model. These parameters describe the body-weight dependent component of systemic Cd uptake, the initial division of Cd uptake between plasma and plasma metallothionein, transfer from red blood cells to plasma metallothionein, transfer from plasma metallothionein, and the two parameters that describe elimination of Cd from the kidney via urinary excretion (the baseline rate, and the age-dependent component). The model was described by the authors as having “moderate” predictive capacity, but was deemed a substantial improvement over the original parameterization.

Table B4. Berthet et al. (2010) human CBTK model for cadmium

Author(s)	Berthet et al. (2010)
Species	Humans
Species details	Adult workers at rest or at an activity level of 50 W
Route(s)	Inhalation

Duration	300 work weeks; 1500 exposure days
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Mathematical equations were represented in a prior publication (Pierrehumbert et al., 2002).
Comments/ Narrative	The generic model structure (applied to 14 chemicals) consists of absorption into a central compartment, blood-flow mediated exchange of parent compound between the central compartment and a peripheral compartment, metabolism of the parent compound to up to 2 metabolites, excretion of parent compound from the central or peripheral compartments, and excretion of metabolites from the central compartment. For the cadmium model, the central compartment was equated to total body water (TBW), the peripheral compartment equated to the kidneys, no metabolism of cadmium assumed, and excretion was assumed to occur via renal clearance. The values of compound-specific parameters (TBW: blood affinity coefficient, kidney permeability coefficient, kidney: blood affinity coefficient, and renal clearance) were based on clearance half-lives and the blood concentration at steady state, but referenced to a paper on PBPK modeling of arsenic (Mann et al., 1996b).

Toxicokinetics of cadmium in the rat

Table B5. Biliary excretion of exogenous cadmium after a single iv dose of cadmium

Author(s)	Sugawara et al. (1996)
Species details	Adult male Sprague-Dawley rat
Test article	Cadmium dichloride
Route(s)	iv, in saline
Duration	Bile collection for 1 h, tissue distribution at 1 h after injection.
Tissue dosimetry	Cd in bile (15-minute collections) up to 1 h; Cd in serum, liver, and kidneys, 1 h after administration
Comments/ Narrative	Comparisons were made to disposition in a strain deficient in biliary excretion of GSH.

Table B6. Whole-body retention and organ distribution of radioactive cadmium after a single ip or oral dose of cadmium

Author(s)	Kostial (1984)
Species details	Random bred albino rats, age 1, 3, 6, 18, or 26 weeks at dosing
Test article	^{115m}Cd
Route(s)	Ip or orally by artificial feeding (1-week old rats) or gastric intubation
Duration	Single doses; dosimetry at 1 or 2 weeks after administration

Tissue dosimetry	Cd in whole body, "carcass" (whole body after removal of GI tract), kidney, liver, brain, and gut (including contents) at one or two weeks after dosing.
Comments/ Narrative	Distribution was similar for the two routes of administration.

Table B7. Organ distribution of radioactive cadmium after a single oral dose of cadmium

Author(s)	Jackl et al. (1985)
Species details	Adults male Wistar rats
Test article	^{109}Cd-labeled Cd_3-phytate or $^{109}CdCl_2$
Route(s)	Oral, via gastric intubation
Duration	Single doses; dosimetry at 10 days after administration
Tissue dosimetry	Cd in liver, kidney, heart, pancreas, intestine, forebrain, "smallbrain" (cerebellum), spleen, testes, and tibia
Comments/ Narrative	Distribution was similar for the two test articles for rats receiving a normal (high phytate) diet.

Table B8. Organ distribution and clearance of radioactive cadmium after a single oral dose

Author(s)	Kanwar et al. (1980)
Species details	Male albino rats, 240-290 g
Test article	^{115m}Cd as $Cd(NO_3)_2$
Route(s)	Oral
Duration	Single doses; dosimetry at several points 30 min to 28 days after administration
Tissue dosimetry	Cd in liver, kidney, spleen, and duodenum (5-cm long section next to the stomach)
Comments/ Narrative	Clearance half time was longest in the kidney (30 days) and shortest in the duodenum (3.5) days. Clearance half-times were similar in liver (6.8 days) and spleen (5.5 days).

Table B9. Organ distribution and clearance of radioactive tracer cadmium after single oral doses (four dose levels)

Author(s)	Kotsonis and Klaassen (1977)
Species details	Male Sprague-Dawley rats, 50-79 days old, 200-300 g
Test article	^{109}Cd with unlabeled $CdCl_2$ (25, 50, 100, and 150 mg Cd/kg)
Route(s)	Oral
Duration	Single doses; dosimetry at 2 and 14 days after administration
Tissue dosimetry	Radioactivity in liver, kidney, spleen, heart, intestine (thoroughly washed), muscle (soleus and gastrocnemius), brain, pancreas, blood, and plasma

Comments/ Narrative	Most tissue concentrations decreased ~50 percent between days 2 and 14, with the exception of the liver (unchanged, at higher doses) and kidney (3-4-fold increase).

Table B10. Organ distribution and clearance of radioactive cadmium after a single iv dose

Author(s)	Horner and Smith (1975)
Species details	Adult male Sprague-Dawley rats
Test article	^{109}Cd as $CdCl_2$
Route(s)	iv in physiological saline
Duration	Single doses; tissue dosimetry at 5, 15, 30, and 60 min.; 5, 15, and 24 h, 3, 10, 15, 20, 25, 30, 40, 50, and 60 days after administration
Tissue dosimetry	Cd in heart, lungs, liver, stomach, spleen, pancreas, duodenum (without contents), colon (without contents), adrenals, kidneys, testes, brain, salivary glands, thymus, muscle (rectus femoris, external oblique, triceps), femur, fat, hair, skin (with hair), plasma, RBC, whole blood, and residual carcass at times noted above, and daily fecal excretion.
Comments/ Narrative	Cd levels in all tissues except kidney decreased as time progressed. The amount in the kidney increased during the duration of the study.

Table B11. Organ distribution of radioactive tracer cadmium after single iv or oral doses (four dose levels)

Author(s)	Lehman and Klaassen (1986)
Species details	Male Sprague-Dawley rats, 200-250 g
Test article	^{109}Cd as $CdCl_2$
Route(s)	Oral (stomach tube) or iv
Duration	Single doses; dosimetry at 7 days after administration in oral and iv "disposition" study, 3 hours after dosing in oral absorption study
Tissue dosimetry	Radioactivity in liver, kidney, spleen, heart, intestine (initial 15 cm), muscle (gastrocnemius), brain, pancreas, lunges, testes, adrenal gland, femur, and blood
Comments/ Narrative	Doses in the oral disposition study were 0.001, 0.01, 0.1, 1, and 10 mg Cd/kg, whereas the doses in the iv disposition study were 0.01, 0.1, 1, 10, 100, or 1000 µg/kg. In the oral absorption study, doses were either 1 µg/kg or 10 mg/kg. Increased relative absorption was observed at higher doses.

Table B12. Biliary and urinary excretion and tissue distribution of cadmium in rats after cadmium injection

Author(s)	Gregus and Klaassen (1986)
Species details	Adult male Sprague-Dawley rat (200-300 g)
Test article	^{109}Cd as $CdCl_2$

Route(s)	iv, in saline
Duration	2 h (biliary excretion and tissue and plasma concentrations); 4 days (fecal and urinary excretion)
Tissue dosimetry	Radiolabel in liver, kidneys, spleen, lung, pancreas, intestine, stomach, testes, brain, blood, and plasma; biliary, fecal, and urinary excretion of radiolabel
Comments/ Narrative	The Cd data were previously published; the above referenced publication represents a compilation of comparable data for 18 metals collected using a consistent protocol. A listing of the other tested metals may be found in **Table A12**. In urinary and fecal excretion studies, excreta were collected for 24-h periods for 4 days. Biliary excretion in bile-cannulated rats was determined at 2 h after administration; tissue distribution was determined in the same rats upon completion of the biliary excretion assessment. Compared to other metals, Cd exhibited relatively low total (fecal and urinary) excretion over four days (16.5 ± 1.2%; SE of 4-6 rats). Urinary excretion of Cd was less than for any other metal evaluated. Biliary excretion of Cd increased with increasing dose. Bile:plasma ratios for Cd were relatively high. Expressed as % of dose/tissue weight or volume, Cd, along with tin, had the highest liver concentrations of the tested metals.

Table B13. Impact of dietary iron on liver and kidney cadmium content in after one week of cadmium ingestion via drinking water

Author(s)	Schümann et al. (1996)
Species details	Male Sprague-Dawley rats, four age groups (44, 49, 57, and 84 days)
Test article	$CdCl_2$
Route(s)	Oral (drinking water)
Duration	Seven days
Tissue dosimetry	Cd in liver and kidney
Comments/ Narrative	Higher tissue concentrations of Cd where observed in rats ingesting iron-deficient diets relative to those with diets containing marginal or high levels of iron.

Table B14. Impact of dose, time, and nutrient status on liver, spleen, and heart cadmium after intraperitoneal administration of cadmium

Author(s)	Yiin et al. (2000)
Species details	Male Sprague-Dawley rats, 330-420 g
Test article	$CdCl_2$
Route(s)	ip in physiological saline
Duration	Single dose
Tissue dosimetry	Cd in liver, spleen, and heart

Comments/ Narrative	In the dose-response portion, tissue Cd was determined 24 h after injection of 25, 125, 500, or 1250 µg Cd/kg. In the time-course study, Cd was measured 6, 12, 24, or 72 h after injection of 25 or 500 µg Cd/kg. In the study to assess the impact of selenium on cadmium disposition, tissue Cd was measured 6, 12, 24, and 72 h after administration of 500 µg Cd/kg, with or without sodium selenate.

Table B15. Clearance of radioactivity from plasma of 21-day old rats and tissue distribution in 15-, 21-, or 63-day old rats after single iv injection of cadmium

Author(s)	Crowe and Morgan (1997)
Species details	Pregnant Wistar rats and their offspring
Test article	$CdCl_2$, $^{109}CdCl_2$
Route(s)	iv in physiological saline
Duration	Single dose; plasma clearance up to 120 min. after injection, distribution 2 h after injection
Tissue dosimetry	Cd in brain, liver, kidneys, heart, femurs, and blood cells (distribution study) and plasma (time course study)
Comments/ Narrative	Plasma clearance in 21-day old rats did not substantially differ among control, iron-loaded, and iron deficient diets (fed to maternal rats starting on gestation day [GD] 20 and to young rats).

Table B16. Tissue distribution of cadmium in iron sufficient and iron deficient rats after single oral exposure

Author(s)	Park et al. (2002), Ryu et al. (2004)
Species details	Male Sprague-Dawley rats fed iron sufficient or iron deficient diet
Test article	$CdCl_2$, $^{109}CdCl_2$
Route(s)	Oral gavage in saline
Duration	Single dose, distribution 24 or 48 h after administration
Tissue dosimetry	Cd in liver, kidney, lung, heart, brain, stomach, duodenum, jejunum, ileum, large intestine, testis, bone, and whole blood; GI contents were removed
Comments/ Narrative	Cd levels were higher in rats fed an iron-deficient diet.

Table B17. Tissue distribution of Cd in pregnant and nonpregnant rats after single oral gavage

Author(s)	Leazer et al. (2002)
Species details	Pregnant (GD 19 at dosing) and nonpregnant female Sprague-Dawley rats, ~60 days old.
Test article	$CdCl_2$, $^{109}CdCl_2$
Route(s)	Oral gavage in physiological saline
Duration	Single dose; tissue levels 24 h after administration.

Tissue dosimetry	Cd in liver, kidneys, large intestine, duodenum, jejunum and ileum.
Comments/ Narrative	Higher levels of Cd were found in pregnant rats all tissues analyzed, but the increase was not statistically significant in the kidney.

Metals: Chromium

Chromium PBPK modeling

Summary: Kirman et al. (2012, 2013b) developed a PBPK model of chromium (CrVI and CrIII) disposition in mice and rats after chronic oral dosing that was extended to humans (Kirman et al., 2013a). These researchers and others have subsequently refined the gastric reduction model and applied the model toward developing toxicity reference values. Berthet et al. (2010) applied a generic CBTK model to biomarker variability analysis and comparisons between ACGIH BEIs and the metrics predicted by the models when simulating 8 h of exposure to 14 chemicals at the TLV; one of those chemicals was chromium.

Table C1. Berthet et al. (2010) human CBTK model for chromium

Author(s)	Berthet et al. (2010)
Species	Humans
Species details	Adult workers at rest or at an activity level of 50 W
Route(s)	Inhalation
Duration	300 work weeks; 1500 exposure days
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Mathematical equations were represented in a prior publication (Pierrehumbert et al., 2002).
Comments/ Narrative	The generic model structure (applied to 14 chemicals) consists of absorption into a central compartment, blood-flow mediated exchange of parent compound between the central compartment and a peripheral compartment, metabolism of the parent compound to up to 2 metabolites, excretion of parent compound from the central or peripheral compartments, and excretion of metabolites from the central compartment. For the chromium model, the central compartment was equated to total body water (TBW), with the peripheral compartment equated to richly perfused tissues (RP; heart, liver, and brain), no metabolism of chromium was assumed, and excretion was assumed to occur via renal clearance. The values of compound-specific parameters (TBW: blood affinity coefficient, RP permeability coefficient, RP: blood affinity coefficient, and renal clearance) were referenced to a paper on PBPK modeling of arsenic (Mann et al., 1996b).

Table C2. Kirman whole-body chromium model development

Author(s)	Kirman et al. (2012, 2013a, b)
Species	Rats, mice, humans

Species details	Adult F344 rats, B6C3F1 mice, and humans. Sex/gender not clearly indicated for any of the three species.
Route(s)	Oral (drinking water, feed)
Duration	4-369 days of dosing
Tissue dosimetry	Blood, bone, carcass, kidney, liver, stomach, erythrocytes, plasma, urine, oral cavity, duodenum, jejunum, ileum
Model language	acslX with Excel interface
Code availability	Provided as supplementary material online
Comments/ Narrative	These papers describe development of PBPK models of CrVI and CrIII with detailed description of the GI tract (lumen and tissue). However, GI absorption parameters are scaled to segment length, and the length is not scaled by body weight. Thus, the model is not readily applicable across a range of body weights as formulated. The rodent models were calibrated/validated with multiple data sets, including new data presented in this paper. The human model calibration/validation relies on data for ex vivo CrVI reduction in human stomach fluid; in vivo plasma and urinary Cr excretion after CrIII exposures as chromium chloride or chromium picolinate, and one volunteer exposed to CrVI as sodium dichromate.

Table C3. Application of Kirman whole-body chromium model to systemic toxicity reference values, with extension to ip route and further validation

Author(s)	Monnot et al. (2014)
Species	Rats, mice, humans
Species details	Adult male and female Wistar, Sprague Dawley, and F344 rats; male Wistar Kyoto, Albino, Zucker, and unspecified rats; male and female BDF1 and B6C3F1 mice; female ICR mice; male C57BL/6 Cr mice; men and women
Route(s)	Oral, ip
Duration	1.5-365 days
Tissue dosimetry	Blood CrIII
Model language	acslXtreme
Code availability	Not stated
Comments/ Narrative	The Kirman et al. (2012, 2013a, b) models were used to estimate blood CrIII levels associated with no observed effect levels (NOELs) and lowest observed adverse effect levels (LOELs) for hematological, hepatic or renal effects in this review. When blood levels were available from the rat, mouse, and human toxicology studies, the reported values were compared to model predictions, and were "reasonably accurate (within a factor of a few-fold) for most of the studies." For ip administration, the initial dose distribution was calibrated based on fit to experimental data (70% in systemic plasma, "with the remaining fraction equally distributed into each of the liver, kidney, and other tissue compartments").

Table C4. Application of Kirman whole-body chromium model to GI tract cancer reference values

Author(s)	Thompson et al. (2014)
Species	Mice, humans
Species details	Not stated
Route(s)	Oral
Duration	Chronic dosing
Tissue dosimetry	Computed “pyloric flux” and “intestinal flux”
Model language	Not stated, but see **Table C2**
Code availability	Not stated, but see **Table C2**
Comments/ Narrative	In this paper, the Kirman et al. (2012, 2013a, b) models are applied to the development of chronic oral reference doses based on observations of intestinal cancer in mice. .

Table C5. Refinement/extension of Kirman gastric reduction model of chromium and application to GI tract cancer reference values

Author(s)	Schlosser and Sasso (2014), Sasso and Schlosser (2015)
Species	Mice, rats, humans
Species details	See **Table C2**
Route(s)	Oral/ex vivo
Duration	1 h experiments
Tissue dosimetry	Gastric fluid concentration
Model language	AcslX
Code availability	.csl file provided as supplementary online material (Schlosser and Sasso, 2014); equations outlined in supplementary materials (Sasso and Schlosser, 2015)
Comments/ Narrative	The Schlosser and Sasso (2014) paper describes modeling of previously published ex vivo studies of gastric reduction. The model was a refinement/extension of the model in Kirman et al. (2012). This new model was more complex (e.g., three pools of reducing agents for mice and rats), but sufficiently parsimonious for parameters to be identifiable. The improvement in fit was not described quantitatively, but is evident from visual inspection. It was asserted that this model "should provide better predictions of Cr-VI reduction when integrated into a corresponding PBPK model", but no publications were identified where this hypothesis has been tested. Kirman et al. (2016) noted that Schlosser and Sasso's optimization "results in lowering a parameter (Ka) that has been determined with a reasonable degree of certainty from a value of 773,000 to 1,070, which detracts from the chemistry-based approach, making it more of an empirical model." The analysis in Sasso and Schlosser (2015) used the Schlosser and Sasso (2014) model of the stomach. As noted by Kirman et al. (2016), resulting reference doses

	were similar (within 2-fold) to those generated by Thompson et al. (2014) using the Kirman et al. (2012, 2013a, 2013b) models.

Table C6. Refinement/extension of Kirman gastric reduction model of chromium based on new human data

Author(s)	Kirman et al. (2016)
Species	Mice, rats, humans
Species details	See **Table C2**
Route(s)	Oral/ex vivo
Duration	Up to 4 h experiments
Tissue dosimetry	Gastric fluid concentration
Model language	Not stated, likely same as Kirman et al. (2012, 2013a, b); see **Table C2**
Code availability	Not stated
Comments/ Narrative	This paper extends the previous models of gastric reduction of CrVI to CrIII (Kirman et al., 2012, 2013 a,b; Schlosser and Sasso, 2014). Various hypotheses regarding pools of reducing agents, pH dependence, and reaction kinetics (first vs. second order) were addressed via optimizations of the pharmacokinetic model to new data and data in the literature. The changes imply greater predicted efficiency in human detoxification at lower vs. higher drinking water concentrations of CrVI.

Toxicokinetics of chromium in the rat

Table C7. National Toxicology Program (NTP) (2008) study of sodium dichromate dehydrate in drinking water

Author(s)	National Toxicology Program (2008); also reported in Collins et al. (2010)
Species details	Adult male F344 rat
Test article	CrVI (sodium dichromate dihydrate)
Route(s)	Oral (drinking water)
Duration	4, 11, 180, 369 days
Tissue dosimetry	Total chromium in erythrocytes, plasma, liver, kidney, glandular stomach, forestomach, feces, urine
Comments/ Narrative	These data were used for calibration of the Kirman model (**Table C2**).

Table C8. NTP (2010) study of chromium picolinate in feed

Author(s)	National Toxicology Program (2010); also reported in Collins et al. (2010)
Species details	Adult male F344 rat
Test article	CrIII (chromium picolinate monohydrate).
Route(s)	Oral (drinking water)

Duration	4, 11, 180, 369 days
Tissue dosimetry	Total chromium in erythrocytes, plasma, liver, kidney, glandular stomach, forestomach, feces, urine
Comments/ Narrative	These data were used for calibration of the Kirman model (**Table C2**).

Table C9. NTP (2010) single gavage studies of chromium picolinate

Author(s)	National Toxicology Program (2010)
Species details	Adult male F344 rat
Test article	CrIII (chromium picolinate monohydrate).
Route(s)	Oral (gavage, in aqueous slurry or propylene glycol)
Duration	Single administration
Tissue dosimetry	Total chromium excretion in feces, urine
Comments/ Narrative	Excreta analyzed for total chromium at 8, 24, 48 h for both vehicles; aqueous also evaluated at 2, 4, and 12 h.

Table C10. $^{51}CrCl_3$ tracer iv study (data collection out to 11 days post-dose)

Author(s)	Onkelinx (1977)
Species details	Adult female Wistar rat
Test article	$^{51}CrCl_3$
Route(s)	iv in 0.9% NaCl solution
Duration	Single administration
Tissue dosimetry	Plasma, erythrocytes, epiphyses, diaphyses, kidney spleen, liver, lung, pancreas, urine, feces
Comments/ Narrative	^{51}Cr distribution was measured from 1-262 h after iv injection of $^{51}CrCl_3$

Table C11. ^{51}Cr tracer iv and ip studies (data collected out to 7 weeks after dosing)

Author(s)	Laschinsky et al. (2012)
Species details	Adult female Wistar rat
Test article	^{51}Cr as picolinate, nicotinate, phenylalaninate, chloride, or proprionate
Route(s)	iv or ip; vehicle not specified (possibly water)
Duration	Single administration
Tissue dosimetry	Spleen, liver, kidney, lung, bone, heart, GI tract, carcass, urine, feces
Comments/ Narrative	^{51}Cr distribution in organs was measured at 7 days after iv or ip injection. Feces and urine excretion were measured 2 days after iv or ip injection (variable spacing and number of time points for different test articles). The whole body-retention time course of ^{51}Cr after ip injection was measured for up to 7 weeks after dosing.

Table C12. Biliary and urinary excretion and tissue distribution of ^{51}Cr in rats after ^{51}Cr injection

Author(s)	Gregus and Klaassen (1986)
Species details	Adult male Sprague-Dawley rat (200-300 g)
Test article	^{51}Cr as $CrCl_3$
Route(s)	iv, in saline
Duration	2 h (biliary excretion and tissue and plasma concentrations); 4 days (fecal and urinary excretion)
Tissue dosimetry	Radiolabel in liver, kidneys, spleen, lung, pancreas, intestine, stomach, testes, brain, blood, and plasma. Biliary, fecal, and urinary excretion of radiolabel.
Comments/ Narrative	The above referenced publication represents a compilation of comparable data, some previously published, for 18 metals collected using a consistent protocol. A listing of the other tested metals may be found in Table A12. In urinary and fecal excretion studies, excreta were collected for 24-h periods for 4 days. Biliary excretion in bile-cannulated rats was determined at 2 h after administration; tissue distribution was determined in the same rats upon completion of the biliary excretion assessment. Compared to other metals, Cr was at the low end of the intermediate range for total (fecal and urinary) excretion over four days (20-50% excretion for the intermediate range; 21.5 ± 3.1% for Cr; SE of 4-6 rats). Likewise, urinary excretion of Cr was moderate, and decreased significantly after the first day. Biliary excretion of Cr decreased with increasing dose. Bile:plasma ratios for Cr were relatively low. Expressed as % of dose/tissue weight or volume, Cr was relatively highly concentrated in kidneys.

Table C13. Cr ion distribution in the rat 24 h after a single ip dose

Author(s)	Afolaranmi and Grant (2013)
Species details	Adult male Sprague Dawley rat
Test article	CrIII as chloride ($CrCl_3$), or CrVI as sodium dichromate dehydrate ($Na_2Cr_2O_2$ $2H_20$)
Route(s)	ip in saline
Duration	Single administration
Tissue dosimetry	Spleen, liver, kidney, lung, heart, brain, testes, blood, urine, feces
Comments/ Narrative	Chromium distribution in organs and cumulative amounts excreted in feces and urine were measured at 24 h after ip injection. Doses were variously expressed as amounts of compound per kg bodyweight and as amounts of metal/kg bodyweight. After CrIII dosing, CrIII was elevated relative to control in all matrices evaluated, but statistical significance was achieved only for the brain, although only 12.6% of the dose was

	recovered in measured tissues, urine, and feces. For CrVI, 75.6% of the dose was recovered, and all increases were statistically significant.

Table C14. Kinetics of potassium chromate in drinking water

Author(s)	Thomann et al. (1994)
Species details	Adult male F344 rat
Test article	CrVI as potassium chromate
Route(s)	Oral (drinking water)
Duration	Up to 6 weeks of exposure
Tissue dosimetry	Blood, spleen liver, kidney,
Comments/ Narrative	Rats ingested 100 ppm CrVI as potassium chromate in water for up to 6 weeks. Cr was measured in listed tissues at 1, 3, and 6 weeks into the accumulation phase; bone and carcass were also measured during the depuration phase (from 6 h to 12 weeks after cessation of exposure).

Metals: Cobalt

Cobalt PBPK modeling

No PBPK models of cobalt disposition in rats were identified in the literature. Two models of cobalt kinetics in humans were identified. The basis of the Berthet et al. (2010) model was not clear, and no validation was provided. The Leggett (2008) human biokinetic model describes intercompartmental transfers of cobalt in a manner that is not amenable to interspecies extrapolation, but does provide a framework that could be considered as a basis for interpretation of data from other species. Unice et al. (2012) extended the Leggett (2008) model in order to estimate oral bioavailability of cobalt.

Table D1. Berthet et al. (2010) human CBTK model for cobalt

Author(s)	Berthet et al. (2010)
Species	Humans
Species details	Adult workers at rest or at an activity level of 50 W
Route(s)	Inhalation
Duration	300 work weeks; 1500 exposure days
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Mathematical equations were represented in a prior publication (Pierrehumbert et al., 2002).
Comments/ Narrative	The generic model structure (applied to 14 chemicals) consists of absorption into a central compartment, blood-flow mediated exchange of parent compound between the central compartment and a peripheral compartment, metabolism of the parent compound to up to 2 metabolites, excretion of parent compound from the central or peripheral compartments, and excretion of metabolites from the central compartment.

	For the cobalt model, the central compartment was equated to total body water (TBW), with the peripheral compartment equated to the richly perfused tissues, there was no metabolism of cobalt assumed, and excretion was assumed to occur via urinary elimination. The values of compound-specific parameters (TBW: blood affinity coefficient, richly perfused tissues permeability coefficient, richly perfused tissue: blood affinity coefficient, and urinary excretion) were based on clearance and transfer half-lives and the blood concentration at steady state, but referenced to a paper on PBPK modeling of arsenic (Mann et al., 1996b).

Table D2. Leggett (2008) human biokinetic model for cobalt

Author(s)	Leggett (2008)
Species	Humans
Species details	Adult humans
Route(s)	Systemic model, paired with standard ICRP models for inhalation and absorption
Duration	Calibrated with human data on time scales of hours to days
Tissue dosimetry	Urinary excretion, fecal excretion, blood content, and whole body retention
Model language	Not stated; Unice et al. (2012) coded the Leggett cobalt model in Berkeley Madonna version 8.3.9.
Code availability	Not provided
Comments/ Narrative	The cobalt biokinetic model reused a model structure previously developed for alkaline earth elements. All kinetic processes were assumed to be first order. The model was primarily developed to be consistent with data from human subjects injected with $^{60}CoCl_2$ and $^{58}CoCl_2$. The human data was supplemented with laboratory animal data on distribution of cobalt among liver, kidneys, skeleton, and other tissues. Blood is described as two subcompartments. Blood 1 exchanges with other tissues, but Blood 2 has a longer retention time and exchanges only with Blood 1. The liver is also described as having two subcompartments. Liver1 both receives transferred cobalt from Blood 1 and returns cobalt to Blood 1. Liver1 also transfers cobalt to the small intestine contents via bile and to Liver2 for longer-term retention. Cobalt from Liver 2 is slowly transferred back to Blood 1. The small intestinal contents, in addition to receiving cobalt from Liver 1, also receive cobalt directly from Blood 1, and is the pathway for fecal excretion of systemic cobalt. Kidneys are likewise described in terms of two compartments, a urinary path (Kidney1) and a slow-turnover pool (Kidney2; other kidney tissue).

	Kidney2 exchanges cobalt only with Blood1. Kidney1 cobalt represents transfer from blood filtered by the glomerulus, which is then transferred to the urinary bladder, and cobalt from the urinary bladder is then then excreted in urine. A direct transfer from Blood1 to urinary bladder contents is meant to be representative of cobalt that is filtered from blood by the glomerulus but not retained in urinary path tissue. The skeleton is described as cortical and trabecular regions. Cobalt is transferred from Blood1 to both trabecular and cortical surfaces; from each surface, cobalt is then transferred to trabecular and cortical volumes, respectively. Cobalt is returned to blood from the bone volumes by turnover. Other (soft) tissues are divided into three compartments ST0, ST1, and ST2, with faster, intermediate, and slower turnover, respectively. These three compartments receive cobalt from Blood1 and return it to Blood1. Leggett (2008) shows comparisons of model predictions to the data from three studies where cobalt was administered by iv injection: both urinary and fecal excretion for a single subject, plasma content, and cumulative urinary excretion. Unice et al. (2012) present further comparisons with data from oral exposures, with predictions for a range of absorption fractions.

Toxicokinetics of cobalt in the rat

Table D3. Cobalt blood and tissue levels time course (36 h) after single gavage of cobalt chloride

Author(s)	Ayala-Fierro et al. (1999), Firriolo et al. (1999)
Species details	Adult male Fischer 344 rat (200-300 g)
Test article	CoII as chloride ($CoCl_2$) hexahydrate (Ayala-Fierro et al., 1999) or CoII as Co naphthenate (CoNap).
Route(s)	Oral (gavage) in ethanol:Emulphor (2:1) mixture or iv ($CoCl_2$ only) in saline
Duration	Single administration
Duration	Single administration; data to 36 h after administration
Tissue dosimetry	Oral: Liver, kidney, heart, blood, urine, and feces (time course); large intestine, small intestine, and stomach tissue; large intestine, small intestine, and stomach content (terminal only for $CoCl_2$; time course for CoNap), and testes and spleen (CoNap only). iv: blood, urine, and feces only
Comments/ Narrative	Cobalt distribution in blood, organs, and GI content and cumulative amounts excreted in feces and urine were measured after administration. After oral administration, blood and tissue levels were determined at various intervals from 0.5 to 36 h postdosing. Urinary and fecal excretion was measured at 8, 12, 16, 24, and 36 h after gavage dosing,

	12, 24, and 36 h after iv administration and the oral blood study. At 36 h after iv dosing of $CoCl_2$, 75% of administered cobalt was eliminated in urine and 10% in feces. After oral dosing of the same compound, 27% was eliminated in urine and 68% in feces, indicating 25-30% absorption by the oral route. In the oral $CoCl_2$ study, peak blood and tissue concentrations of cobalt were achieved 6-8 h after administration. Distribution patterns for Co derived from $CoCl_2$ and CoNap were similar.

Table D4. Cobalt whole-body time course (8 days) and terminal distribution after single gavage administration of cobalt chloride

Author(s)	Nishimura et al. (1976)
Species details	Wistar rats 7, 14, 21, or 100 days old (sex not stated; Nishimura et al., 1976); 120-day old males (Inaba et al., 1982)
Test article	CoII as chloride, $^{60}CoCl_2$
Route(s)	Oral (gavage) in distilled water
Duration	Single administration
Duration	Single administration
Tissue dosimetry	Whole body time course. Adults only: terminal cobalt content of liver, kidney, GI tract with contents, cumulative urinary and fecal excretion (~days 1, 2, 3, 5, 7, and 9) (Nishimura et al., 1976). In Inaba et al. (1982), terminal cobalt concentrations were determined in blood; heart, lungs, spleen and pancreas (grouped), liver, kidneys, GI tract with content, femurs, muscle, testicles, and remaining carcass relative to whole-body concentration.
Comments/ Narrative	Nishimura et al. (1976): Whole body retention was higher after iv than po dosing. For po dosing of animals of various ages, adults retained less cobalt than younger animals. The liver and kidney had substantial fractions of the body burden at termination. The highest relative concentrations were found in the kidneys and liver by Inaba et al. (1982).

Table D5. Biliary and urinary excretion and tissue distribution of ^{57}Co in rats after ^{57}Co injection

Author(s)	Gregus and Klaassen (1986)
Species details	Adult male Sprague-Dawley rat (200-300 g)
Test article	^{57}Co as $CoCl_2$
Route(s)	iv, in saline
Duration	2 h (biliary excretion and tissue and plasma concentrations); 4 days (fecal and urinary excretion)
Tissue dosimetry	Radiolabel in liver, kidneys, spleen, lung, pancreas, intestine, stomach, testes, brain, blood, and plasma. Biliary, fecal, and urinary excretion of radiolabel

Comments/ Narrative	The above referenced publication represents a compilation of comparable data, some previously published, for 18 metals collected using a consistent protocol. A listing of the other tested metals may be found in Table A12. In urinary and fecal excretion studies, excreta were collected for 24-h periods for 4 days. Biliary excretion in bile-cannulated rats was determined at 2 h after administration; tissue distribution was determined in the same rats upon completion of the biliary excretion assessment. Compared to other metals, cobalt was the most rapidly excreted (fecal and urinary excretion over four days; 87.7 ± 14% for cobalt; SE of 4-6 rats). Likewise, urinary excretion of cobalt was dramatically higher than that of other metals; 72.6 ± 13% over days 1-4, vs. 26.5% of excreted in urine for cesium, the next most highly excreted compound. Biliary excretion of cobalt was relatively high and increased with increasing dose. Bile:plasma ratios for cobalt were intermediate, compared to other tested metals. Expressed as % of dose/tissue weight or volume, cobalt was relatively highly concentrated in kidneys.

Table D6. Co ion distribution in the rat 24 h after a single ip dose

Author(s)	Afolaranmi and Grant (2013)
Species details	Adult male Sprague Dawley rat
Test article	CoII as chloride ($CoCl_2$)
Route(s)	ip in saline
Tissue dosimetry	Spleen, liver, kidney, lung, heart, brain, testes, blood, urine, feces
Comments/ Narrative	Cobalt distribution in organs and cumulative amounts excreted in feces and urine were measured 24 h after injection. Doses variously expressed as amounts of compound per kg bodyweight and as amounts of metal/kg bodyweight. After cobalt dosing, statistically significant increases in cobalt levels were observed in all biological matrices evaluated. The cobalt recovered was 41.6% of the dose.

Table D7. Measurements of ^{60}Co organ burdens in rats and their use in calculations of equilibrium dose-rates to various organs of man

Author(s)	Smith et al. (1971)
Species details	Sprague-Dawley rat (adult male)
Test article	^{60}Co as $^{60}CoCl_2$
Route(s)	Oral, ad lib. or gastric intubation ($^{60}CoCl_2$ in water)
Duration	Ad lib. 6 – 170 days or gastric intubation 20 days or ad lib. 20 days
Tissue dosimetry	Equilibrium dose-rate (mrad/week) due to absorbed ^{60}Co in whole body, liver, kidneys, skeleton, pancreas, spleen, muscle, stomach, salivary gland, small intestines, upper large intestine and lower large intestine.

Comments/ Narrative	Gastric intubation was compared to ad lib. to normalize absorption of ^{60}Co when comparing single-dose gastric intubation data from other studies to data in this study. Given the data at the time the paper was written regarding the metabolism of ^{60}Co in humans, the maximum permissible concentration would be similar to the value derived from the study in rats. However, due to the longer term retention in humans, organ dose rates of absorbed ^{60}Co may be around twenty times greater than predicted by extrapolating from rat to human. Author says the results suggest that the MPC of ^{60}Co in water is similar to that determined in the rat studies (4.5×10^{-5} μCi ^{60}Co/mL) and is in good agreement with the ICRP value.

Table D8. Tissue dosimetry of the radioisotopes of cobalt after ip and oral administration

Author(s)	Barnaby, Smith, and Thompson (1967)
Species details	Albino and Sprague-Dawley rats (both were specified) (male; age not stated; size varies, but likely corresponds to young adult to adult rats)
Test article	$^{60}CoCl_2$ in 0.9% NaCl
Route(s)	iv, ip, or gastric intubation
Duration	1-132 days, depending on group and end point analyzed
Tissue dosimetry	Whole body retention is compared between iv, ip, and oral administration, but the iv group was small enough that only the ip and oral data was used in dosimetry analysis. Fractional retention of ^{60}Co following oral administration is calculated for total body, liver, skeleton, muscle, kidneys, gut, pelt, pancreas, salivary gland, spleen, brain, adrenals, thymus, and testes. The same end points were analyzed for ip with the additions of the urogenital system minus kidney, the lung and trachea, and the eyes, but with the exception of the testes which are probably included in the urogenital system.
Comments/ Narrative	The author makes the following conclusions: The critical organ following ip administration of ^{56}Co and ^{58}Co to man would be the liver, but the pancreas would be critical organs for the longer-lived ^{57}Co and ^{60}Co isotopes. Eighty percent of cobalt radioisotopes pass unabsorbed through the GI tract following oral administration. Following ingestion of radioisotopes of cobalt, the retention in the male gonads will result in a very low dose. Tissue elimination curves fit to an exponential decay indicated similar clearance half-lives after ip and oral dosing. Total body, kidneys, and salivary gland had the fastest clearance; clearance rates were slightly slower from pancreas, spleen, brain, pelt, lungs, and testes, but similar within that group, and somewhat slower from muscle and skeleton.

Table D9. Distribution and clearance of cobalt after iv administration

Author(s)	Jansen et al. (1995)
Species details	Wistar rat (adult male) and human (healthy adult male)
Test article	^{55}Co from $^{55}CoCl_2$
Route(s)	Catheter injection leading to right atrium for rat, iv for human
Duration	55 hours
Tissue dosimetry	Rat PET scans were made at 0.5, 24, and 48 h after administration to find areas of radioactive accumulation. Postmortem distribution to the rat heart, kidney, lung, testis, liver, pancreas, spleen, stomach, and skin was determined at 55 h after administration. Urine and feces of rats were collected continuously. In the human study, blood was drawn at regular intervals for 5 h.
Comments/ Narrative	Liver time course data (not shown) were used to derive an effective half-life of 10.4 h, and biological half-life of 25.5 h for ^{55}Co in the rat. Approximately 50% of the dose was associated with the liver, 40% was excreted in urine, and 5% excreted in feces. Authors believe an estimate of dose commitment to the total body can be obtained by considering only the liver burden in combination with the bladder and GI burden.

Table D10. Comparative pharmacokinetics of radionuclides in mammals (mouse, rat, monkey, and dog)

Author(s)	Thomas et al. (1976)
Species details	RF mice, Sprague-Dawley rat (male), *Macaca speciose* monkeys, Beagle dog. Age/size not stated.
Test article	^{60}Co as $^{60}CoCl_2$
Route(s)	Tail vein iv to rodents, iv saphenous vein to monkeys, iv cephalic vein to dogs, all in normal saline. Intragastric (ig) administration to rats (vehicle not clear—possibly saline) under anesthesia. Orally to rats in solution of 2.9% dextrose and 0.12% saccharin, orally to monkeys as the isotope absorbed into sugar cubes, orally to dogs using a gelatin capsule. All routes were single dose.
Duration	Rat had multiple time points including 7 days (ig), 22 days (ig), 461 days (iv), 167 days (iv) and 147 days (oral)
Tissue dosimetry	Retention was measured whole body, liver, spleen, bone, brain, muscle, kidney, heart, lung, and gonads, but starts around day 20 and was measured for oral and iv only. Measured whole body retention only after ig dose. Ratios of urinary to fecal elimination were reported daily for the first 4 days after administration, and for longer periods thereafter, but absolute amounts eliminated were not presented.
Comments/ Narrative	Author believes that cobalt is a metabolite with which an extrapolation from rodent data to man may be very deceiving, because of species dependence observed in non-rodents.

Table D11. Whole body clearance and tissue distribution after ip administration of cobalt

Author(s)	Hollins and McCullough (1970)
Species details	Albino rats (adult male)
Test article	^{58}Co from $^{58}CoCl_2$ in carrier-free form
Route(s)	ip for tissue distribution, ip or "force fed" for whole body exposure
Duration	Tissue distribution: 1, 2, 3, 5, 7, 10, 15, 21, 40, and 72 days; whole body up to 386 days
Tissue dosimetry	19 tissues listed, as well as whole body data
Comments/ Narrative	A detailed whole-body time course after iv administration was presented. Tissue: whole body ratios were presented for kidney, liver, bone marrow, and blood were presented for days 1-10; tissue/body ratios for days 10-72 were presented as averages for each of the tissues and blood.

Table D12. Gastrointestinal Iron and Cobalt absorption and Iron Status in Young Rats and Guinea Pigs

Author(s)	Naylor and Harrison (1995)
Species details	Harwell Mouth Tumour Rats (male) and Dunkin-Hartley guinea pigs, age 1-200 days at dosing
Test article	^{57}Co and ^{59}Fe in 0.01M HNO_3 and equal parts of 0.07 M citrate
Route(s)	Orally in above solution or ip in above solution
Duration	1-14 days
Tissue dosimetry	Whole body only
Comments/ Narrative	Whole-body retention at 2 weeks after dosing was assessed at ages 1, 10, 20, 25, 30, 60, and 200 days. A time course of whole body activity after administration to 20-day old rats was reported, with data 1, 2, 3, 4, 7, 10, and 14 days after dosing.

Table D13. Absorption of cobalt from the GI tract of the rat

Author(s)	Taylor (1961)
Species details	Adult inbred "August" strain rats (male)
Test article	^{58}Co as Co++, Co+++, $CoCl_3$, or $CoCl_2$
Route(s)	iv injection or gastric intubation
Duration	3 days
Tissue dosimetry	Whole body only
Comments/ Narrative	When administered iv as a complex with serum protein or with glycine, cumulative 1-day and 3-day urinary elimination averaged 64 and 73%, respectively. Gastric administration with cow's milk, lactose, August rat serum, glycine, casein, histidine, lysine, or EDTA influenced the absorption of cobalt (range of 11 to 43 percent). When administered with glycine, the percent absorption of cobalt was generally observed to decrease as the dose increased.

Table D14. Compartment analysis of cobalt(II) metabolism in rats of various ages

Author(s)	Onkelinx (1976)
Species details	Wistar rats (female), ages 35, 60, and 116 days at dosing
Test article	$^{57}CoCl_2$ in 0.5M HCl diluted by 33 with distilled water
Route(s)	iv injection or infusion into jugular
Duration	1 h to 11 days
Tissue dosimetry	Liver, spleen, pancreas, kidney, bone, plasma (total and ultrafiltered) and whole body concentrations (time course), cumulative 3-day excretion in urine and feces, blood concentrations during iv infusion (up to 11 h).
Comments/ Narrative	Three-day urinary excretion increased with age, and fecal excretion decreased with age, with average urinary elimination of 66 to 76 %, and fecal excretion of 5 to 10% of dose.

Table D15. Toxicokinetics of cobalt after ip, ig, subcutaneous (sc), and intratracheal administration

Author(s)	Roschchin et al. (1989)
Species details	Albino rats (male; age or size not stated)
Test article	^{56}Co in the form of sulphate
Route(s)	Single doses ig, ip, sc, and intratracheally
Duration	Single dose; data for 5 minutes – 15 d after administration
Tissue dosimetry	Data shown for blood and plasma (1, 4, and 24 h after dosing; all routes) and fecal and urinary excretion (days 1, 2, 8, and total for 8 days; ip and intratracheal routes only)
Comments/ Narrative	The largest accumulation was reportedly in liver, kidneys, and lungs, but data were not shown. Blood and plasma levels at 24 h after dosing were typically ~$1/10^{th}$ of the concentrations observed 10 minutes after dosing. For ip and intratracheal dosing, total urinary and fecal elimination over 8 days ranged from 70 to 86% of initial dose, with the 50-69% excreted in urine within the first 24 h.

Table D16. Tissue distribution of cobalt after iv injection

Author(s)	Edel et al. (1994)
Species details	Sprague-Dawley rats (adult male)
Test article	^{57}Co as $CoCl_2$ in saline
Route(s)	Single dose iv or ip or daily ip for 7 days
Duration	Single dose iv (data at 24 h after dosing) or ip (data at 100 days after dosing), or daily ip dose for 3 days or 7 days before data collection
Tissue dosimetry	Blood (plasma and RBC), lung, kidney, liver, spleen, ribs, femur, skull, large intestine, small intestine, pancreas, heart, stomach, skin, testis, epididymis, and vas deferens.

Comments/ Narrative	The distribution to all of the listed tissues was determined for single iv injection or single ip injection. For repeated ip injection, data were reported only for lung, kidney, liver, spleen, large intestine, small intestine, pancreas, testis, and epididymis.

Table D17. Disposition kinetics of cobalt mesoporphyrin in mouse, rat, monkey, and dog

Author(s)	Feng et al. (1997)
Species details	Adult male Wistar and obese Zucker rats
Test article	[^{14}C]CoMP ([^{14}C] cobalt mesoporphyrin trisodium bisglycinate)
Route(s)	Single dose iv or intramuscular (im) injection
Duration	Data at 10 minutes – 60 days after dose
Tissue dosimetry	Plasma concentration; daily fecal and urinary elimination; tissue radioequivalents for adrenal, blood, heart, kidney, liver, lung, lymph node, pituitary, spleen, thymus, and brain; whole-body autoradiography.
Comments/ Narrative	Plasma time courses for Wistar and Zucker rats were reported out to ~19 and 21 days, respectively, after iv injection and, for Wistar rats only, ~6 days after sc administration, and as much as ~28 days after im injection. Elimination after im administration to the Wistar rat was primarily via feces (total of 54% over 7 days, peaking on day 2), with limited urinary elimination (total of 1% over 7 days, with 0.5% on day 1). Tissue clearance after im injection generally appeared biphasic, with highest early concentrations in the liver, but at and after day 10, kidney had the highest levels of radioequivalents.

Table D18. Blood and tissue concentration and urinary and fecal elimination time courses of cobalt after iv injection

Author(s)	Weber et al. (2012)
Species details	Adult F344 rats (male and female)
Test article	$^{60}CoCl_2$ in 0.1M HCl
Route(s)	Single dose iv via a jugular vein catheter
Duration	Blood and tissue data at 1, 4, and 24 h, 2, 4, 8, 16, and 28 days; urine and feces collected daily.
Tissue dosimetry	Blood, liver, spleen, kidneys, lungs, muscle, GI tract, gonads (testes or ovaries), bone (femur), pelt, eviscerated carcass, and soft tissue remains (brain, eyes, thymus, pancreas, heart, tongue and any other small tissues not defined above); daily urine and fecal samples.
Comments/ Narrative	Within 8 days, 93 % of the administered dose had been eliminated, primarily via urine (61% eliminated in urine within 1 day).

Table D19. Pharmacokinetics of cobalt chloride and cobalt-protoporphyrin

Author(s)	Rosenberg (193)
Species details	Adult Sprague-Dawley rats (male)

Test article	$CoCl_2$ in saline or cobalt protoporphyrin in NaOH, NaCl
Route(s)	Single dose subcutaneously
Duration	30 minutes – 4 weeks
Tissue dosimetry	Whole blood, plasma, red blood cells, kidney, spleen, liver, testes
Comments/ Narrative	After administration of cobalt chloride, plasma levels of cobalt peaked within 30 minutes, while after cobalt protoporphyrin administration, peak plasma concentrations were not achieved until 24 h after dose administration. Tissue concentrations were measured 4 weeks after dosing; levels were highest in the kidney.

Table D20. Cobalt distribution after iv injection

Author(s)	Korf et al. (1998)
Species details	Wistar rat (adult male)
Test article	^{57}Co from $^{57}CoCl_2$
Route(s)	Catheter injection leading to right atrium for rat, iv
Duration	24 hours
Tissue dosimetry	Liver, kidney, lung, heart, spleen
Comments/ Narrative	Radiolabel distribution was measured 24 h after iv injection; radioactivity was present primarily in liver and kidney. However, since data were presented only as ratios to concentration found in the heart, they are unlikely to usefully inform any model development.

Table D21. Cobalt excretion and tissue distribution after iv injection

Author(s)	Levitskaia et al. (2011)
Species details	Male Wistar-Han rats
Test article	^{60}Co from $^{60}CoCl_2$
Route(s)	Indwelling jugular vein cannula injection
Duration	48 hours
Tissue dosimetry	24 & 48 hours for urine and feces, 48 hours for liver, kidney, skin, muscle, femur, heart, blood, lung, spleen, and brain
Comments/ Narrative	Radiolabel was excreted primarily in urine during the first day after dosing (~60% of dose). The radioactivity recovered in the carcass at 48 h after dosing totaled 14 percent of the initial dose. The highest concentrations were found in kidney and liver. When considered as percentage of total dose, the largest proportions were found in liver, muscle, skeleton, skin, and kidney (3.8, 0.98, 0.97, 0.88, and 0.79%, respectively).

Metals: Lead (Pb)

Pb PBPK modeling

PBPK models of Pb in the rat have been developed by O'Flaherty (1991) and Dalley et al. (1990). The Dalley et al. (1990) model was limited to the kinetics of Pb administered by iv injection, and its performance with regard to predicting observed blood and tissue concentrations was poor. The O'Flaherty (1991) rat model was develop using data from repeated dose exposures of 31 days or more, but was successfully extended to descriptions of shorter term data by Timchalk et al. (2001). For validated human models of Pb (Vork et al., 2013 and O'Flaherty, 2013), the reader is referred to Sweeney (2015). The Berthet et al. (2010) human PBPK model of Pb, described below, has not been validated.

Table E1. PBPK model for injected (iv) Pb in the rat

Author(s)	Dalley et al. (1990)
Species	Rat
Species details	None provided; but model was "normalized for a 250 g rat"
Route(s)	iv
Duration	Single dose; data to 120 h post dosing
Tissue dosimetry	No validation or calibration data were shown
Model language	IMSL (International Mathematics and Statistical Library, Houston, TX)
Code availability	Not provided; mathematical equations were provided in the appendix
Comments/ Narrative	The model consisted of the following compartments: plasma, RBC, liver, lung, bone, kidney and carcass. The anatomical equivalent for the "carcass" is unclear, as the volume of 25 ml is insufficient to account for the other, unspecified tissues. Mass balance equations for the liver and carcass were implemented as flow limited compartments, while lung, bone, and kidney were described as membrane limited. While the model diagram indicates Pb loss via urine and biliary excretion, only "intrinsic clearance" from the liver is included in the equations for the Pb model, and no value for that parameter is reported. The model was calibrated using data previously collected by the authors. The calibration data consisted of blood, femur, kidney, and liver concentrations of Pb collected 0.5, 2, 12, 40, and 120 h after dosing with lead acetate. The earliest measured concentrations of Pb in blood were substantially underestimated by the model, and clearance from all tissues except bone appeared to be underestimated.

Table E2. O'Flaherty PBPK models for Pb disposition in the rat and in humans

Author(s)	O'Flaherty (1991, 1993); rat model extended by Timchalk et al. (2001).
Species	Rat and human
Species details	Rat model based on data from Long-Evans and Sprague-Dawley rats; does not account for pregnancy, lactation, aging or disease

Route(s)	Drinking water ingestion by rats; does not account for exposure during gestation and suckling (O'Flaherty, 1991). Gavage, ip (Timchalk et al., 2001).
Duration	Exposures of 31 days to 18 months (O'Flaherty, 1991).
Tissue dosimetry	Blood, bone (total skeleton); partition coefficients for liver, kidney, and bone set based on study data that was not shown.
Model language	Not stated
Code availability	Not provided; some mathematical equations were provided in the appendix
Comments/ Narrative	The O'Flaherty (1991) model consisted of the following compartments: plasma (including binding), liver, kidney, other well-perfused tissues, bone, and other poorly perfused tissues. Exchange of lead with bone tissue is described as being diffusion limited. Plasma clearance is described as occurring from the plasma. The plasma clearance rate was estimated from data that were not shown. The model calibration/validation was based on three studies conducted by the authors, with varying designs: some of the time course data were collected during continuous exposures, while others reflect Pb clearance after exposure. In general, the clearance data were better described by the model than the accumulation data. Timchalk et al. (2001) extended the O'Flaherty (1991) model to include simulation of Pb in rat saliva, using previously collected time course data (5 blood and saliva samples over 21 days) by the ip route (3 doses to Sprague Dawley rats; spacing not specified by Timchalk et al.). The extended model was then used to evaluate further experiments by the oral route in F344 rats (blood and saliva concentrations 24 h after gavage dosing with 20, 50, 100, 200, and 500 mg Pb/kg body weight). Agreement between the model and data were good (model predictions typically within the standard deviation of the experimental data). A human model with a similar structure was published by O'Flaherty (1993). For a detailed assessment of this model, the reader is directed to Sweeney (2015).

Table E3. Berthet et al. (2010) human CBTK model for Pb

Author(s)	Berthet et al. (2010)
Species	Humans
Species details	Adult workers at rest or at an activity level of 50 W
Route(s)	Inhalation
Duration	300 work weeks; 1500 exposure days
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Mathematical equations were represented in a prior publication (Pierrehumbert et al., 2002).

Comments/ Narrative	The generic model structure (applied to 14 chemicals) consists of absorption into a central compartment, blood-flow mediated exchange of parent compound between the central compartment and a peripheral compartment, metabolism of the parent compound to up to 2 metabolites, excretion of parent compound from the central or peripheral compartments, and excretion of metabolites from the central compartment. For the Pb model, the central compartment was equated to total body volume (TBV), with the peripheral compartment equated to the skeleton, there was no metabolism of Pb assumed, and excretion was assumed to occur via renal clearance. The values of compound-specific parameters (TBV: blood affinity coefficient, bone: blood partition coefficient, and renal clearance) were based on clearance half-lives and renal clearance from Araki et al. (1986).

Leggett+ human PBPK model

Vork et al. (2013) extended a human PBPK model developed by Leggett. A detailed assessment of this model can be found in Sweeney (2015).

Toxicokinetics of lead in the rat

Table E4. Biliary and urinary excretion and tissue distribution of ^{210}Pb in rats after ^{210}Pb injection

Author(s)	Gregus and Klaassen (1986)
Species details	Adult male Sprague-Dawley rats (200-300 g)
Test article	^{210}Pb as lead nitrate, with cold lead acetate
Route(s)	iv, in saline
Duration	2 h (biliary excretion and tissue and plasma concentrations); 4 days (fecal and urinary excretion)
Tissue dosimetry	Radiolabel in liver, kidneys, spleen, lung, pancreas, intestine, stomach, testes, brain, blood, and plasma. Biliary, fecal, and urinary excretion of radiolabel
Comments/ Narrative	Pb data were previously published; the above referenced publication represents a compilation of comparable data for 18 metals collected using a consistent protocol. A listing of the other tested metals may be found in Table A12. In urinary and fecal excretion studies, excreta were collected for 24-h periods for 4 days. Biliary excretion in bile-cannulated rats was determined for 2 h after administration; tissue distribution was determined in the same rats upon completion of the biliary excretion assessment.

	Compared to other metals, Pb exhibited intermediate total (fecal and urinary) excretion over four days (20-50% for intermediate excretion; 37.8 ± 2.5% for Pb; SE of 4-6 rats). Fecal excretion of Pb was also in the intermediate range, while urinary excretion of Pb was considered to be in the low range. Biliary excretion of Pb was in the intermediate range and decreased with increasing dose. Bile:plasma ratios for Pb were relatively high, compared to other tested metals. Expressed as % of dose/tissue weight or volume, liver Pb levels increased with dose, while kidney levels decreased with dose.

Table E5. Pb in saliva and blood after oral exposure

Author(s)	Timchalk et al. (2006)
Species details	Adult male Sprague-Dawley rats
Test article	Lead acetate
Route(s)	Gavage (vehicle not stated)
Duration	Study 1: single gavage, samples at 0, 30 min, 1, 5, 12, and 24-h after dosing. Study 2: 5 sequential daily gavage doses, with samples collected 5 days after final dose.
Tissue dosimetry	Pb in whole blood, RBC, plasma, saliva, parotid saliva gland, and femur.
Comments/ Narrative	Pb was readily detected in tested matrices, including early saliva samples, peaking in blood at 1 h after dosing. Pb concentration in bone increased throughout Study 1 (up to 24 h). Saliva and blood Pb levels 1 h or more after dosing exhibited a linear correlation ($r^2 = 0.922$); the correlation was stronger when only data 24 h or 5 days after dosing were considered ($r^2 = 0.983$). The authors did not compare these data to their earlier PBPK model for Pb in rat blood and saliva (Timchalk et al., 2001).

Metals: Nickel

Nickel PBPK modeling

The only identified PBPK model for nickel that describes disposition outside of the lung was that reported by Menzel (1988). Unfortunately, the model was not described in adequate detail to warrant further consideration.

Toxicokinetics of nickel in the rat

Table F1. Uptake and distribution of orally administered nickel in relation to solubility

Author(s)	Ishimatsu et al. (1995)
Species details	Adult male Wistar rats

Test article	Nickel metal, nickel oxide (green), nickel oxide (black), nickel subsulfide, nickel sulfide, nickel sulfate, nickel chloride, and nickel nitrate.
Route(s)	Gavage in starch saline
Duration	Single administration; measurements at 24 h
Tissue dosimetry	Nickel in lung, liver, kidney, spleen, pancreas, heart, brain, blood, and cumulative 24 h urinary excretion.
Comments/ Narrative	At 24 h after dosing, amounts of nickel in tissues of rats administered nickel oxide (green) were not significantly different from control rats. Based on amounts in organs, blood, and urine, estimated absorbed fractions ranged from 0.01% of nickel oxide (green) to 33.8% of nickel nitrate. On a per gram tissue basis, nickel concentrations after administration of other nickel compounds were highest in the kidney for all compounds, but the % of total in the organs was higher for the more soluble compounds (e.g., 80-90% of recovered nickel).

Table F2. Uptake distribution of nickel from in situ intestinal perfusion

Author(s)	Arnich et al. (2000)
Species details	Adult male Wistar rats
Test article	Nickel chloride
Route(s)	Intestinal perfusion in saline
Duration	Single 30 or 60-minute session of perfusion with nickel-containing solution
Tissue dosimetry	Nickel concentration in blood and small intestine after 60 minutes (multiple nickel concentrations), concentrations after 30-60 minutes of perfusion in blood, duodenum, jejunum, ileum, brain, heart, liver, lungs, spleen, kidneys and testicles.
Comments/ Narrative	Intestinal perfusion was implemented via catheterization of the duodenum, with effluent collection via catheterization of the ileum. After perfusion with saline only (15 min., 2 ml/min), perfusion with nickel-containing solution was conducted for 30-60 minutes. Nickel concentrations in brain did not differ from control after 30 or 60 min of perfusion. In other tissues, nickel concentrations were elevated at 30 minutes (some) and 60 minutes (all except brain), with concentrations increased at 60 min relative to 30 min for jejunum, ileum, lungs, spleen, testicles, and blood. The relationships between tissue or blood concentration vs. perfusate concentrations were interpreted as supporting active transfer of nickel in the jejunum and passive transfer in the ileum. Based on non-intestinal tissue concentrations, the authors estimated that 1.2% of the nickel perfused based through the intestinal barrier and was available for distribution to blood and other tissues.

Table F3. Plasma clearance and urinary elimination after iv administration of nickel

Author(s)	Tempelton et al. (1994)
Species details	Adult male Wistar rats
Test article	Isotopically-enriched nickel metal (^{61}Ni, ^{62}Ni), $^{63}NiCl_2$
Route(s)	Intravenous injection in saline
Duration	Single administration; data reporting to 80 h after dosing
Tissue dosimetry	Plasma concentration
Comments/ Narrative	Plasma concentrations were reported at 1, 6, and 24 h after dosing with 3.3 mg/kg nickel chloride. Plasma concentrations after doses of 0.12, 0.36, 1.1, and 3.3 mg/kg were also reported, but the timing was not specified. Based on comparison to the time course at a 3.3 mg/kg, the time may have been 1 h after dosing.

Table F4. Plasma clearance and urinary and fecal elimination after iv administration of nickel

Author(s)	Onkelinx et al. (1973)
Species details	Adult male Wistar rats
Test article	$^{63}NiCl_2$
Route(s)	Intravenous injection or infusion in saline
Duration	Single administration or continuous infusion (6.6., 23.5, or 30 h); data reporting to 9 d after dosing
Tissue dosimetry	Plasma concentration, total urinary and total fecal excretion
Comments/ Narrative	Within three days after a single injection, 78% of nickel was eliminated in urine and 15% in feces. Plasma concentrations were measured from 1 h to 9 days post-dosing; biphasic elimination was indicated. Under conditions of continuous intravenous infusion, plasma nickel concentrations were measured at 6.6, 23.5 and 30 h after the beginning of infusion.

Table F5. Plasma clearance, tissue dosimetry, and urinary and fecal elimination after iv administration of nickel

Author(s)	Smith and Hackley (1968)
Species details	Adult female Sprague-Dawley rats
Test article	$^{63}NiCl_2$
Route(s)	Intravenous injection in saline
Duration	Single administration; data reporting to 72 h after dosing
Tissue dosimetry	Kidney, adrenal, ovary, lung, heart, eye, thymus, pancreas, spleen, liver, skin, GI tract, muscle, teeth, femur, brain, adipose, carcass, plasma, and whole blood concentrations, percent of dose excreted in urine and feces (hourly amount per collection period and cumulative excretion).
Comments/ Narrative	Distribution studies were conducted in two studies with differing doses and collection times, with fewer times but more tissues in the second study. In the first study, urinary and fecal excretion were also assessed.

	Urinary excretion peaked in the first collection period (0-2 h), with fecal excretion peaking at the 6-8 h period. Tissue concentrations were highest in the kidney, but the % of dose in the kidney consistently was lower in the high-dose study at comparable collection times, while % dose/tissue volume tended to be similar in other tissues.

Table F6. Nickel time course in plasma, tissue distribution, and urinary and fecal elimination after ip injection of nickel chloride and biliary excretion after im injection

Author(s)	Sunderman et al. (1976)
Species details	Adult female Fischer 344 rats
Test article	$^{63}NiCl_2$
Route(s)	Intraperitoneal or intramuscular injection in saline
Duration	Single administration, data reporting to 5 days
Tissue dosimetry	Plasma (time course), kidney, liver, lung, heart, and spleen (6 h) concentrations, urinary and fecal excretion (% of dose) for 24-h (or smaller) intervals; biliary excretion (concentration and % dose) for 3 h after im injection.
Comments/ Narrative	Plasma nickel concentrations were determined at 10, 20, and 40 minutes, 1, 1.5, 2, 6, ad 24 h after ip injection of nickel chloride. At 6 h after dosing, the highest nickel concentrations were found in the kidneys. Urinary excretion was ~36 % of dose within 6 h, 65% within 24 h, and declined to 7.4, 1.9, 0.94, and 0.55 % of dose on days 2, 3, 4, and 5 postdosing. Fecal elimination was approximately 0.95% on day 1, and 0.65% of dose on day 2. Biliary excretion of nickel in cannulated rats receiving nickel via im injection was 0.17% of dose in 3 h.

Table F7. Plasma nickel levels after ip injection of nickel chloride

Author(s)	Harkin et al. (2003)
Species details	Adult male Sprague-Dawley rats
Test article	Nickel chloride
Route(s)	Intraperitoneal injection in saline
Duration	Single administration, data reported out to 80 h
Tissue dosimetry	Single administration; feces, urine, and serum collected up to 7 days, per the authors, but time course data were reported for up to 80 h.
Comments/ Narrative	Cumulative excretion of nickel up to 80 h was 60 percent of dose in urine and 5.4 % of dose in feces. Time course data indicate that roughly two thirds of that urinary excretion occurred within the first 12 h. Serum clearance was fit to a biexponential formula with half-lives of 0.21 and 7.1 h.

Table F8. Plasma and bile concentrations and biliary elimination rate of nickel after subcutaneous injection of nickel chloride

Author(s)	Marzouk and Sunderman (1985)
Species details	Adult male Fischer 344 rats
Test article	Nickel chloride ($^{63}NiCl_2$)
Route(s)	Subcutaneous injection in saline
Duration	Single exposure, detailed time course with radioactive nickel for 6 h. At higher doses of nonradioactive nickel chloride, plasma was collected at 6, 16, and 30 h after injection, and bile was collected from 1-6 and 11-16 h after injection.
Tissue dosimetry	Plasma and bile concentrations and biliary excretion rate as expressed as mass and as percent of dose.
Comments/ Narrative	Bile concentrations of nickel were highest during the 1-2 h interval after dosing, and then declined exponentially. Plasma nickel levels declined with a half-life of 3 h. At the low dose (1.7 µmol/kg), 6 h cumulative biliary excretion of nickel was 0.26% of dose, and the higher doses, 1-6 h biliary excretion was 0.095% and 0.077% of dose at 125 and 250 µmol/kg, respectively.

Table F9. Tissue levels and urinary and biliary elimination of nickel after subcutaneous injection of nickel chloride

Author(s)	Srivastava et al. (1988a, b), Athar et al. (1987)
Species details	Adult male and female albino rats
Test article	Nickel chloride ($^{63}NiCl_2$)
Route(s)	Subcutaneous injection; vehicle not stated
Duration	Single exposure, urinary and tissue data at 16 h (Srivastava et al., 1988a, b) biliary data after 3 h and urinary data after 1, 2, and 3 days (Athar et al., 1987)
Tissue dosimetry	Liver, kidney, lung, spleen, heart, and plasma concentrations, total urinary and biliary elimination.
Comments/ Narrative	The highest nickel concentrations were found in the kidney and approximately 50% of the administered dose was eliminated in urine and 1 percent via feces within 16 h of injection. Partial hepatectomy had no significant impact on clearance or distribution of nickel. Excretion in bile accounted for 0.41% of dose within 3 h of dosing. Urinary elimination accounted for 54, 63, and 68 % of dose at 1, 2, and 3 days after dosing.

Table F10. Time course of tissue levels of nickel after intraperitoneal injection of nickel chloride

Author(s)	Gupta et al. (2000)
Species details	Adult male albino rats
Test article	Nickel chloride ($^{63}NiCl_2$)

Route(s)	ip injection; vehicle not stated
Duration	Single exposure, data at 1,2, and 4 h after dosing
Tissue dosimetry	Nickel concentrations in adrenals, brain, and pancreas
Comments/ Narrative	The highest concentrations in these tissues were observed 1 h after dosing.

Table F11. Tissue levels of nickel after gavage administration of nickel chloride

Author(s)	Tallkvist et al. (1994)
Species details	Male Sprague-Dawley rats (age unclear; rats were 3 weeks old at the start of the experiment, and were on specific diets for 15-25 days prior to evaluation)
Test article	Nickel chloride ($^{63}NiCl_2$)
Route(s)	Gastric intubation, in saline
Duration	Single exposure, data at 24 h after dosing
Tissue dosimetry	Concentrations of nickel in kidney, lungs, liver, cerebrum, heart, spleen, pancreas, eyes, and serum
Comments/ Narrative	The highest nickel concentrations were found in the kidney and cerebrum. Tissues from iron-deficient rats had consistently higher concentrations of nickel than what was observed in iron-sufficient rats.

Table F12. Tissue levels of nickel after gavage or ip administration of nickel chloride

Author(s)	Tallkvist and Tjälve (1997)
Species details	Male Sprague-Dawley rats, 7 weeks old
Test article	Nickel chloride ($^{63}NiCl_2$)
Route(s)	Gastric intubation or intraperitoneal injection, in saline
Duration	Single exposure, data at 3, 6, 24, 48 and 120 h after dosing (oral) or 24 h only (ip)
Tissue dosimetry	Concentrations and percent of dose of nickel in kidney, skin, lungs, liver, testis, and serum
Comments/ Narrative	The highest nickel concentrations were found in the kidney for both oral and ip exposure. In iron-sufficient rats, tissue and serum concentrations were highest at 6 h after oral dosing with the exception of the kidney, where concentrations were highest at 3 h after dosing. Tissues from iron-deficient rats had consistently higher concentrations of nickel than what was observed in iron-sufficient rats.

Table F13. Tissue levels of nickel after ip administration of nickel chloride and the effect of co-exposure to cadmium chloride

Author(s)	Li et al. (2010)
Species details	Adult female Wistar rats
Test article	Nickel chloride ($^{63}NiCl_2$)

Route(s)	Intraperitoneal injection, in saline
Duration	Single exposure, tissue data at 3 and 24 h after dosing; blood data at 14 points between dosing and 3 h; urinary and fecal excretion up to 24 h after dosing.
Tissue dosimetry	Nickel concentration in blood, brain, eye, ovary, bladder, retroperitoneal fat, bone, muscle, spleen, blood vessel, kidney, uterus, large intestine, small intestine, heart, pancreas, stomach, liver, lung, and hair. Excretion (% of total) in urine and feces for 0-3, 3-6, and 6-24 h after dosing; feces amounts for 0-3 and 3-6 h were combined.
Comments/ Narrative	The highest nickel concentrations were found in the kidney and uterus. In the absence of cadmium approximately 89 percent of the dose of nickel was eliminated in urine, and 4.6 percent eliminated in feces within 24 h. Based on the blood, tissue, and urine time courses of nickel, the presence of cadmium appeared to delay nickel absorption and inhibit the elimination of absorbed nickel.

Solvents: allyl alcohol

Allyl alcohol PBPK modeling

One PBPK model for allyl alcohol was identified in the literature. Mielke et al. (2011) used an in silico algorithm to predict tissue:plasma partition coefficients on the basis of other chemical-specific properties, but assumed no metabolism of allyl alcohol would occur. The oral absorption fraction was reportedly derived from in vivo rat data, but the details of the derivation were unclear. No validation of the model was shown.

Table G1. Mielke et al. (2011) PBPK model of orally administered allyl alcohol in the rat

Author(s)	Mielke et al. (2011)
Species	Rat
Species details	None provided
Route(s)	Oral
Duration	Not specified
Tissue dosimetry	No validation or calibration data were shown
Model language	Not stated
Code availability	Not provided. Details were reported as having been described elsewhere.
Comments/ Narrative	The generic model structure (applied to 29 chemicals) consisted of a fraction of the administered dose being delivered to the portal vein to transport to the liver, seven perfusion-limited organ compartments, and arterial and venous blood. Tissue:plasma partition coefficients were calculated using a published algorithm which relies on inputs regarding pKa, logP, and the fraction unbound. The values of these inputs were reported for all 29 chemicals, but it was not clear whether the values used for allyl alcohol were measured values or computed. The model does not include any metabolism or excretion, though allyl alcohol is

	known to be metabolized to acrolein. The fractional absorption was assumed to be 20% based on experimental data in rats. The source cited was a reference sheet in French, and it was not clear how the value of 20% absorption was derived. Based on the judgment of this report's lead author (LMS), the absorption is likely much greater, but the apparent availability (perhaps estimated via urinary elimination, etc.) is reduced due to the high reactivity of allyl alcohol and/or its metabolites.

Toxicokinetics of allyl alcohol in the rat (<1 week of exposure)

Table G2. Blood levels of allyl alcohol after ip administration

Author(s)	Belinsky et al. (1984)
Species details	Adult female Sprague-Dawley rats
Test article	Allyl alcohol
Route(s)	Intraperitoneal injection, in normal saline
Duration	Single exposure, one measurement 30 minutes after dosing.
Tissue dosimetry	Concentrations in blood collected from the portal vein and vena cava
Comments/ Narrative	Blood concentrations of allyl alcohol were measured 30 minutes after ip injection of 42 mg/kg allyl alcohol, a level that produced liver necrosis. The concentrations were 1210 ± 240 and 530 ± 210 μM in the portal vein and vena cava, respectively.

Table G3. Blood and liver levels of allyl alcohol after ip administration

Author(s)	Anand et al. (2003, 2005)
Species details	Adult male Sprague-Dawley rats
Test article	Allyl alcohol
Route(s)	Intraperitoneal injection, in distilled water
Duration	Single exposure, data up to 60 minutes after dosing.
Tissue dosimetry	Blood and liver concentrations
Comments/ Narrative	Blood and liver concentrations of allyl alcohol were measured at 5, 10, 15, 30, 45, and 60 (Anand et al., 2003 only) minutes after injection of AA alone, or in a binary mixture (with chloroform) or ternary mixture (with chloroform and trichloroethylene). Data were presented only for 20 and 35 mg/kg doses, although the methods sections indicated additional doses to be tested. Blood levels of AA peaked at the first measurement (5 minutes), while liver levels peaked at 10 minutes after dosing, and rapidly declined. Co-administration had a limited impact on blood and liver concentrations of allyl alcohol.

Solvents: bromobenzene

Bromobenzene PBPK modeling

No PBPK models describing the disposition of bromobenzene in any species were identified.

Toxicokinetics of bromobenzene in the rat

Table H1. Plasma and tissue levels of bromobenzene and excretion of urinary metabolites after ip administration

Author(s)	Reid et al. (1971)
Species details	Adult male Sprague-Dawley rats
Test article	Bromobenzene, ^{3}H-bromobenzene or ^{14}C-bromobenzene
Route(s)	Intraperitoneal injection, in sesame oil
Duration	Single exposure, plasma and tissue concentrations up to 24 h after dosing, urinary metabolites cumulative to 4, 8, and 24 h after dosing.
Tissue dosimetry	Plasma, liver, kidney, brain heart, lung, stomach, and fat concentrations; total, mercapturic, and phenolic metabolites.
Comments/ Narrative	Plasma and all tissue concentrations were reported at 4 and 24 h after a 750 mg/kg ip dose; further time course data for earlier and intermediate times were shown graphically for fat, liver, and plasma, with peaks at around 2 h after dosing, and initial gradual decline until 12 h, then a more steep decline between 12 and 24 h (with no intervening sampling to clarify points of inflection). An additional plasma bromobenzene time course was collected for a 225 mg/kg ip dose, which displayed a peak at about 2 h, gradual decline to 6 h, more rapid decline to a sample at about 11 h, then slow decline between that sample and the 24 h sample. In rats given a 750 mg/kg ip dose, extensive centrilobular hepatic necrosis was observed 24 h after dosing and liver and plasma concentrations of bromobenzene were measured. At the 225 mg/kg dose, approximately 85% of the dose was excreted in urine within 24 h, chiefly as mercapturic acids and phenolic metabolites.

Table H2. Plasma, tissue, and whole body levels of bromobenzene and urinary levels of metabolites after iv or administration

Author(s)	Zampaglione et al. (1973)
Species details	Adult male Sprague-Dawley rats
Test article	Bromobenzene or ^{14}C-bromobenzene
Route(s)	Intravenous injection in plasma or intraperitoneal injection in sesame oil
Duration	Single exposure, plasma, tissue, and whole-body concentrations up to 70 min after iv dosing, liver concentrations up to 24 h after ip dosing. Urinary metabolites cumulative to 48 h after dosing.
Tissue dosimetry	Plasma, liver, fat, and whole body concentrations of (spleen, brain, heart, and testes not shown); urinary bromophenyl mercapturic acid, 1-

	bromophenol, bromocatechol, bromophenyldihydrodiol, and 3-bromophenol.
Comments/ Narrative	Triphasic declines of bromobenzene in plasma and liver (shown in paper) and spleen, brain heart and testes (not shown in paper) were observed within 70 minutes after administration of a tracer dose via iv injection; levels in adipose increased for roughly 20 minutes, then displayed a limited decline. Whole body bromobenzene levels demonstrated a rapid biphasic decline after iv administration (9.8 minute initial half-life), with 60-70 percent biotransformation within 30 minutes; whole body radioactivity was constant during the 70-minute experiment. After administration of a hepatotoxic dose via ip injection in sesame oil, liver concentrations increased for two hours, slowly declined until 10 h after dosing, then declined more rapidly (final measurement 24 h after dosing). After a nontoxic (0.5 mmol/kg) iv dose, 70% of the dose was excreted as mercapturic acids, 21% as phenols, 4% as bromocatechol, and 4% as the dihydrodiol. In contrast, after a toxic ip dose (10 mmol/kg), mercapturic acids decreased to 48% of dose and phenols increased to 41% of dose.

Table H2. Biliary excretion of bromobenzene-GSH conjugates after injection of bromobenzene into the portal vein

Author(s)	Madhu and Klaassen (1992)
Species details	Adult male rats (strain not specified)
Test article	Bromobenzene
Route(s)	Injected into the portal vein in saline
Duration	Single exposure, bile collection for 90 minutes after exposure (15-minute intervals).
Tissue dosimetry	Biliary excretion rate of bromobenzene-GSH conjugates.
Comments/ Narrative	The biliary excretion rate of bromobenzene-GSH conjugates was approximately proportional to dose for doses of 62, 125, and 250 µmol bromobenzene/kg, but less than proportional at 500 µmol/kg, a dose which significantly depleted hepatic GSH.

Table H3. Blood concentrations of bromobenzene after 4 h of inhalation

Author(s)	Aarstad et al. (1990)
Species details	Adult male Sprague-Dawley rats
Test article	Bromobenzene
Route(s)	Inhalation (dynamic chamber, 6 air changes/h)
Duration	4 h
Tissue dosimetry	Blood bromobenzene
Comments/ Narrative	The blood concentrations were 10 and 102 mg/L after 4 h of inhalation of bromobenzene, respectively, in which target concentration in the chambers 2342 250 and 1000 ppm (1.61 and 6.42 mg/L), respectively.

	The chamber concentration time course indicated that steady state levels of inhaled concentration were achieve ~45 minutes into the 4-h exposure.

Solvents: carbon tetrachloride

Carbon tetrachloride PBPK modeling

Several publications describe PBPK models for the disposition carbon tetrachloride in the rat (see below). While most addressed the inhalation route of exposure, quantification of uptake from ip and gavage administration was also assessed via exhaled breath. A human PBPK model for carbon tetrachloride was developed by Paustenbach et al. (1988) using in vivo data, and has been adapted by other modelers.

Table I1. Gargas et al. (1986) PBPK model inhaled carbon tetrachloride in the rat

Author(s)	Gargas et al. (1986, 1990); Evans and Andersen (1995); El-Masri et al., 1996; Semino et al. (1997); Thrall et al. (2000)
Species	Rat
Species details	Male Fischer 344
Route(s)	Inhalation (closed chamber), intraperitoneal injection of neat chemical (rats placed in exhalation chamber), and gavage (corn oil and Emulphor vehicles)
Duration	4-6 h inhalation
Tissue dosimetry	Not measured in inhalation and ip studies—disposition inferred from changes in chamber concentration; blood concentrations and exhaled breath chamber concentrations after gavage dosing
Model language	Simusolv (Gargas et al., 1990), Simusolv v. 3.0 (Evans and Andersen, 1995)
Code availability	Not provided; equations previously presented elsewhere. Equations for oral absorption (Semino et al., 1997) were provided.
Comments/ Narrative	The generic model structure employed by Gargas et al. (1986, 1990) (applied to as many as eight chemicals in the listed series of papers) consisted of an inhalation chamber, a blood/air gas exchange compartment, four perfusion limited tissue compartments (liver, fat, slowly perfused tissues and rapidly perfused tissues), and a venous blood mixing equation. Potential nonspecific losses to the chamber and/or animal fur, etc. were provided for in the model. Blood:air and tissue:air (liver, fat, and muscle) partition coefficients were measured by Gargas et al. (1986), with the slowly perfused tissue partition coefficient set at a value double the measured muscle: air partition coefficient. Tissue:blood partition coefficients were computed as the ratio of tissue:air to blood:air partition coefficient. Metabolism was limited to the liver and for carbon tetrachloride, was described as saturable. The metabolic parameters were determined by best fit to closed chamber

	concentration time course data with initial concentrations of 0.65, 10, 100, and 230 ppm. In both Gargas et al. (1986 and 1990), the VmaxC was reported as 0.4 mg/h-kg$^{0.7}$ and KM = 0.25 mg/L. Evan and Andersen (1995) slightly modified the model by including a lung tissue compartment (with no metabolism), use the Gargas et al. (1986, 1990) value of 0.25 mg/L for the KM, and a lower value for Vmax (0.11 mg/h, or VmaxC = 0.3 mg/h/kg$^{0.7}$ for a 0.225 kg rat). Evans and Andersen (1995) found that predicted chamber concentration were more sensitive to Vmax and Km values at lower initial concentrations. Thrall et al. (2000) determined that the same metabolic parameters derived by Gargas et al. (1986, 1990) also adequately simulated a new set of closed chamber uptake data that they collected (initial concentrations of 34, 40, 163, 316, and 1293 ppm). El-Masri et al. (1996) calibrated the rate of uptake of carbon tetrachloride from ip injection using the Gargas et al. (1986) model to predict carbon tetrachloride concentrations in an exhalation chamber (< 1 h after dosing). Semino et al. (1997) described disposition of carbon tetrachloride delivered by gavage in a corn oil or Emulphor vehicle (data also reported in Kim et al., 1990), using a multicompartmental description of the gastrointestinal tract. Semino et al. (1997) optimized absorption rates, fractional availability for uptake, and transit time for each of 9 sub-compartments to describe disposition in three individual rats, which resulted in multiple pulses in rat blood concentrations in these studies. The generalizability of these parameters was unclear.

Table I2. Evans et al. (1994) PBPK model inhaled carbon tetrachloride in the rat

Author(s)	Evans et al. (1994); Evans and Simmons (1996), Yoon et al. (2007)
Species	Rat
Species details	Male Fischer 344
Route(s)	Inhalation; closed chamber
Duration	6 h
Tissue dosimetry	Not measured; disposition inferred from declines in chamber concentration
Model language	Simusolv v. 3.0 (Evans et al., 1994; Evans and Simmons, 1996); acslXtreme, version 2.0.1.7 (Yoon et al., 2007)
Code availability	Not provided; equations previously presented elsewhere.
Comments/ Narrative	The generic model structure employed by Gargas et al. (1986, 1990), described above, (Table I1) was also used by Evans and colleagues. Blood:air and tissue:air (liver, fat, and muscle) partition coefficients were measured by Evans et al. (1994). Blood or tissue:air values determined by Evans et al. (1994) were slightly higher than the Gargas et al. (1986) values for blood (21%), liver (14%) and muscle (47%), but lower for fat (22%). As a result, tissue:blood partition coefficients were only modestly changed for muscle and liver, but the change in the

	fat:blood partition coefficient was more substantial (decreased by 35%). Following the precedent of Gargas et al. (1986), Evans et al. (1994) also used a value of 2x the measured muscle:air value to compute the tissue:blood partition coefficient for slowly perfused tissues. The metabolic parameters were determined by best fit to closed chamber concentration time course data with initial concentrations of 25, 100, 250 and 1000 ppm. Compared to Gargas et al. (1986 and 1990), the VmaxC was approximately the same (0.37 vs. 0.4 mg/h-kg$^{0.7}$). The Evans et al. (1994) KM of 1.3 mg/L was larger than the Gargas et al. values (0.25 mg/L). Yoon et al. (2007) modified the Gargas et al. (1986)/Evans et al. (1994) model structure to accommodate lung and kidney tissue compartments with possible metabolism and non-metabolizing brain and GI tissue compartments for an analysis of potential extrahepatic metabolism of volatile organic compounds. Yoon et al. (2007) used the Evans et al. (1994) partition coefficients in their optimizations, and yielded optimal values of KM = 1.10 (similar to that of Evans et al. (1994), but a VmaxC of 0.13 mg/h-kg$^{0.75}$. Considering that Simusolv and acslXtreme are similar, it is unclear if the difference between Evans et al (1994) and Yoon et al. (2007) is the result of somewhat different anatomical parameters, model structure (splitting out specific richly perfused tissues), or differences in optimization approaches (e.g., heteroscedasticity).

Table I3. Paustenbach et al. (1988) PBPK model inhaled carbon tetrachloride in the rat, monkey and human

Author(s)	Paustenbach et al. (1988); Thrall et al. (2000) (only human model based on Paustenbach model); Mumtaz et al. (2012).
Species	Rat, monkey, and human
Species details	Male Sprague-Dawley or Fischer 344 rats; rhesus monkeys; adult humans
Route(s)	Inhalation; rats: closed chamber (see Gargas et al., 1986), open chamber; humans: constant concentrations
Duration	Rats: 6-11.5 h per day, up to 12 days (5 days on, 2 days off, 5 days on); humans: 70 or 180 minutes.
Tissue dosimetry	Disposition inferred in part from declines in chamber concentration; ^{14}C in urine, feces, exhaled as CCl_4 or CO_2, and in fat
Model language	Not stated in Paustenbach et al. (1988); Thrall et al. 2000: Simusolv 3.0; Mumtaz et al. (2012); Berkeley Madonna
Code availability	Not provided; equations previously presented elsewhere.
Comments/ Narrative	The model structure was the same as used by Gargas et al. (1986), described above (Table I1), as were the rat partition coefficients. A human blood:air partition coefficient was reported by Paustenbach, but it is not clear what values for tissue:blood partition coefficients were

	used for humans (i.e., computed rat tissue:blood ratios, or human tissue: blood ratios estimated as rat tissue:air value divided by the human tissue:air value). The metabolic parameters derived for smaller F344 rats (Gargas et al., 1986) were adjusted to fit the repeated exposure data for larger Sprague-Dawley rats (previously reported by Paustenbach and colleagues), with KM the same as the Gargas et al. (1986, 1990) value of 0.25 mg/L, but with VmaxC = 0.65 mg/r-kg$^{0.7}$. The same partitioning and biochemical parameters were applied to simulation of data for monkeys and human volunteers collected by other researchers. The human data consisted of post exposure exhaled breath measurements of carbon tetrachloride. The physiological parameters that Paustenbach et al. (1988) used for humans included a fat volume of only 10 percent. Thrall et al. (2000) used the Paustenbach et al. (1988) physiological values, human partition coefficients, and KM, but based their VmaxC value on in vitro metabolism data, adjusted for in vivo (optimized): in vitro ratios determined for rats, mice, and humans. Mumtaz et al. (2012) report using chemical-specific parameters of Thrall et al. (2000) as the basis for their human PBPK model of carbon tetrachloride, paired with physiological parameters standardized for use in predicting the human toxicokinetics for various parameters. Their model includes liver, kidney, skin, fat, slowly perfused tissue, richly perfused tissues, blood, and air exchange. The Mumtaz et al. (2012) uses the original Paustenbach et al. (1988) value for VmaxC (not the value Thrall et al., 2000 derived from in vitro data) adjusted for the change in body weight scaling coefficient (from 0.7 to 0.75), and blood:air partition coefficient. The tissue: blood partition coefficients reported by Mumtaz et al. (2012) are consistent with the approach of estimating human tissue:blood partition coefficients as the rat tissue:air partition coefficient divided by the human blood:air partition coefficient. The Mumtaz et al. (2012) simulations of human exhaled breath data were visibly different from those of Thrall et al. (2000). The use of different anatomical/physiological parameters (e.g., body fat percentage, cardiac output, alveolar ventilation rate) may contribute to the observed differences in the simulations.

Toxicokinetics of carbon tetrachloride in the rat

Table I4. Closed chamber inhalation uptake of low concentrations of carbon tetrachloride by rats

Author(s)	Yoshida et al. (1999)
Species details	Adult male Sprague-Dawley rats
Test article	Carbon tetrachloride
Route(s)	Inhalation (closed chamber)
Duration	6 h
Tissue dosimetry	None; disposition was inferred from chemical disappearance

Comments/ Narrative	Chemical distribution within and losses to the closed chamber system were characterized in the absence of a rat. Chemical disappearance in the presence of a rat was then attributed to net uptake into the rat and metabolism. Five different starting concentrations (1 ppm or less) were used to evaluate chemical kinetics. Using a three-compartment model (tank, chamber, and rat), first order rates of carbon tetrachloride exhalation and metabolism were derived. The exhalation rate constant was observed to exceed the metabolism rate constant, consistent with findings of Reynolds et al. (1984a, b) in rats exposed by gavage (see below, Table I6).

Table I5. Radiolabel body burden and clearance after inhalation of 20 ppm ^{14}C-carbon tetrachloride by rats

Author(s)	Benson et al. (2001)
Species details	Adult male Fischer 344 rats
Test article	^{14}C-labeled carbon tetrachloride
Route(s)	Inhalation (nose-only)
Duration	4 h exposure, specimen collection up to 48 h (excreta)
Tissue dosimetry	Radiolabel in urine, feces, exhaled air (fractionated into volatiles [carbon tetrachloride and chloroform] and carbon dioxide), blood, lung, liver, kidneys, brain, spleen, perirenal fat, and carcass.
Comments/ Narrative	While excreta collection over several intervals and blood and tissue collection reportedly occurred at the conclusion of exposure, and 2, 6, 24, and 48 h after exposure, only data from the conclusion of exposure and at 48 h were explicitly reported. Data from intermediate time points were likely used in the derivation of elimination half-lives, but were not presented for inspection. Elimination of radiolabel from blood and lung was monophasic during the 48 h of monitoring after exposure, while elimination from liver and kidney was biphasic.

Table I6. Exhalation and excretion of ^{14}C-carbon tetrachloride after gavage

Author(s)	Reynolds et al. (1984a, b)
Species details	Adult male Sprague Dawley rats
Test article	^{14}C-labeled carbon tetrachloride
Route(s)	Gavage in mineral oil
Duration	Single exposure, specimen collection up to 24 h
Tissue dosimetry	Exhaled $^{14}CCl_4$, $^{14}CO_2$, and $CHCl_3$; ^{14}C in urine and feces, and ^{14}C bound in liver
Comments/ Narrative	Exhaled air was collected for intervals of increasing duration during the first 24 h after dosing with 0, 0.1, 0.3, 2, 4, 10, or 26 mmol/kg in mineral oil. Urine and feces collection intervals were less clearly delineated, but only 24-h cumulative data were reported. As dose increased, a decreasing proportion of radiolabel was recovered as CO_2.

Table I6. Serial blood concentrations of carbon tetrachloride in rats after iv dosing and gavage dosing in various vehicles

Author(s)	Kim et al. (1990), Sanzgiri and Bruckner (1997)
Species details	Adult male Sprague Dawley rats
Test article	Carbon tetrachloride
Route(s)	Intravenous injection in polyethylene glycol (PEG) 400; gavage as neat chemical or in corn oil, water, and various concentrations of Emulphor (0.25, 1, 2.5, 5, or 10%) as an aqueous emulsion. Equal doses of carbon tetrachloride were used in the various trials (25 mg/kg).
Duration	Single exposure, blood collection up to 19 h after dosing
Tissue dosimetry	Blood carbon tetrachloride
Comments/ Narrative	Serial blood samples were taken with decreasing frequency (2- to 60-minute intervals for 19 h for gavage dosing in corn oil and for up to 9 h for other routes and vehicles. In the tested range, Emulphor produced no hepatotoxicity and kinetics were unaltered by the differences in Emulphor concentrations. Pure (neat) chemical and chemical in corn oil were more slowly absorbed and displayed lower peak concentrations. The time course for carbon tetrachloride (plotted as average blood concentration for 5 rats) displayed two distinct peaks.

Table I7. Effect of route and pattern of exposure on blood and tissue concentrations of carbon tetrachloride after equal systemic doses via inhalation, gavage, and oral infusion

Author(s)	Sanzgiri et al. (1995, 1997),
Species details	Adult male Sprague Dawley rats
Test article	Carbon tetrachloride
Route(s)	Inhalation, gavage or gastric infusion in aqueous Emulphor emulsion
Duration	Single gavage, 2 h inhalation or gastric infusion, blood collection up to 12 h after dosing, tissue collection up to 24 h after dosing.
Tissue dosimetry	Carbon tetrachloride in blood, liver, kidney, skeletal muscle, heart, lung, brain, perirenal fat, spleen (not shown), and GI tract (not shown; inhalation only)
Comments/ Narrative	2-hr inhalation exposures were conducted at 100 and 1000 ppm through a one-way breathing valve; the minute volume and the difference between inhaled and exhaled concentrations were determined so that total systemically absorbed dose could be computed. The systemic doses computed for the inhalation studies were then used for the gavage studies and for two-hour gastric infusions. Time course data for blood were available for both high and low doses (Sanzgiri et al., 1995), while tissue data were available only for high doses.

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DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

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