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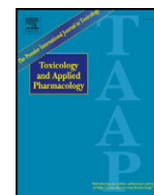

Reduction of hexavalent chromium by fasted and fed human gastric fluid. II. *Ex vivo* gastric reduction modeling

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ABSTRACT

To extend previous models of hexavalent chromium [Cr(VI)] reduction by gastric fluid (GF), *ex vivo* experiments were conducted to address data gaps and limitations identified with respect to (1) GF dilution in the model; (2) reduction of Cr(VI) in fed human GF samples; (3) the number of Cr(VI) reduction pools present in human GF under fed, fasted, and proton pump inhibitor (PPI)-use conditions; and (4) an appropriate form for the pH-dependence of Cr(VI) reduction rate constants. Rates and capacities of Cr(VI) reduction were characterized in gastric contents from fed and fasted volunteers, and from fasted pre-operative patients treated with PPIs. Reduction capacities were first estimated over a 4-h reduction period. Once reduction capacity was established, a dual-spike approach was used in speciated isotope dilution mass spectrometry analyses to characterize the concentration-dependence of the 2nd order reduction rate constants. These data, when combined with previously collected data, were well described by a three-pool model (pool 1 = fast reaction with low capacity; pool 2 = slow reaction with higher capacity; pool 3 = very slow reaction with higher capacity) using pH-dependent rate constants characterized by a piecewise, log-linear relationship. These data indicate that human gastric samples, like those collected from rats and mice, contain multiple pools of reducing agents, and low concentrations of Cr(VI) (<0.7 mg/L) are reduced more rapidly than high concentrations. The data and revised modeling results herein provide improved characterization of Cr(VI) gastric reduction kinetics, critical for Cr(VI) pharmacokinetic modeling and human health risk assessment.

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1. Introduction

Drinking water consumption of high concentrations (5 to 180 mg/L) of hexavalent chromium [Cr(VI)] has been found to produce tumors in the small intestines of mice following lifetime oral exposures (NTP, 2008). However, it has been recognized for several decades that Cr(VI) can be detoxified via extracellular reduction to inert trivalent chromium [Cr(III)] in the gastrointestinal lumen (De Flora et al., 1987; De Flora, 2000). Characterization of the rates and capacities for Cr(VI) reduction by gastric fluid (GF) prior to reaching critical target tissues in the small intestine (i.e., intestinal mucosa cells) is important for informing extrapolations of toxicity observed across species and for understanding the potential cancer risk posed by environmental exposure to Cr(VI) in the drinking water supply. The rate of Cr(VI) reduction can be described by the following generalized equation:

$$RateofReduction\ (mg/hr) = C_{CrVI}\ x\ \left[(K_{Red}\ x\ C_{RE})_{Pool\ 1} + \ldots (K_{Red}\ x\ C_{RE})_{Pool\ N}\right] \quad (1)$$

Where K_{Red} is a second order rate constant for reduction (L^2/mg-hr) for a specific pool of reducing equivalents, C_{RE} is the concentration of reducing equivalents or reduction capacity (mg/L) for a specific pool of

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reducing agents, C_{CrVI} is the concentration of Cr(VI) (mg/L), and N is the number of pools; and values for K_{Red} and C_{RE} differ between pools (i.e., reduction reactions can occur at different rates, with different capacities). The term reducing equivalent is used here for the sake of simplicity to refer to a pool of three-electron donors needed to reduce Cr(VI) to Cr(III). By collecting and modeling time-course data collected for the reduction of Cr(VI) by GF, we can characterize the rates, capacities, and pH-dependence of the reaction, which is then used in a physiologically based pharmacokinetic model for chromium (Fig. 1).

The capacity of GF for Cr(VI) reduction (C_{RE}) has been characterized in human and animal studies. Based on an *s*-diphenylcarbazide (DPC) colorimetric method, De Flora et al. (1987) reported time-dependent changes in the capacity of GF to reduce Cr(VI) in 16 hospital patients with duodenal ulcer and one healthy volunteer. Shortly after a meal, peak reduction capacities were reported as a single pool ranging from 40 to 60 mg/L, while reduction capacities between meals were generally below 10 mg/L. Confirming the latter value, Kirman et al. (2013) estimated a reduction capacity for a single pool of 7 mg/L in combined GF samples from ten fasted, preoperative cardiac patients using a simple (single, 2nd order reaction) reduction model. Analyzing the same data as Kirman et al. (2013) with a more complex reduction model, Schlosser and Sasso (2014) reported a slightly higher reduction capacity for a single pool of approximately 10 mg/L in fasted human samples. Overall, despite differences in analytical methods or modeling approaches, the capacity estimates for fasted samples from these studies (De Flora et al., 1987; Kirman et al., 2013; Schlosser and Sasso, 2014) are generally consistent. With respect to capacity in GF from laboratory rodents, Proctor et al. (2012) reported that the reduction capacity for GF samples from fed rats and mice was approximately 16 mg/L using a simple, single reduction pool model. Reanalysis of the same data by Schlosser and Sasso (2014) using a multi-pool model, including fast and slow reduction reactions, yielded slightly higher reduction capacities. Specifically, reduction capacities in mouse GF of 2.9 and 31 mg/L for the fast and slow pools, respectively, were reported, while values of 4.1 and 18 mg/L were reported for the fast and slow pools, respectively, in rat GF.

The number of reducing agent pools present in GF (*N* in Eq. (1)) is an important determinant of risk that can affect interspecies extrapolation as well as high-to-low dose extrapolation. In our previous work characterizing the reduction of Cr(VI) by human and rodent GF, we modeled all data using a single-pool model (Proctor et al., 2012; Kirman et al., 2013). Using a revised gastric model, Schlosser and Sasso (2014) relied upon a single-pool model for humans, and a three-pool model for laboratory rodents based upon available *ex vivo* reduction data, and in so doing may have created an apparent species difference (three pools in rodents vs. one pool in humans). However, the single pool used to model the human data may reflect insufficient information that was previously available to allow for differentiation of more than one pool, rather than a true species difference. Specifically, to address the presence of multiple reducing agent pools, GF samples need to be assessed using a wide range of Cr(VI) spike concentrations. In our previous study of human GF (Kirman et al., 2013), a limited number of human fasted samples were used to characterize reduction across different pH values using a fairly narrow range of Cr(VI) spike concentrations. In rodent GF, pH is far less variable than in humans, and we were able to characterize Cr(VI) reduction across a wide range of concentrations (Proctor et al., 2012). Samples were spiked at a range of concentrations representative of the high concentrations used in the rodent cancer bioassay (180 ppm) as well as much lower concentrations consistent with the federal drinking water standard (0.1 ppm).

The reduction of Cr(VI) by human GF is pH dependent, with faster rates of reduction occurring at low pH compared to those at high pH

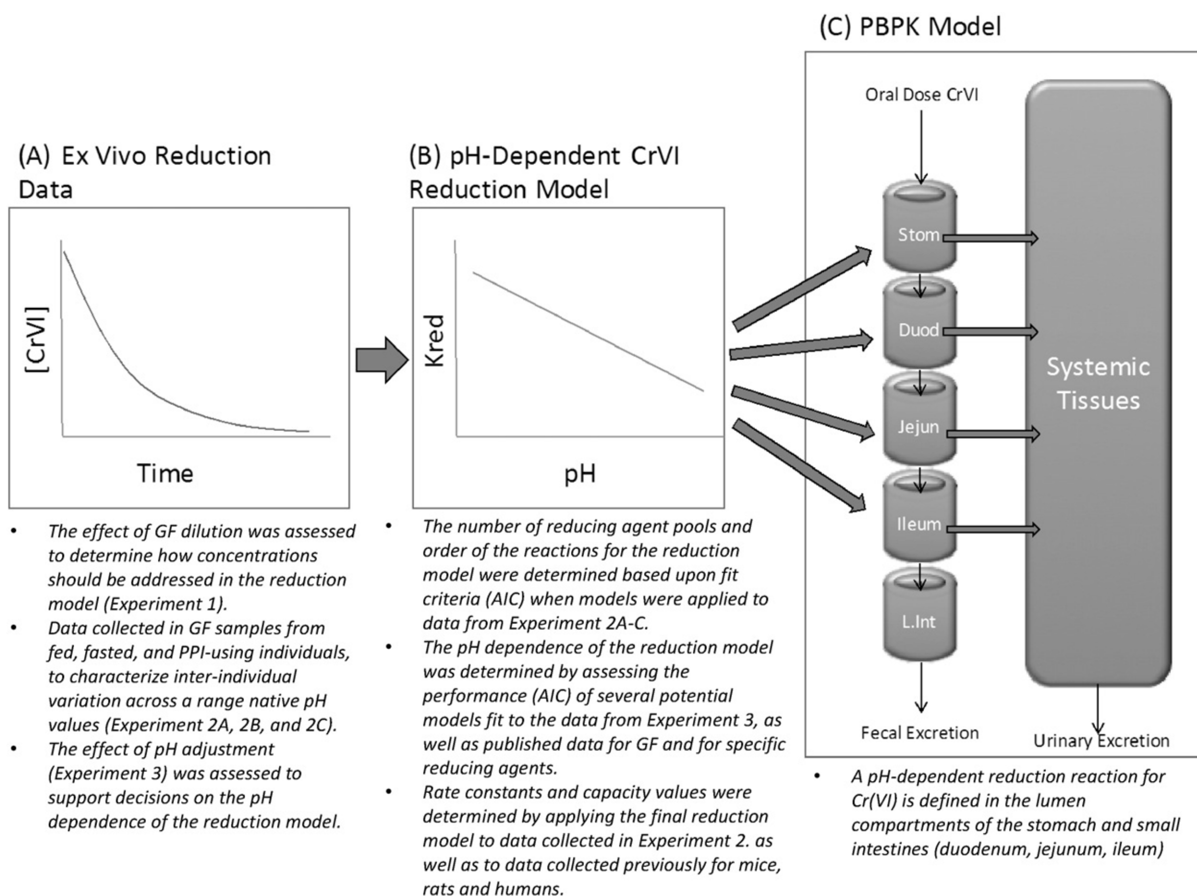

Fig. 1. Role of ex vivo reduction data (A) in developing a reduction model (B) and a PBPK model for Cr(VI) (C).

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