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Consideration of non-linear, non-threshold and threshold approaches for assessing the carcinogenicity of oral exposure to hexavalent chromium

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ABSTRACT

A non-linear approach, consistent with available mode of action (MOA) data, is most scientifically defensible for assessing the carcinogenicity of oral exposure to hexavalent chromium (CrVI). Accordingly, the current paper builds upon previous studies (Haney, 2015a, 2015b) to first develop a non-linear, non-threshold approach as well as a non-linear threshold approach for assessing the oral carcinogenicity of CrVI, and then utilizes available MOA analyses and information for selection of the most scientifically-supported approach. More specifically, a non-linear, non-threshold dose–response function was developed that adequately describes the non-linearity predicted for potential human excess risk versus oral dose due to the sub-linear relationship between oral dose and internal dose (added mg Cr/kg target tissue) across environmentally-relevant doses of regulatory interest. Additionally, benchmark dose modeling was used to derive a reference dose (RfD of 0.003 mg/kg-day) with cytotoxicity-induced regenerative hyperplasia as a key precursor event to carcinogenesis in the mouse small intestine. This RfD value shows remarkable agreement with that published previously (0.006 mg/kg-day) based on a more scientifically-sophisticated, physiologically-based pharmacokinetic modeling approach (Thompson et al., 2013b). The RfD approach is the most scientifically-defensible approach based on the weight-of-evidence of available MOA information and analyses conducted for the most scientifically-supported MOA.

1. Introduction

A significant amount of new research has been conducted over the past several years to generate data specifically to better inform the mode of action (MOA) analysis for hexavalent chromium-induced carcinogenesis due to oral exposure and to improve the extrapolation of rodent oral study results to humans (e.g., Thompson et al., 2011a, 2011b, 2012a, 2013a; Kirman et al., 2012, 2013; Proctor et al., 2012; Kopec et al., 2012a, 2012b; O'Brien et al., 2013; Suh et al., 2014; Thompson et al., 2015a, 2015c). Thorough evaluation of these research project data is essential to a better scientific understanding of the carcinogenic MOA operating in relevant rodent studies (e.g., NTP, 2008) and hexavalent chromium (CrVI) toxicokinetics following oral exposure, both of which are of particular importance considering the significant regulatory challenge of extrapolating high oral dose results from laboratory animal studies to environmentally-relevant human doses that are orders of magnitude lower in a meaningful (not just conservative), toxicologically-predictive manner (e.g., the mouse dose at the lowest water concentration used in NTP, 2008 is about 74,000 times higher than the approximate human dose corresponding to the 35-city geometric mean drinking water concentration reported in EWG, 2010). Consequently, regulatory agencies should duly consider these data to inform key areas of chemical dose–response assessment such as the MOA (e.g., key events), toxicokinetics (e.g., dose-dependent differences in target tissue absorption), and biologically-plausible expectations about potential thresholds and any low-dose risk.

Failure of a chemical assessment's low-dose extrapolation to appropriately consider and incorporate (if scientifically robust and defensible) relevant CrVI research project data on MOA and toxicokinetics may result in significantly overestimating environmental risk. For example, recent analyses of CrVI toxicokinetic data (Kirman et al., 2012) revealed appreciable dose-dependent differences in target tissue absorption (Haney, 2015a, 2015b). More

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specifically, the dose fraction absorbed (or CrVI absorbed by target tissues per unit dose) progressively decreases with decreasing oral dose, resulting in non-linearity (i.e., sub-linearity) between oral dose and target tissue dose across doses of environmental interest (Fig. 1, reproduced from Fig. 2 in Haney, 2015b). This type of toxicokinetic information that reveals a non-linear relationship between oral and internal dose should be taken into account in assessing the potential for a non-linear dose–response (USEPA, 2005). Taking this non-linear/sub-linear relationship between oral and internal target tissue CrVI dose into account, Haney (2015b) concluded:

- Decreasing target tissue absorption as doses decrease to lower, more environmentally-relevant doses is inconsistent with linear low-dose extrapolation as the shape of the dose–response curve accounting for this toxicokinetic phenomenon would be non-linear;
- The magnitude of risk overestimation by a linear low-dose extrapolation approach (e.g., the USEPA draft oral slope factor or SFo) increases significantly as it is used to predict risk at lower, more environmentally-relevant CrVI doses where the dose fractions absorbed by target tissues progressively decrease; and
- A non-linear approach, consistent with available MOA data, is most scientifically defensible for assessing CrVI-induced carcinogenesis.

Accordingly, consistent with results from prior toxicokinetic analyses demonstrating a non-linear/sub-linear relationship between oral dose and internal dose (i.e., target tissue concentration), the current paper builds upon previous studies (Haney, 2015a, 2015b) to:

1) Develop two non-linear approaches (i.e., non-linear, non-threshold and threshold) for assessing the carcinogenicity of oral exposure to CrVI; and
2) Utilize available published MOA analyses and information for selection of the most scientifically-supported approach.

The non-linear, non-threshold approach considered is a novel one for assessing the potential risk of oral exposure to CrVI. The non-linear, threshold approach is represented by the derivation of a reference dose (RfD). While other RfD values have been developed, the RfD derived herein is based on an internal dose metric (unlike the draft RfD in USEPA, 2010), focuses specifically on the duodenum as the most tumorigenically responsive target tissue (unlike Thompson et al., 2013b), and converts internal dose to external dose based on an independently modeled relationship (Haney, 2015a), thus providing an important point of comparison for previously derived values. Lastly, while the MOA data reviewed herein have been discussed in various studies elsewhere (e.g., Thompson et al., 2013a), this study represents the first review and interpretation of all these data (including newly published studies) to appear in a peer-reviewed scientific journal by staff of a regulatory agency. The regulatory perspective is important because regulatory agencies ultimately determine what low-dose extrapolation approaches are scientifically justified and any impact of new MOA research on health-protective regulations.

2. Materials and methods

Pursuant to prior analyses and justification provided in Haney (2015b), this paper considers two non-linear approaches for assessing the carcinogenicity of oral exposure to CrVI:

- A non-linear, non-threshold low-dose extrapolation approach; and
- A non-linear threshold approach.

The non-linear, non-threshold low-dose extrapolation approach is exemplified by the development of a mathematical model (i.e., dose–response function) that adequately describes the non-linearity that would be predicted in excess risk versus oral dose, under the preliminary assumption that excess risk is proportional to target tissue concentration of absorbed CrVI down to zero dose (i.e., under an assumed mutagenic MOA for the sake of comparison), when dose-dependent differences in target tissue absorption are appropriately considered. These differences are discussed in Haney (2015a), which provides a peer-reviewed approach to calculate dose-specific adjustment factors for the draft SFo (USEPA, 2010) based on dose-dependent differences in absorption. These dose-specific adjustment factors that account for the non-linearity in oral dose versus target tissue concentration were used in a second study (Haney, 2015b) to estimate potential excess risk at environmentally-relevant doses (e.g., doses at the federal maximum contaminant level (MCL), 1/3 the MCL, measured drinking water concentrations) and produce an associated dose–response curve (Fig. 2, reproduced from Fig. 3 of Haney, 2015b). The dose–response is non-linear due to the non-linear (i.e., sub-linear) toxicokinetics of CrVI absorption by target tissues being taken into account (Fig. 1) (also see Fig. 4 of Haney, 2015a). It is this non-linear/sub-linear dose–response for excess risk which must be

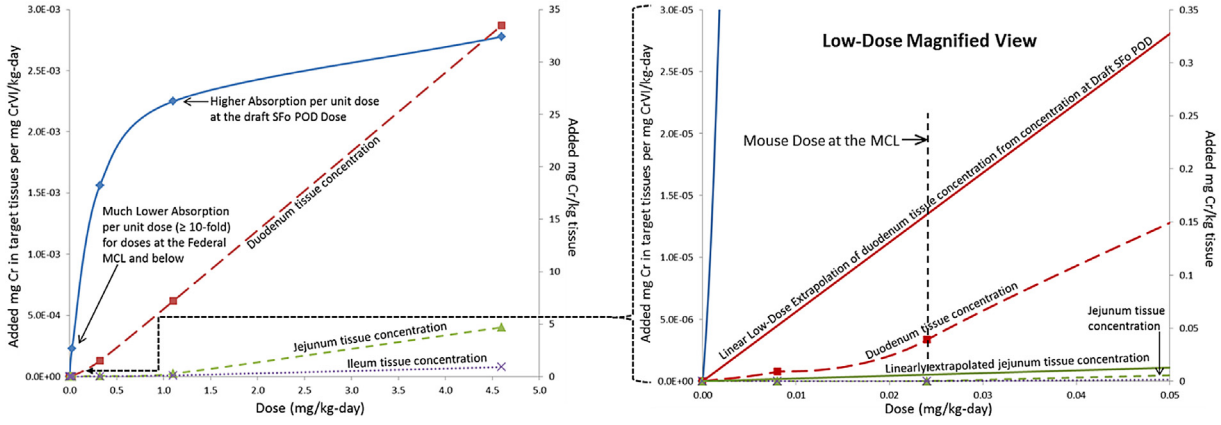

Fig. 1. Dose-dependent changes in mouse target tissue absorption per unit dose and low-dose nonlinearity in absorbed tissue concentration versus dose.