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Implications of dose-dependent target tissue absorption for linear and non-linear/threshold approaches in development of a cancer-based oral toxicity factor for hexavalent chromium

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ABSTRACT

Dose-dependent changes in target tissue absorption have important implications for determining the most defensible approach for developing a cancer-based oral toxicity factor for hexavalent chromium (CrVI). For example, mouse target tissue absorption per unit dose is an estimated 10-fold lower at the CrVI dose corresponding to the federal maximum contaminant level (MCL) than at the USEPA draft oral slope factor (SFo) point of departure dose. This decreasing target tissue absorption as doses decrease to lower, more environmentally-relevant doses is inconsistent with linear low-dose extrapolation. The shape of the dose–response curve accounting for this toxicokinetic phenomenon would clearly be non-linear. Furthermore, these dose-dependent differences in absorption indicate that the magnitude of risk overestimation by a linear low-dose extrapolation approach (e.g., SFo) increases and is likely to span one or perhaps more orders of magnitude as it is used to predict risk at progressively lower, more environmentally-relevant doses. An additional apparent implication is that no single SFo can reliably predict risk across potential environmental doses (e.g., doses corresponding to water concentrations $\leqslant$ the federal MCL). A non-linear approach, consistent with available mode of action data, is most scientifically defensible for derivation of an oral toxicity factor for CrVI-induced carcinogenesis.

1. Introduction

A great deal of recent scientific debate and research concerns exactly how and under what conditions hexavalent chromium (CrVI) is likely to induce cancer following oral exposure (e.g., Thompson et al., 2011a, 2011b; McCarroll et al., 2010; USEPA, 2010). The mode of action (MOA) for CrVI-induced carcinogenicity is a primary topic of debate since it typically determines whether the excess risk observed at very high mouse study oral doses of CrVI is assumed to extrapolate downward to significantly lower, truly environmentally-relevant human doses in a linear manner or if a non-linear/threshold dose–response should be expected at such low doses. More specific topics of debate include the roles of mutagenicity and chronic hyperplasia in CrVI-induced carcinogenicity in target tissues, if gastrointestinal (GI) extracellular reductive capacity likely imparts a non-linear/threshold character to the dose–response, and the potential that mouse oral doses in NTP (2008) exceeded the extracellular CrVI reductive capacity of the GI tract. Indeed, the CrVI MOA research project (e.g., Thompson et al., 2011a) reports that stomach reducing capacity was likely exceeded at doses causing cancer in the mouse small intestine based on CrVI intake per drinking water bout (mg CrVI) exceeding the empirically-based mouse stomach CrVI reducing equivalent (mg CrVI) at water concentrations greater than 20 mg CrVI/L (see Table 3 of Proctor et al., 2012), water concentrations associated with at least minimal neoplastic effects in the mouse small intestine in NTP (2008). Moreover, based on drinking water mouse study data (e.g., histological, biochemical, toxicogenomic, pharmacokinetic) collected specifically to assess the MOA in the mouse small intestine in the context of regulatory agency MOA frameworks, Thompson et al. (2013a) present a weight of evidence in support of a cytotoxic MOA with the following key events:

- Absorption of CrVI from the intestinal lumen.
- Toxicity to intestinal villi.
- Crypt regenerative hyperplasia.
- Clonal expansion of mutations within the crypt stem cells, resulting in late onset tumorigenesis.

Under relevant regulatory agency guidelines (e.g., TCEQ, 2012; USEPA, 2005), low-dose extrapolation approaches (e.g., linear, non-linear/threshold) are evaluated on an assessment-by-assessment basis in the context of the relevant data available. For

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example, USEPA (2005) indicates that a non-linear dose–response approach can be applied when consistent with the current understanding of the carcinogenic MOA. Carcinogenic MOA information and data supporting mechanisms or key events expected to impart a non-linear or threshold dose–response at low doses may sufficiently support considering (and ultimately adopting) carcinogenic assessment approaches other than linear low-dose extrapolation. This should be particularly true in cases when the resulting toxicity factor will be used to assess low, environmentally-relevant oral doses from a health perspective where based on available information, non-linearity in response is expected. The data collected and analyses conducted for the CrVI MOA research project (e.g., Thompson et al., 2013a) support consideration of a non-linear/threshold carcinogenic assessment. Accordingly, in addition to a linear low-dose extrapolation approach for CrVI-induced carcinogenicity due to oral exposure, a non-linear/threshold approach will be considered in this paper for its utility in the development of a scientifically-defensible, cancer-based oral toxicity factor for CrVI. These approaches will be evaluated in the context of analyses conducted based on toxicokinetic information that reveal non-linear relationships between applied oral and internal dose (e.g., Haney, 2015; Kirman et al., 2012), which should be taken into account in dose–response assessment by assessing the potential for a non-linear dose–response (USEPA, 2005).

2. Materials and methods

This paper considers two approaches for deriving a cancer-based, chronic oral toxicity factor for CrVI. The linear low-dose extrapolation method is exemplified by the draft oral slope factor (SFo) developed in USEPA (2010). The non-linear/threshold approach considered is represented by the derivation of the reference dose (RfD) contained in Thompson et al. (2013b). While the scientific debate on the overall weight of evidence for the most likely and plausible MOA(s) continues in light of the recent MOA research of the past few years, that debate is beyond the scope of this paper. However, even outside of the MOA debate, some of the data (e.g., toxicokinetic) collected in recent years have apparent and significant implications for the linear low-dose and non-linear/threshold extrapolation approaches, which are the focus of this paper.

More specifically, based on the target tissue data provided in Kirman et al. (2012), there are dose-dependent differences in absorption by mouse target tissues (duodenum, jejunum, and ileum) that have important implications for the derivation of toxicity factors such as the draft SFo and the proposed RfD (USEPA, 2010; Thompson et al., 2013b). These differences are discussed and quantified in Haney (2015), which provides a peer-reviewed approach to calculate dose-specific SFo adjustment factors based on these differences to more accurately estimate risk at a given dose. That paper also provides several example adjustment factors for the draft SFo to more accurately estimate risk at lower, more environmentally-relevant doses (e.g., federal maximum contaminant level (MCL), 1/3 the MCL, measured drinking water concentrations). The current paper:

- Highlights dose-dependent differences in target tissue absorption (e.g., changes in target tissue absorption per unit dose, non-linearity of tissue concentration versus dose).
- Utilizes the approach published in Haney (2015) (accounting for dose-dependent changes in absorption by target tissues) and associated results (dose-specific SFo adjustment factors) to explore some important implications for linear and non-linear/threshold approaches in development of a cancer-based oral toxicity factor for CrVI.
- Considers the implications of dose-dependent target tissue absorption to draw conclusions concerning the most appropriate low-dose extrapolation approach for the oral carcinogenic assessment of CrVI.

The implications considered include the extent to which these dose-dependent changes in absorption are consistent with linear and non-linear approaches. This can be assessed simply by examining the toxicokinetic relationship between target tissue absorption/concentration and dose across relevant doses (e.g., the relationship is non-linear if target tissue absorption per unit dose changes appreciably with dose, resulting in a departure from linearity for tissue concentration versus dose). Another implication of dose-dependent target tissue absorption considered is the magnitude to which linear low-dose extrapolation is likely to overestimate risk at lower, more environmentally-relevant CrVI doses. The methods and dose-specific adjustment factors published in Haney (2015) adjust for the extent to which linear low-dose extrapolation (based on the draft SFo) overestimates target tissue absorption and risk at a given dose. These adjustment factors provide dose-specific estimates of risk overestimation by linear low-dose extrapolation (i.e., the magnitude of departure from linearity) for the current paper. In addition to being valuable in the consideration of the linear approach, they also provide the ability to better characterize uncertainty when evaluating a non-linear/threshold approach (see Section 3.2.2).

In considering the implications of dose-dependent absorption for evaluating the defensibility of using a linear or non-linear/threshold approach as the most appropriate basis for developing a cancer-based oral toxicity factor for CrVI, an inherent assumption is that any carcinogenic risk is a function of target tissue concentration. This is common practice for regulatory risk assessment in general and applies regardless of the carcinogenic MOA assumed for CrVI (i.e., mutagenicity versus a threshold for regenerative hyperplasia). Additionally, it appears to be valid in this specific case based on Fig. 1, for example, which shows that the incidence of adenoma/carcinoma in the mouse duodenum (Tables 5 and 6 of NTP (2008)) appears related to the mouse duodenum tissue concentrations resulting from oral CrVI exposure (Table 8 of Kirman et al. (2012)). Additional details are provided in the relevant sections below.

3. Results and discussion

3.1. Consideration of linear low-dose extrapolation

An SFo is the toxicity factor that results from implementation of the linear low-dose extrapolation approach for assessment of carcinogenicity due to oral exposure. The units for an SFo are risk per unit oral dose, or more specifically in this case, excess risk per mg CrVI/kg body weight-day. USEPA (2010) provides a draft SFo of 0.5 per mg/kg-day based on the incidence of neoplasms (i.e., adenomas, carcinomas) in the mouse small intestine (primarily in the duodenum and jejunum) in the National Toxicology Program (NTP) mouse drinking water study (NTP, 2008).

The assumption inherent in using linear low-dose extrapolation to derive an SFo (and in the SFo itself) is that risk is linearly related to target tissue concentration (internal dose metric), and that the toxicokinetic relationship between target tissue concentration and oral dose is essentially the same (more-or-less constant) across the doses for which the SFo will be used to estimate risk (e.g., there are not appreciable dose-dependent changes in the dose fraction absorbed by target tissues). That is, in assuming (as does the SFo) that risk is linearly related to oral dose, it is assumed that an oral