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Why Oral Cavity Tumors Should Not be the Basis of the Hexavalent Chromium Oral Cancer Slope Factor: Weight of Evidence Review

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Abstract:

Background and Purpose: In 2024, EPA IRIS departed from its approach, developed over the last 14 years, of setting the oral cancer slope factor (CSF) for hexavalent chromium [Cr(VI)] using small intestine tumor data in mice, as observed in a 2008 NTP cancer bioassay. This approach included the partial use of a PBPK model accounting for gastric reduction of Cr(VI) to inert trivalent chromium [Cr(III)]. An external review board expressed concern that the CSF, indicating cancer risk below typical background exposures, overestimated risk at low exposures. The final EPA IRIS CSF was decreased only slightly and based (for the first time) on rat oral cavity tumors. Oral cavity tumors were only significantly elevated at chronic drinking water exposures of 180 ppm Cr(VI), and were not observed in mice. Significant mechanistic data for the oral cavity indicate a lack of molecular response to Cr(VI) from 7 to 90 days of exposure. Additionally, dozens of occupational and environmental epidemiology studies, including several meta-analyses, have been conducted, many of which inform the potential oral cavity cancer risk among humans, yet the EPA IRIS meta-analysis did not include oral cavity tumors.

The purpose of this study is to evaluate mechanistic, toxicology and epidemiology data to assess the weight of evidence (WOE) regarding the potential for Cr(VI) to pose an oral cavity cancer hazard in humans, and the relevance of EPA's oral CSF for human health risk assessment.

Methods: The original publications of mechanistic studies related to oral cavity cancers which were used in the EPA IRIS review (EPA 2024) were identified for inclusion in WOE evaluation. Additional recent publications, published since 2020, were identified using PubMed. Because EPA's meta-analysis did not include oral cavity tumors, we focused our review of the epidemiological literature on two meta-analyses which included oral cavity tumors (Gatto et al. 2010 and Deng et al. 2019), both of which evaluated only occupational studies, as well as the studies selected by EPA for its meta-analysis of other tumor sites. An additional literature search was conducted in PubMed to identify new studies published since 2016 in English that include data on oral cavity cancer incidence and/or mortality among both occupationally and environmentally exposed populations. Search terms were consistent with those used in the earlier meta analyses, but limited to oral cavity cancer.

Results: Positive *in vivo* animal carcinogenicity data are limited to observations among rats in the NTP (2008) bioassay. Therein, non-neoplastic lesions in the oral cavity were not observed. The dose response for oral tumors, combining males and females, is highly non-linear and only statistically significant at the highest dose in each sex. Margin of exposure (MOE) calculations indicate values ranging from 30,000 to ≥100,000 (Thompson et al. 2018). Consistent with the large MOE, molecular analyses support a lack of response in the oral cavity. In rats and mice exposed to ≤180 ppm Cr(VI) for 7 and 90 days, no gene changes were observed in the oral cavity (Thompson et al. 2016). In TgF344 rats exposed to 180 ppm

Cr(VI) for 28 days, following OECD TG 488, Cr(VI) did not increase mutation frequency relative to controls in gingival-buccal or gingival-palate regions of the oral cavity, yet Cr tissue accumulation was observed in both regions (Thompson et al. 2015). Occupational epidemiological studies do not support an increased risk of oral cancers with even very high-level exposure to Cr(VI). The Gatto et al. (2010) meta-analysis of occupational epidemiology papers published 1950 to 2009, identified 18 papers reporting on oral cavity cancers, and reported no increase in oral cavity cancers (Meta SMR 1.02, CI: 0.77-1.34). The Deng et al. (2019) meta-analysis of studies published 1957-2016, reported increased incidence (SIR 1.3, CI:1.1-1.5), but not mortality (SMR 0.91 CI: 0.75-1.1), for oral cavity and pharynx cancer. The increased SIR was among cement workers and welders, using a fixed effect model. Papers published since 2016, did not report increased oral cancer risk associated with Cr(VI) exposure. Importantly, historical chromate production industry workers in the mid-20th century had extremely high exposures to particulate chromium, so high that it resulted in discolored teeth and tongues with a yellowish appearance (PHS 1953). However, oral cavity cancers were not increased among these workers (PHS 1953). In follow-up epidemiological studies of these workers, oral cavity SMRs were not significantly increased. Specifically, among Painesville Ohio workers, the oral cavity SMR equaled 0.67 (CI: 0.02-3.75, based on 1 case), and among the Baltimore Maryland workers, oral cavity SMR equaled 1.20 (CI: 0.52-2.36) based on 8 cases (Gibb et al. 2000; Gatto et al. 2010). The overall weight of evidence from the epidemiological literature does not support an association between environmental or occupational exposure to Cr(VI) and oral cavity cancers.

Conclusions: In this WOE review, multiple lines of evidence were evaluated. Although rat oral cavity tumors were observed at the highest doses in the NTP study, *in vivo* mechanistic data in rats found no early transcriptomic responses or increase in mutation responses in oral cavity tissues at carcinogenic doses. Also, human evidence does not support an association between Cr(VI) and oral cancer. As such, indirect MOAs, potentially specific to rats, appear to be responsible for oral tumors in rats in the NTP bioassay, which is consistent with the limited accumulation of chromium in these tissues. These findings suggest that oral tumors are a result of a secondary/indirect process, occurring only in rats and/only at high exposures, and not relevant to relevant human exposures. As such the CSF or oral exposure to Cr(VI) based on oral tumors observed in rats should not be used for human health risk assessment.