Science Question 4: Mechanistic Studies Database—MOA in the Lung

Key Points

- **Considerations regarding the lung cancer MOA based on recent review (Proctor et al. 2014 *Toxicology 325:*160-179)**
- **Integrated analysis of toxicokinetic, epidemiology, mechanistic and animal data**
- **Findings support a non-mutagenic MOA**

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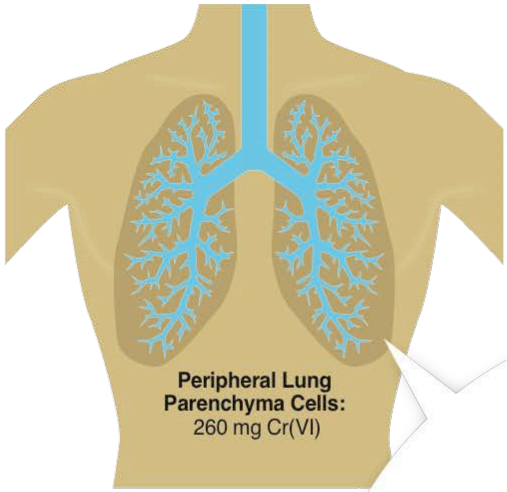
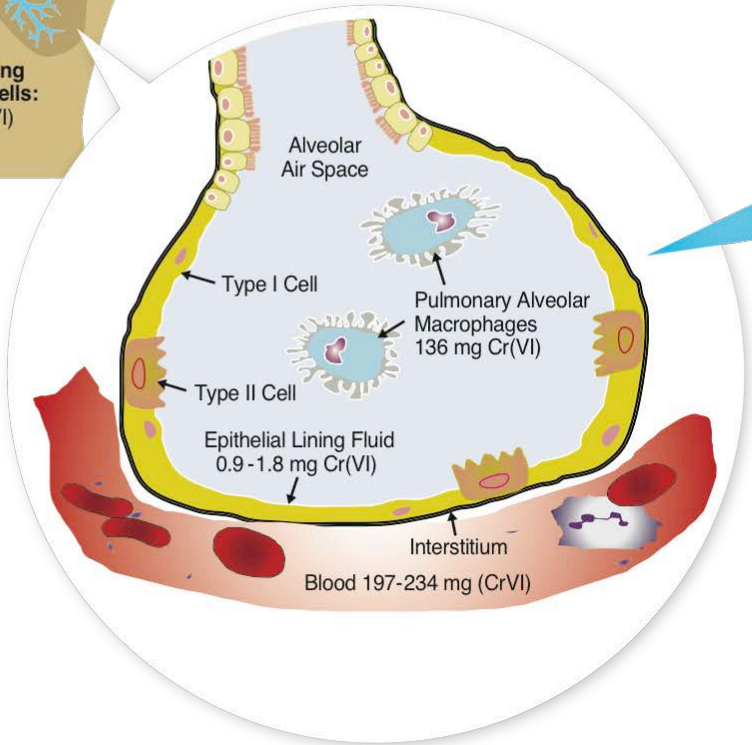
Literature Review and Analysis

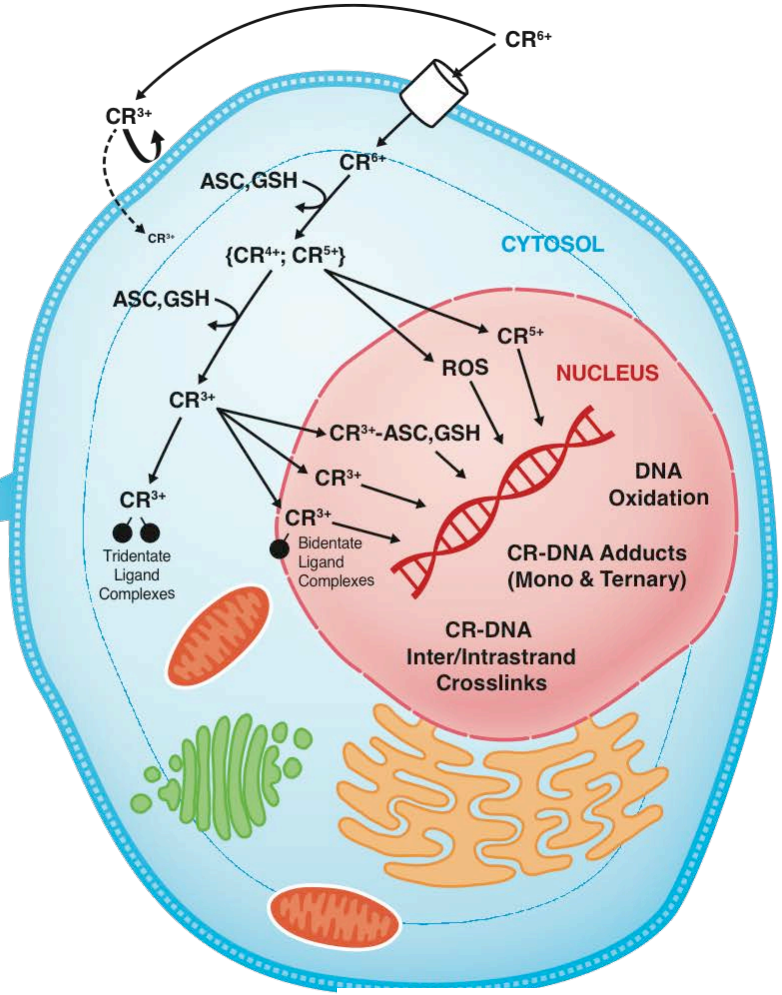
- **Kinetics Are Important**
  - *Provide biological basis for non-linearity in exposure-response (Haney et al. 2012)*
- **Focus on *in vivo* mechanistic data**
  - *Most in vivo mutagenicity data are negative*
- **Epidemiology**
  - *Strongest Cr(VI)-lung cancer associations for industries with respiratory irritation*
  - *Dose-rate effect (Gibb et al. 2011)*
  - *Some industries have no increased risk [welding (Gerin et al. 1993), aerospace (Boice et al. 1999)] but significant exposure*
- **Animal data (repeat dosing)**
  - *Role for inflammation (Beaver et al. 2009; Nickens et al. 2010)*
  - *Dose-rate effect (Steinhoff et al. 1986)*
  - *Weak carcinogen (Glaser et al. 1986)*
  - *Recovery from early tissue damage (hyperplasia and fibrosis) (Glaser et al. 1990)*

Reductive Capacity of Cr(VI) in the Lung and Published Mechanisms of DNA Damage





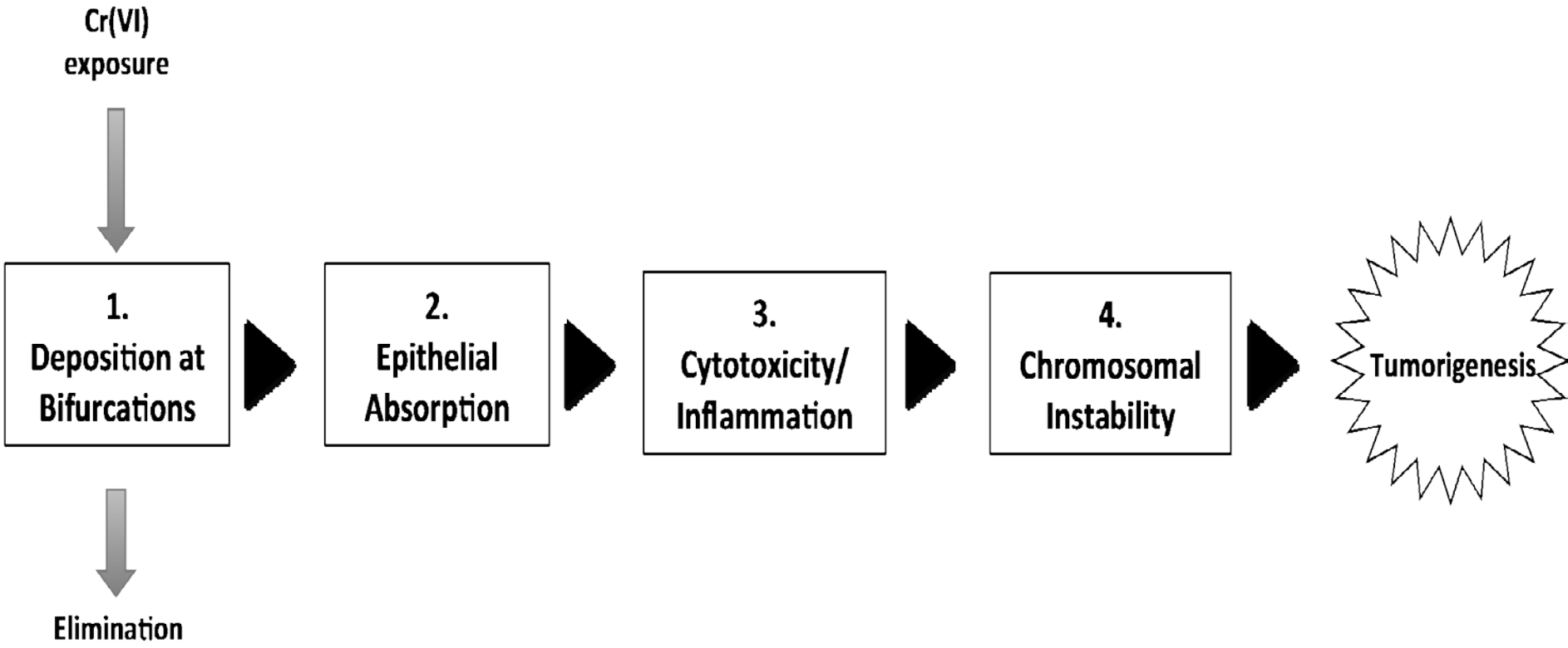
Based on DeFlora et al. 1997



Based on O'Brien et al. 2003

Source: Proctor et al. (2014) *Toxicology*

Proposed Lung Cancer MOA



Source: Proctor et al. 2014 *Toxicology*

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Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Dose-response and temporal concordance	Extracellular reduction provides biological basis for non-linearity Lung tumors preceded by irritation and inflammation in both dose and time, and early hyperplasia is reversible (Glaser et al. 1986, 1990; Steinhoff et al.) Early tissue injury and inflammation in the lung in animals (Beaver et al.2009a,b) and humans (Gibb et al. 2000) In workers, lung cancer occurs after long latency period, clear evidence for cancer limited to the lung	Intratracheal instillation increased MF in Big Blue mice (Cheng et al., 2000) DNA damage after 3 days dosing at 0.25 mg/day (Izzotti et al. 1998) DNA breaks in leukocytes of mice, within 24 hrs of gavage dosing (0.18 to 24 mg/kg Cr(VI) (Danadevi et al., 2001)

Approach adapted from Meek et al. 2013)

Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Consistency, specificity	Two chronic bioassays found similar non-neoplastic and neoplastic lesions in rodent lungs (Steinhoff et al., 1986; Glaser et al., 1986) Mechanistic data supports oxidative lesions, inflammation, and proliferation Clinical evidence of respiratory irritation and tissue damage in occupational cohorts with lung cancer Dose-rate effect in animals and humans (Steinhoff et al 1986; Gibb et al. 2011)	Cr(VI) is mutagenic and genotoxic in numerous *in vitro* assays, in some animal studies but by unnatural routes and at toxic doses DNA damage reported in peripheral blood lymphocytes and buccal cells among workers in two studies (Danadevi 2004; Benova 2002); however negative data are published (Gao 1994, Sarto1990) and these are not target tissues for cancer

Comparative WOE for Non-mutagenic and Mutagenic MOA in the lung using WHO/IPCS framework

Modified Bradford Hill	Supporting Non-Mutagenic	Supporting Mutagenic MOA
Biologic Plausibility	Many chromium researchers believe that Cr(VI) mutagenic potency is weak (ERD, 2011; Holmes et al. 2008). Epigenetic mechanisms identified in tumors of Cr(VI)-exposed workers (Takahashi et al. 2005); microsatellite instability (Hirose et al. 2002); low P53 mutation frequency (Kondo et al. 1997). Non-mutagenic MOA for other Cr(VI)-induced tumors (intestine and oral)	Cr(VI) is mutagenic and genotoxic in numerous *in vitro* assays, in some animal, and in humans studies