Noncancer Hazards Associated with Cr(VI) Exposure

Ted Simon, Ph.D., DABT

IRIS Bimonthly Meeting

June 25-27, 2014

Noncancer Endpoints

- Choosing the critical endpoint means that the POD and resulting RfD will be protective of other endpoints
- What is the critical noncancer endpoint?
- Arrays of NOAELs and LOAELs

Array of NOAELs and LOAELs

Endpoint Classification	Specific Endpoint	NOAEL / BMDL10	Specific Endpoint	LOAEL
Liver Toxicity	Basophilic focus in male rats (NTP, 2008)	0.21 / NA	Chronic inflammation in female rats (NTP, 2008)	0.24
Potential immune / inflammatory changes	Histiocytic inflammation of abdominal lymph nodes in male rats (NTP, 2008)	0.21 / NA	Histiocytic inflammation of abdominal lymph nodes in male and female mice (NTP, 2008)	0.38
Hematotoxicity	Changes in hematocrit, MCV, and hemoglobin in rats (NTP, 2008)	0.21 / NA	Changes in hematocrit, MCV, and hemoglobin (NTP, 2008)	NA
Gastrointestinal Toxicity	Diffuse Epithelial Hyperplasia, small intestine, male and female mice (NTP, 2008)	**0.38 / 0.09**	Diffuse Epithelial Hyperplasia, small intestine, male and female mice	0.38
Genotoxicity	Micronuclei in RBCs of bone marrow and fetuses of mice (De Flora et al., 2006)	0.91 / NA	brain DNA single-strand breaks in female rats (Bagchi et al., 1997	1
Reproductive Toxicity	Changes in male reproductive function in monkeys (Subramanian et al., 2006)	4.4 / NA	Change is male reproductive function in rabbits (Yousef et al., 2006)	3.6 / NA
Developmental Toxicity	A range of endpoints in F Swiss albino rats (Kanojia et al., 1996)	31	Adverse changes in fetal development in rats (Elsaieed and Nada, 2002)	8.4
Kidney toxicity	Renal lesions	NA	Renal lesions in male rats	1

Liver Toxicity PODs as an Process Example

Study	Specific Endpoint	Sex/Lifestage/ Strain/Species	Doses (mg/kg/d Cr6)	NOAEL	LOAEL	Potential MOA Considerations
NTP, 2008	Basophilic foci	M F344 rats	0, 0.21, 0.77, 2.1, 5.9 for 2 years in drinking water	**0.21**	0.77	Associated with inflammation, likely due to tissue damage in the small intestine and possibly lymph nodes and liver. Possible oxidative stress at higher doses.
	Chronic Inflammation			0.77	2.1	Possibly due to release of cytokines from damaged intestinal tissue. Possible oxidative stress at higher doses.
	Histiocytic infiltration			2.1	5.9	Likely reflects migration of immune cells as part of the inflammatory process. Possible oxidative stress at higher doses.
	Chronic inflammation	F F344 rats	0, 0.24, 0.94, 2.4, 7.0 for 2 years in drinking water		**0.24**	Possibly due to release of cytokines from damaged intestinal tissue. Possible oxidative stress at higher doses.
	Histiocytic inflammation			0.24	0.94	Likely reflects migration of immune cells as part of the inflammatory process
	Fatty change			0.24	0.94	May be associated with tissue damage due to chronic inflammation; unknown why effects occurs in females only
	Clear cell focus			0.94	0.24	Unknown
	Clear cell focus	M B6C3F1 mice	0, 0.38, 0.91, 2.4, 5.9 for 2 years in drinking water	2.4	5.9	Possibly due to release of cytokines from damaged intestinal tissue. Possible oxidative stress at higher doses.
	Eosinophilic focus			2.4	5.9	
	Hyperplasia	F B6C3F1 mice	0, 0.38, 1.4, 3.1, 8.7 for 2 years in drinking water	NA	0.38	Possibly due to release of cytokines from damaged intestinal tissue. Possible oxidative stress at higher doses.
	Histiocytic infiltration			NA	0.38	
	Chronic inflammation			1.4	3.1	
	Eosinophilic focus			1.4	3.1	
Acharya et al. 2001	Degeneration, necrosis	M adult Wistar rats	0, 1.1 for 22 weeks in drinking water		1.1	High doses only; mechanism is likely oxidative stress.
Chopra et al., 1996	Hepatocyte degeneration, necrosis	F adult Wistar rats	0, 1.4 for 22 weeks in drinking water		1.4	High doses only; mechanism is likely oxidative stress.
NTP, 1997a	Cytoplasmic vacuolization in hepatocytes	M BALB/c mice	0, 1.1 3.5, 7.4, 29.3 (M) 0, 1.8, 5.6, 11.9, 48 (F) for 9 weeks in diet followed by 9 week recovery	1.1 M; 1.8 F;	3.5	High doses only; mechanism is likely oxidative stress.

Take Home

- Using the BMDL for epithelial hyperplasia in the small intestine in mice, which is the lowest POD, will very likely be protective of all other observed endpoints